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

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**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 ■ tissue factor pathway inhibitor activity

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.\(^\text{1,2}\) 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.\(^\text{3}\) Oral contraceptives (OCs) and post-menopausal hormone therapy are known to increase markers of activated coagulation, decrease markers of fibrinolysis, reduce coagulation inhibitors, and increase acquired activated protein C (APC) resistance.\(^\text{4-12}\)

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.\(^\text{13}\) 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.\(^\text{1,4}\)

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.\(^\text{5,9}\) 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.\(^\text{15-17}\) 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...
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 was less than the lower quartile of placebo. EPT significantly increased nAPC-sr (or vice versa) did not change the estimates of their associations with CHD risk (data not shown). Baseline TFPI levels and activity were not correlated with 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

### 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). 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 analyses 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).
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 ($P$ for 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).

Sensitivity analyses excluding women with genotypic FVL (n=29) or women with prevalent cardiovascular disease at baseline did not have an appreciable effect on our results (data not shown). Analyses excluding women not adherent

### Table 1. Baseline Characteristics of Women in the Nested Case–Control Study (n=686)

<table>
<thead>
<tr>
<th></th>
<th>Case (n=205)</th>
<th>Control (n=481)</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>183</td>
<td>423</td>
<td>0.79</td>
</tr>
<tr>
<td>Black</td>
<td>12</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Other/Unspecified</td>
<td>10</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>90</td>
<td>268</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Past</td>
<td>66</td>
<td>171</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>42</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td><strong>Alcoholic drinks per d</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinker</td>
<td>106</td>
<td>220</td>
<td>0.23</td>
</tr>
<tr>
<td>≤1 drink/d</td>
<td>78</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>&gt;1 drink/d</td>
<td>19</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td><strong>Total expenditure from physical activity (METS/wk)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>40</td>
<td>61</td>
<td>0.02</td>
</tr>
<tr>
<td>&lt;5</td>
<td>43</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>5 to &lt;12</td>
<td>43</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>≥12</td>
<td>47</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td><strong>Treated diabetes mellitus (pills or shots)</strong></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Never hypertensive</td>
<td>86</td>
<td>273</td>
<td>0.001</td>
</tr>
<tr>
<td>Untreated hypertensive</td>
<td>20</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Treated hypertensive</td>
<td>66</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td><strong>History of high cholesterol requiring pills</strong></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>LVH on electrocardiography</td>
<td>11</td>
<td>23</td>
<td>0.77</td>
</tr>
<tr>
<td>Aspirin use ≥80 mg for at least 30 d</td>
<td>59</td>
<td>111</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Baseline statin use</strong></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Inactive</td>
<td>32</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>
| *Based on $\chi^2$ test of association for categorical variables and t test for continuous variables.*
Coronary Heart Disease Risk by Treatment Assignment

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

<table>
<thead>
<tr>
<th></th>
<th>Low Tertile</th>
<th></th>
<th>Middle Tertile</th>
<th></th>
<th>High Tertile</th>
<th></th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n‡</td>
<td>n</td>
<td>Odds Ratio (CI)</td>
<td>n</td>
<td>Odds Ratio (CI)</td>
<td>n</td>
<td>Odds Ratio (CI)</td>
</tr>
<tr>
<td>Total TFPI, ng/mL§</td>
<td>56 (ref)</td>
<td>69</td>
<td>1.11 (0.69–1.79)</td>
<td>69</td>
<td>1.26 (0.77–2.04)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Free TFPI, ng/mL∥</td>
<td>45 (ref)</td>
<td>83</td>
<td>1.57 (0.97–2.53)</td>
<td>75</td>
<td>1.38 (0.84–2.29)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>TFPI activity, %¶</td>
<td>51 (ref)</td>
<td>69</td>
<td>1.24 (0.76–2.01)</td>
<td>77</td>
<td>1.43 (0.88–2.31)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>nAPC-sr (ratio)#</td>
<td>50 (ref)</td>
<td>66</td>
<td>1.23 (0.74–2.04)</td>
<td>79</td>
<td>1.55 (0.94–2.53)</td>
<td>0.004</td>
<td></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, left ventricular hypertrophy 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).

‡N 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.
#Tertiles of nAPC-sr based on controls and correspond to <2.697, 2.697 to <4.988, and ≥4.988.

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 v-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 against clinical CHD. In the single 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

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></th>
<th>EPT</th>
<th></th>
<th>Placebo</th>
<th></th>
<th>P Value for Interaction†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Tertile</td>
<td>Middle Tertile</td>
<td>High Tertile</td>
<td>Low Tertile</td>
<td>Middle Tertile</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>Odds Ratio (CI)</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Total TFPI, ng/mL</td>
<td>37 (ref)</td>
<td>39</td>
<td>1.15 (0.61–2.14)</td>
<td>40</td>
<td>1.05 (0.56–1.97)</td>
</tr>
<tr>
<td>Free TFPI, ng/mL</td>
<td>24 (ref)</td>
<td>50</td>
<td>1.97 (1.04–3.73)</td>
<td>48</td>
<td>1.52 (0.78–2.95)</td>
</tr>
<tr>
<td>TFPI activity, %</td>
<td>27 (ref)</td>
<td>44</td>
<td>1.72 (0.90–3.29)</td>
<td>47</td>
<td>1.76 (0.91–3.40)</td>
</tr>
<tr>
<td>nAPC-sr (ratio)</td>
<td>32 (ref)</td>
<td>36</td>
<td>1.06 (0.54–2.06)</td>
<td>46</td>
<td>1.50 (0.78–2.86)</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, left ventricular hypertrophy 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).
could identify free TFPI levels below the 10th percentile were associated adversely with future CHD in men.24 We did not confirm this observation for free TFPI in this study in women, and indeed we found that TFPI activity below the 10th percentile was associated with reduced risk. Cross-sectional studies of subclinical atherosclerosis and of patients with clinical CHD have in general also shown a positive association with increasing levels of TFPI.19,24,25 These include a retrospective case–control study of acute myocardial infarction in young women, which showed increased TFPI levels and increased TFPI activity in cases compared with controls.19 In this study, we found a positive association of TFPI activity with incident CHD in women. Similarly, we have previously published a positive association of TFPI with incident ischemic stroke in this WHI cohort.17 It is possible that increased TFPI levels or activity in arterial disease reflect endothelial dysfunction and platelet activation are a compensatory mechanism for a procoagulant state or are a reaction to high levels of TF in arterial lesions.21 Paradoxical results have also been observed for activation of the endogenous fibrinolytic system as a marker for future thrombo-occlusive events, where tissue-type plasminogen activator levels were positively rather than inversely associated with CHD and stroke risk.24,29

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. 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.2,30,31 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 |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|
|                                 | Low Tertile (OR (95% CI)) | Middle Tertile (OR (95% CI)) | High Tertile (OR (95% CI)) | P Value for Interaction† |
| Total TFPI, ng/mL‡               | 0.53 (0.17–1.63)          | 1.82 (0.75–4.41)          | 0.89 (0.30–2.58)          | 0.75            |
| Free TFPI, ng/mL§                | 0.94 (0.39–2.31)          | 0.75 (0.34–1.65)          | 3.42 (1.12–10.45)         | 0.11            |
| TFPI activity, %‖                | 1.95 (0.70–5.39)          | 0.86 (0.38–1.95)          | 1.89 (0.37–9.58)          | 0.51            |
| nAPC-sr (ratio)¶                 | 2.14 (0.85–5.38)          | 0.89 (0.36–2.22)          | 0.61 (0.23–1.62)          | 0.08            |

CI 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 ng/mL.
§Tertiles of change in free TFPI were ≥0.2, −3.6 to <0.2, and <−3.6 ng/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.
activity, total, and free TFPI. We did not measure other indica-
tors of anticoagulant activity, such as protein S and antithrom-
bin. We only examined data derived from 1 trial of a particular 
combination estrogen plus progesterin preparation, which limits 
the generalizability of some findings.

We conclude that TFPI activity and acquired APC resist-
ance 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 ther-
apy. 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 manu-
script. All authors have contributed, and all have read and agreed to 
its submission.

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Disclosures

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Dahm has received a personal fee from Pfizer for 2 lectures since 
2012. M. Cushman receives research funding from diaDexus. 
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References

1. Rosouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, 
Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, 
Kotchen JM, Ockene J; Writing Group for the Women’s Health Initiative 
Investigators. Risks and benefits of estrogen plus progesterin in healthy post-

Trevisan M, Black HR, Heckert SR, Detrano R, Strickland OL, Wong ND, 


5. Kim RJ, Becker RC. Association between factor V Leiden, prothromb 
gin G20210A, and methylenetetrahydrofolate reductase C677T muta-
tions and events of the arterial circulatory system: a meta-analysis of 


7. Winckers K, Siegristink B, Duckers C, Maurissen LF, Tans G, Castoldi E, Spronk HM, Ten Cate H, Algra A, Hackeng TM, Rosendaal FR. Increased tissue factor pathway inhibitor activity is associ-

Oberhollenzer F, Mayr A, Gasperi A, Poeke W, Willeit J. Poor response to 
activated protein C as a promoter of advanced atheroscle-

9. Winckers K, ten Cate H, Hackeng TM. The role of tissue factor path-

10. Dahm A, Van Hylckama Vlieg A, Bendz B, Rosendaal F, Beritina RM, 
Sandset PM. Low levels of tissue factor pathway inhibitor (TFPI) increase the 
blood-2002-10-3188.

11. Zakai NA, Lutsey PL, Folsom AR, Heckbert SR, Cushman M. Total tis-
 sue factor pathway inhibitor and venous thrombosis. The Longitudinal 

12. Morange PE, Simon C, Alessi MC, Luc G, Arveiler D, Ferrières J, 
Amouyel P, Evans A, Ducimetiere P, Juhana-Vague I; PRIME Study 
Group. Endothelial cell markers and the risk of coronary heart 


Significance

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

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