Tissue Factor Pathway Inhibitor, Activated Protein C Resistance, and Risk of Coronary Heart Disease Due To Combined Estrogen Plus Progestin Therapy

Karen C. Johnson, Aaron K. Aragaki, Rebecca Jackson, Alex Reiner, Per Morten Sandset, Jan Rosing, Anders E.A. Dahm, Frits Rosendaal, JoAnn E. Manson, Lisa W. Martin, Simin Liu, Lewis H. Kuller, Mary Cushman, Jacques E. Rossouw

Objective—To examine whether tissue factor pathway inhibitor or acquired activated protein C (APC) resistance influences the increased risk of coronary heart disease (CHD) due to estrogen plus progestin therapy.

Approach and Results—Prospective nested case–control study of 205 cases of CHD and 481 matched controls in the Women’s Health Initiative randomized trial of estrogen plus progestin therapy. After multivariable covariate adjustment, both baseline tissue factor pathway activity (P=0.01) and APC resistance (P=0.004) were associated positively with CHD risk. Baseline tissue factor pathway activity and APC resistance singly or jointly did not significantly modify the effect of estrogen plus progestin on CHD risk. Compared with placebo, estrogen plus progestin decreased tissue factor pathway inhibitor activity and increased APC resistance but these changes did not seem to modify or mediate the effect of estrogen plus progestin on CHD risk.

Conclusions—Tissue factor pathway inhibitor activity and APC resistance are related to CHD risk in women, but may not explain the increased CHD risk due to estrogen plus progestin therapy. The data from this study do not support the clinical use of measuring these hemostatic factors to help stratify risk before hormone therapy.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000611.

Key Words: activated protein C resistance coronary disease estrogens hemostatics progestins

The Women’s Health Initiative (WHI) trial of estrogen plus progestin therapy (EPT) demonstrated an increased risk of coronary heart disease (CHD), particularly in the first few years after randomization. The exact biological mechanism(s) to explain this increased risk with EPT use have not been fully elucidated, but an activated coagulation system that is associated with an increased risk for CHD and ischemic stroke is a possibility. Oral contraceptives (OCs) and postmenopausal hormone therapy are known to increase markers of fibrinolysis, reduce coagulation inhibitors, and increase acquired activated protein C (APC) resistance.4–12

In the WHI trial, EPT increased plasmin–antiplasmin levels and decreased fibrinogen and plasmin activator inhibitor-1, but these changes did seem to explain the increased risk of CHD resulting from EPT use.13 However, in the same trial EPT increased the risk of venous thromboembolism (VT) especially in women with factor V Leiden (FVL), which is consistent with a possible role for changes in other hemostatic factors in contributing to the increased risk of CHD.14 Changes in coagulation inhibitors may be particularly relevant to the pathogenesis of the increased CHD risk with EPT use. The coagulation inhibitors protein C, tissue factor pathway inhibitor (TFPI), protein S, and antithrombin are all reduced by EPT.15–17 APC is thought to counteract thrombin formation and clot propagation. The FVL mutation that increases resistance to APC has been shown to be a strong risk factor for VT, and it is also associated with a modestly increased risk of arterial disease.15–17 The most common form of APC resistance in the absence of FV Leiden is acquired APC resistance, which particularly occurs in women who use OCs. Acquired APC resistance during OC use is especially well detected with the thrombin generation–based APC resistance test in which coagulation is triggered via the extrinsic coagulation pathway.

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but not with the classical APC resistance test, a clotting-based assay in which coagulation is triggered via the intrinsic coagulation pathway. APC resistance determined with the thrombin generation–based test used in this study predicts the risk of VT both in carriers and in noncarriers of the FV Leiden mutation.18

However, little is known about the association of acquired APC resistance with arterial disease, and we could not identify any prospective studies of this relationship. In a retrospective case–control study of myocardial infarction in young women cases compared with controls showed a decrease (rather than the expected increase) in APC resistance using the thrombin generation–based APC resistance test.19 However, a positive association of APC resistance with severity of arterial disease was found using the classical APC resistance test.20 EPT induces an acquired resistance to APC in women without genotypic FVL, increases resistance in those with FVL, and increases risk of VT in women with and without FVL.5,6,14

TF is a key initiator of the coagulation cascade and seems to be involved in the pathogenesis of atherosclerosis and acute plaque rupture in CHD events.21 TFPI produced in endothelial cells regulates the TF-dependent pathway of blood coagulation and lower TFPI plasma concentrations increase coagulation activation and thrombin generation. The association of lower TFPI levels with increased risk of VT varies across studies.22,23 Both EPT and OCs reduce total and free concentrations of TFPI and TFPI activity.24–26 TFPI also seems to have antiatherogenic properties by interfering with endothelial cell activation, monocyte recruitment, and smooth muscle cell migration.21 Paradoxically, however, higher TFPI levels have been noted in patients with subclinical or symptomatic atherosclerosis compared with controls.19,24–26 Reductions in TFPI and of protein S are thought to be key determinants underlying the activation of coagulation and the development of acquired APC resistance associated with OCs.4,10,11 Protein S binds to TFPI and as a cofactor has a biological interaction, increasing TFPI activity in laboratory studies, but an interaction on venous thrombosis was not found in an epidemiological study.27 Although free TFPI is considered to be the most biologically active form, epidemiological studies have variably measured total TFPI, free TFPI, or TFPI activity; where >1 form was measured the results were generally concordant.9,19,26 In this study, we investigated all 3 forms of TFPI as well as acquired APC resistance, but not protein S or antithrombin levels.

To our knowledge, the associations of acquired APC resistance and changes in TFPI levels and activity subsequent to menopausal hormone therapy with CHD risk have not been investigated previously in a prospective study. In this study, we use a prospective case–control design with 205 cases of CHD and 481 controls nested within the WHI clinical trial of EPT to examine the associations of acquired APC resistance and of TFPI with CHD risk, and whether either baseline values or EPT-induced changes in these factors influence the effect of EPT on CHD risk.

### Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

### Results

The baseline characteristics of the CHD cases and controls are displayed in Table 1. As expected, case–control status was strongly associated with known CHD risk factors. At baseline, cases were more likely to currently smoke, be physically inactive, and have a history of diabetes mellitus, hypertension, hyperlipidemia or cardiovascular disease than controls. Cases also had higher body mass index, higher measured blood pressure, higher waist/hip ratio, higher baseline TFPI activity, and higher baseline normalized APC sensitivity ratio.

Consistent with the published trial results, cases and controls included in these analyses showed odds ratio (OR)s of 1.41 (95% confidence interval [CI], 1.01–1.97) for the effects of EPT versus placebo on CHD risk during the first 4 years of the trial follow-up (data not shown).2 After multivariable adjustment, both higher baseline TFPI activity (P=0.01) and normalized activated protein C resistance ratio (nAPC-sr; P=0.004) were positively associated with CHD risk (Table 2). Findings for baseline total and free TFPI levels were consistent with those for TFPI activity but were not statistically significant. In the analysis comparing the extremes of TFPI (highest and lowest 10% to the middle 80%), neither total TFPI nor free TFPI were associated with CHD risk (data not shown), but the lowest TFPI activity category was associated with nonsignificantly reduced CHD risk (OR, 0.47; CI, 0.19–1.17) compared with the middle 80%, and the highest TFPI activity category was associated with a significantly increased CHD risk (OR, 1.87; CI, 1.02–3.43; P=0.01). Baseline TFPI levels and activity were not correlated with nAPC-sr (r values ranged from −0.063 to −0.15) and adding TFPI to the models for nAPC-sr (or vice versa) did not change the estimates of their associations with CHD risk (data not shown).

Table 3 shows the associations of baseline biomarkers with CHD risk by treatment group. Although EPT seemed to amplify the association between TFPI activity and CHD, whereas placebo attenuated the association, the interaction was not statistically significant (P interaction=0.37). EPT did not influence the association of nAPC-sr with CHD (P interaction=0.99). Finally, the joint relationship of TFPI activity and nAPC-sr to CHD risk was not modified by EPT (3-way P interaction=0.67; data not shown).

EPT decreased TFPI measures at year 1 compared with placebo (all P<0.001; Figure I in the online-only Data Supplement). The largest effect was observed for a decrease in TFPI activity, where the upper quartile of the EPT group was less than the lower quartile of placebo. EPT significantly
increased nAPC-sr compared with placebo ($P<0.001$) and absolute change in TFPI activity was inversely correlated with change in nAPC-sr ($r=-0.38$). However, degree of change in biomarkers did not modify the effect of EPT versus placebo on CHD risk significantly ($P_{interaction}$ values varied between 0.08 and 0.75, Table 4). A possible exception is that women in the tertile experiencing the greatest decrease in free TFPI had an OR for CHD of 3.42 (CI, 1.12–1.45); however, on a linear scale the statistical test was not significant ($P_{interaction}=0.11$). After including change in biomarker as a covariate, we found modest attenuation of CHD risk after 1 year associated with EPT but the degree of attenuation was not compelling enough to suggest mediation. For example, after including change in TFPI activity due to hormone therapy as a covariate the estimated OR (95% CI) for CHD attenuated to 1.14 (CI, 0.64–2.04) from 1.29 (CI, 0.80–2.07). Likewise, after including change in nAPC-sr, the estimated OR attenuated to 1.09 (CI, 0.64–1.88) from 1.13 (CI, 0.68–1.88).
We have previously shown that nAPC-sr, normalized activated protein C resistance ratio, and TFPI, tissue factor pathway inhibitor, shows TFPI activity and acquired APC resistance are positively associated with CHD risk in postmenopausal women. We report the first prospective nested case–control study that could identify free TFPI levels below the 10th percentile were against clinical CHD. In the single prospective study that we performed in prevalent cases, and therefore it is uncertain whether the findings reflect a compensating mechanism for an increased procoagulant state associated with underlying arterial disease. The prospective design of this study is better suited toward identification of risk factors preceding incident disease.

The biology of TFPI (which colocalizes with tissue factor in the atherosclerotic plaque) might predict a protective effect against clinical CHD. In the single prospective study that we could identify free TFPI levels below the 10th percentile were to study medication also yielded results similar to the main analyses. However, an intriguing but not statistically significant interaction ($P_{interaction}=0.08$; Table 4) between change in nAPC-sr and treatment effect became significant ($P_{interaction}=0.01$) after accounting for adherence. Specifically, the OR for EPT at each tertile of change in nAPC-sr went from 2.14, 0.89, and 0.61 to 5.17, 1.07, and 0.51. The associations of baseline TFPI and nAPC-sr and their interactions with EPT on CHD risk were similar during the first and second 2-year periods after randomization, as were the associations of EPT-induced changes in these factors.

### Discussion

We report the first prospective nested case–control study that shows TFPI activity and acquired APC resistance are positively associated with CHD risk in postmenopausal women. We have previously shown that d-dimer, factor VII, and von Willebrand factor levels were associated with CHD risk in this cohort of women. Associations of hemostatic factors with CHD risk were independent of the standard risk factors, such as treatment for high blood cholesterol, hypertension, smoking, diabetes mellitus, and obesity. Even though this was a prospective study and the associations persisted after excluding the first 2 years of follow-up, we cannot tell whether these hemostatic factors are simply markers of underlying arterial pathology or are true risk factors for CHD. Nonetheless, these prospective findings underscore the potential importance of hemostasis in the evolution of coronary arterial events. The finding of increased risk of CHD with increasing nAPC-sr values (ie, decreased sensitivity to APC) is consistent with an adverse role for a more prothrombotic state. Our findings that decreased APC sensitivity are associated with CHD risk stand in contrast to another large study, which found increased (rather than decreased) sensitivity to APC in young women with myocardial infarction. However, as this was a retrospective case–control study the measurement of APC sensitivity was performed in prevalent cases, and therefore it is uncertain whether the findings reflect a compensating mechanism for an increased procoagulant state associated with underlying arterial disease. The prospective design of this study is better suited toward identification of risk factors preceding incident disease.

The biology of TFPI (which colocalizes with tissue factor in the atherosclerotic plaque) might predict a protective effect against clinical CHD. In the single prospective study that we could identify free TFPI levels below the 10th percentile were

### Table 2. Multivariable Adjusted* CHD Risk by Tertile of Baseline Tissue Factor Pathway Inhibitor and Activated Protein C Resistance

<table>
<thead>
<tr>
<th>Low Tertile</th>
<th>Middle Tertile</th>
<th>High Tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total TFPI, ng/mL</strong></td>
<td>n†</td>
<td>Odds Ratio (CI)</td>
</tr>
<tr>
<td>56 (ref)</td>
<td>69</td>
<td>1.11 (0.69–1.79)</td>
</tr>
<tr>
<td><strong>Free TFPI, ng/mL</strong></td>
<td>n‡</td>
<td>Odds Ratio (CI)</td>
</tr>
<tr>
<td>45 (ref)</td>
<td>83</td>
<td>1.57 (0.97–2.53)</td>
</tr>
<tr>
<td><strong>TFPI activity, %¶</strong></td>
<td>n¶</td>
<td>Odds Ratio (CI)</td>
</tr>
<tr>
<td>51 (ref)</td>
<td>69</td>
<td>1.24 (0.76–2.01)</td>
</tr>
<tr>
<td><strong>nAPC-sr (ratio)#</strong></td>
<td>n#</td>
<td>Odds Ratio (CI)</td>
</tr>
<tr>
<td>50 (ref)</td>
<td>66</td>
<td>1.23 (0.74–2.04)</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; CI, confidence interval; nAPC-sr, normalized activated protein C resistance ratio; and TFPI, tissue factor pathway inhibitor.

*Logistic regression models adjusted for treatment assignment, age, race, body mass index, waist/hip ratio, smoking, alcohol use, diabetes mellitus, prevalent cardiovascular disease, systolic and diastolic blood pressures, LVH on ECG, use of antihypertensive medications, aspirin, statins, and ever treated for high cholesterol.

†P value corresponds to a 1 degree-of-freedom test of association between CHD and biomarker (linear; log transformed).

‡No. of cases.

§Tertiles of total TFPI based on controls and correspond to <79.5, 79.5 to <96.7, and ≥96.7 ng/mL.

¶Tertiles of free TFPI based on controls and correspond to <12.8, 12.8 to <18.1, and ≥18.1 ng/mL.

#Tertiles of TFPI activity based on controls and correspond to <103, 103 to <124, and ≥124%

### Table 3. Multivariable Adjusted* Associations of Baseline Tissue Factor Pathway Inhibitor and Activated Protein C Resistance With Coronary Heart Disease Risk by Treatment Assignment

<table>
<thead>
<tr>
<th>EPT</th>
<th>Low Tertile</th>
<th>Middle Tertile</th>
<th>High Tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total TFPI, ng/mL</strong></td>
<td>n</td>
<td>Odds Ratio (CI)</td>
<td>n</td>
</tr>
<tr>
<td>37 (ref)</td>
<td>39</td>
<td>1.15 (0.61–2.14)</td>
<td>40</td>
</tr>
<tr>
<td><strong>Free TFPI, ng/mL</strong></td>
<td>n</td>
<td>Odds Ratio (CI)</td>
<td>n</td>
</tr>
<tr>
<td>24 (ref)</td>
<td>50</td>
<td>1.97 (1.04–3.73)</td>
<td>48</td>
</tr>
<tr>
<td><strong>TFPI activity, %¶</strong></td>
<td>n¶</td>
<td>Odds Ratio (CI)</td>
<td>n</td>
</tr>
<tr>
<td>27 (ref)</td>
<td>44</td>
<td>1.72 (0.90–3.29)</td>
<td>47</td>
</tr>
<tr>
<td><strong>nAPC-sr (ratio)#</strong></td>
<td>n#</td>
<td>Odds Ratio (CI)</td>
<td>n</td>
</tr>
<tr>
<td>32 (ref)</td>
<td>36</td>
<td>1.06 (0.54–2.06)</td>
<td>46</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; EPT, estrogen plus progestin therapy; nAPC-sr, normalized activated protein C resistance ratio; and TFPI, tissue factor pathway inhibitor.

*Logistic regression models adjusted for treatment assignment, interaction of biomarker with randomization group, age, race, body mass index, waist/hip ratio, smoking, alcohol use, diabetes mellitus, prevalent cardiovascular disease, systolic and diastolic blood pressure, LVH on ECG, use of antihypertensive medications, aspirin, statins, and ever treated for high cholesterol.

†P value corresponds to a 1 degree-of-freedom test for interaction between randomization group and biomarker (linear; log transformed).
The statistically significant findings from adherence-adjusted analyses (excluding noncompliant women) suggest that this finding is real, because hormone effects would be expected to be more robust in women who are actually compliant with the study medications.

The primary objectives of this study were to elucidate whether either baseline levels of these hemostatic factors or treatment-induced changes contributed to the excess risk of CHD observed during the first several years after the initiation of EPT. The results do not provide evidence that TFPI or acquired APC resistance singly or in combination modify or mediate the effect of EPT on CHD risk. WHI investigators have previously shown that high low-density lipoprotein cholesterol levels or the presence of metabolic syndrome are useful for identifying women at higher risk of CHD when exposed to hormone therapy. However, to date we have not been able to identify any hemostatic or inflammatory factors that may help to stratify risk before initiating hormone therapy.

The main strength of this study is the prospective design in the context of a randomized controlled trial, which allows for an unbiased examination of the interplay of hemostatic factors and hormone therapy. Clinical outcomes were ascertained with a rigorous standardized methodology by blinded medical adjudicators. This study is comparable in size with the retrospective case-control study of Winckers et al19 and the associations of baseline measurements with future CHD could thus be measured with similar precision. However, the number of clinical outcomes remains relatively modest, which may have limited the statistical power to examine the interaction of treatment-induced changes in hemostatic factors with the smaller numbers of CHD outcomes after 1 year. Also, the hormone effects on CHD risk were less pronounced after the first year, further diminishing statistical power. Nonetheless, in the case of nAPC-sr the observation that treatment-induced increases in the ratio were associated with reduced rather than increased CHD risk, which makes it rather unlikely that a positive relationship would have emerged if the study were larger. Another limitation is the variability in laboratory measurements, which would tend to obscure real effects. The relatively modest study size and variability in measurements may underlie the somewhat variable strength of association with CHD risk for TFPI.

**Table 4. Effect of Hormone Therapy on Coronary Heart Disease Risk by Change in Tissue Factor Pathway Inhibitor and Activated Protein C Resistance**

<table>
<thead>
<tr>
<th></th>
<th>Low Tertile*</th>
<th>Middle Tertile</th>
<th>High Tertile</th>
<th>P Value for Interaction†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total TFPI, ng/mL‡</td>
<td>0.53 (0.17–1.63)</td>
<td>1.82 (0.75–4.41)</td>
<td>0.89 (0.30–2.58)</td>
<td>0.75</td>
</tr>
<tr>
<td>Free TFPI, ng/mL§</td>
<td>0.94 (0.39–2.31)</td>
<td>0.75 (0.34–1.65)</td>
<td>3.42 (1.12–10.45)</td>
<td>0.11</td>
</tr>
<tr>
<td>TFPI activity, ‰</td>
<td>1.95 (0.70–5.39)</td>
<td>0.86 (0.38–1.95)</td>
<td>1.89 (0.37–9.58)</td>
<td>0.51</td>
</tr>
<tr>
<td>nAPC-sr (ratio)¶</td>
<td>2.14 (0.85–5.38)</td>
<td>0.89 (0.36–2.22)</td>
<td>0.61 (0.23–1.62)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; nAPC-sr, normalized activated protein C resistance ratio; OR, odds ratio; and TFPI, tissue factor pathway inhibitor.

*Categories are shown as lowest to highest tertiles of absolute change.

†P values for interaction of randomization group×change in biomarker adjusting for baseline level of biomarkers, and the same covariates as in Table 3, based on 131 cases and 319 controls for TFPI and 119 cases and 262 controls for nAPC-sr. Tertile cut points for change are derived from controls.

‡Tertiles of change in total TFPI were ≥−2.9, −15.6 to <−2.9, and −15.6 mg/mL.

§Tertiles of change in free TFPI were ≥0.2, −3.6 to <0.2, and −3.6 mg/mL.

¶Tertiles of change in TFPI activity were ≥−2, −19 to <−2, and −19%.

||Tertiles of change in nAPC-sr ratio were ≤−0.099, −0.099 to <−1.455, ≥−1.455.

The interplay between TFPI and acquired APC resistance is more complex than the simple paradigm that decreased TFPI will result in increased APC resistance, and therefore increased risk of disease associated with a procoagulant state. We found only a weak inverse correlation of TFPI levels and activity with APC resistance at baseline, suggesting that much of the acquired APC resistance in our population is because of factors such as variations in protein S levels (not measured here), or other hemostatic and endogenous hormonal variations, in addition to the contribution made by inherited FVL. Hormonal factors are clearly important, as shown by the substantial decreases in TFPI activity and increases in nAPC-sr in the group receiving EPT compared with placebo, and the somewhat stronger inverse correlations between TFPI and nAPC-sr after receiving active treatment. However, contrary to expectation these procoagulant changes were not associated significantly with CHD risk and indeed (although not statistically significant) increased nAPC-sr due to therapy tended to be inversely associated with CHD risk.
activity, total, and free TFPI. We did not measure other indicators of anticoagulant activity, such as protein S and antithrombin. We only examined data derived from 1 trial of a particular combination estrogen plus progestin preparation, which limits the generalizability of some findings.

We conclude that TFPI activity and acquired APC resistance are associated with CHD risk in postmenopausal women and that that EPT hormone therapy induces potentially adverse changes in these indicators of anticoagulant activity. However, these hemostatic factors do not seem to offer a mechanistic explanation for the increase in CHD risk due to hormone therapy. Neither baseline levels nor treatment-induced changes seem to interact with hormone therapy to modify or mediate CHD risk. Measurement of these hemostatic factors is not likely to be useful to determine whether a particular woman will be at higher risk of CHD due to hormone therapy.

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The first and senior author share equal responsibility for this manuscript. All authors have contributed, and all have read and agreed to its submission.

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R. Jackson has an investigator initiated study on Electronic Health Record decision support for Healthy 7 from Pfizer and clinical contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN27120110004C.

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5. Hoibraaten E, Qvigstad E, Andersen TO, Mowinckel MC, Sandset PM. The effects of hormone replacement therapy (HRT) on hemostatic variables in women with previous venous thromboembolism—results from a randomized, double-blind, clinical trial. Thromb Haemost. 2001;85:775–781.
We and others have previously shown that several hemostatic factors are related to future risk of coronary heart disease. This study in women adds variations in natural anticoagulant activities of tissue factor pathway inhibitor and activated protein C to the list. These and other hemostatic factors are adversely affected by menopausal hormone therapy; however, neither the baseline levels nor the treatment-induced changes seem to contribute to the increased risk of coronary heart disease on hormone therapy. Therefore, measurement of these factors is unlikely to be clinically useful to identify women at increased risk of coronary heart disease before initiating hormone therapy.
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