Soluble P-Selectin and the Risk of Future Cardiovascular Events
Paul M. Ridker, MD; Julie E. Buring, ScD; Nader Rifai, PhD

Background—P-selectin, a cell-surface adhesion molecule involved in leukocyte rolling and attachment, has been hypothesized to play a role in the initiation of atherosclerosis. However, little clinical data are available evaluating the role of soluble P-selectin in determining vascular risk.

Methods and Results—In a large-scale prospective study of apparently healthy women, we measured baseline plasma concentration of soluble P-selectin among 115 participants who subsequently developed cardiovascular events and among 230 age- and smoking-matched participants who remained free of disease during 3.5 years of follow-up. Overall, mean levels of soluble P-selectin were significantly higher at baseline among women who subsequently experienced cardiovascular events compared with those who did not (83.2 versus 69.3 ng/mL; P = 0.003). The risk of future cardiovascular events increased with increasing quartiles of soluble P-selectin (P = 0.02), such that women in the highest quartile at study entry had an age- and smoking-matched relative risk 2.2 times higher than those in the lowest quartile (95% confidence interval, 1.2 to 4.2; P = 0.01). This effect was independent of traditional risk factors. For each quartile increase in soluble P-selectin, the risk of future cardiovascular events increased 28% (P = 0.03) after additional adjustment for obesity, hypertension, hyperlipidemia, diabetes, and exercise frequency. The highest risks were observed among women with the very highest levels of P-selectin (>137.3 ng/mL, the 95th percentile cut point of the control distribution).

Conclusions—Soluble P-selectin levels are elevated among apparently healthy women at risk for future vascular events.

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Key Words: inflammation • selectins • atherosclerosis • risk factors • cell adhesion molecules • myocardial infarction

Inflammation plays a major role in atherosclerosis,1 and plasma markers of inflammation such as high-sensitivity C-reactive protein may have clinical utility in the detection of atherothrombotic risk.2,3 Among the earliest inflammatory steps leading to atherogenesis is the slowing, tethering, and subsequent attachment of circulating leukocytes to the vascular endothelium, a process mediated partly by the selectin family of cell adhesion molecules.4,5 In particular, P-selectin is an adhesion receptor expressed on activated endothelial cells that mediates initial leukocyte “rolling.”6 Evidence supporting a role for P-selectin in atherogenesis includes the observation that P-selectin is preferentially expressed in the endothelium overlying atherosclerotic plaques,7 that P-selectin-deficient mice develop reduced fatty streaks,8–10 and that anti-P-selectin antibodies inhibit monocyte rolling and attachment across carotid endothelium.11 In addition, atherogenic factors, including oxidized LDL,12,13 induce P-selectin expression.

Levels of soluble P-selectin can be measured in plasma and derive from both platelet and endothelial sources. However, clinical data relating soluble P-selectin to atherogenesis are sparse and limited to cross-sectional or retrospective studies describing elevated levels of soluble P-selectin among hypertensive,14 hyperlipidemic,15 and atherosclerotic patients.16–19 To date, no prospective data are available describing the role of soluble P-selectin among apparently healthy individuals being followed for incident myocardial infarction or stroke. Thus, whether plasma levels of soluble P-selectin are a marker for a high risk of future vascular events is uncertain.

Methods
We evaluated the role of soluble P-selectin as a potential marker for cardiovascular risk among initially healthy participants in the Women’s Health Study, an ongoing trial of aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer.20 Details of the Women’s Health Study have been provided elsewhere; in brief, 28,263 women free of reported cardiovascular disease provided baseline plasma samples, which were collected in EDTA and stored in liquid nitrogen until the time of analysis. All study participants were then prospectively followed over an average period of 3.5 years for the occurrence of first-ever cardiovascular events (myocardial
Results

Table 1 shows the baseline clinical characteristics of the study participants. As expected, initially healthy women who subsequently developed cardiovascular events (cases) were more likely at baseline to have a history of hypertension, obesity, diabetes, or hyperlipidemia when compared with women who remained free of reported disease (controls). Because of matching, age and smoking status were similar in the 2 study groups.

The distribution of soluble P-selectin levels observed in our study is consistent with that expected in studies of unselected healthy individuals (R&D Systems; Figure 1). However, as shown in Table 1 and Figure 2, both mean (83.2 versus 69.3 ng/mL; \( P = 0.003 \)) and median (68.6 versus 62.7 ng/mL; \( P = 0.02 \)) levels of soluble P-selectin were significantly higher at baseline among study participants who subsequently developed a first-ever cardiovascular event (cases) than in those who did not (controls).

In these data, increasing levels of soluble P-selectin at baseline were associated with increased risks of future cardiovascualr events over the 3.5-year follow-up period. As shown in Table 2, the age- and smoking-matched relative risk of future cardiovascular events increased 27% (95% confidence interval, 4% to 56%) for each quartile increase in baseline level of soluble P-selectin (\( P = 0.02 \)). These effects persisted after controlling for other baseline clinical characteristics, such that the adjusted relative risks of future cardiovascular events for women with the lowest (referent) to...
highest baseline quartiles of soluble P-selectin were 1.0, 1.3, 1.3, and 2.2 (P-trend=0.03) after additional control for body mass index (kg/m²), hypertension, hyperlipidemia, family history of coronary disease, diabetes, and exercise frequency (Table 2).

Cigarette consumption was associated with elevated levels of soluble P-selectin, such that nonsmokers had significantly lower levels of P-selectin (67.9 ng/mL) than did former (76.8 ng/mL) or current smokers (80.6 ng/mL; P=0.01; Figure 3). However, because our study design matched cases and controls on smoking status, the potential for confounding on this basis is minimal. To assess for effect modification, analyses limited to nonsmokers were performed; they had almost identical overall results.

To evaluate potential threshold effects, we repeated these analyses using a series of prespecified cut points for soluble P-selectin. As shown in Table 3, the relative risks associated with baseline soluble P-selectin concentrations exceeding the 50th, 75th, 90th, and 95th percentiles of the control distribution were 1.4 (P=0.1), 1.9 (P=0.01), 2.0 (P=0.03), and 2.3 (P=0.04), respectively. Thus, much of the excess risk associated with baseline soluble P-selectin was due to an excess of high values among the case subjects. Similar effects were observed in analyses stratified by the presence or absence of hypertension, obesity, diabetes, and hyperlipidemia.

In prior work from this cohort, the inflammatory markers soluble intercellular adhesion molecule 1 (sICAM-1), high-sensitivity C-reactive protein, and interleukin-6 were also predictive of future cardiovascular events.3 In these data,

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**TABLE 2.** Crude and Adjusted Relative Risks of Future Cardiovascular Events According to Baseline Plasma Concentration of Soluble P-Selectin

<table>
<thead>
<tr>
<th>Quartile of Soluble P-selectin</th>
<th>1 (&lt;45.5 ng/mL)</th>
<th>2 (45.5–62.5 ng/mL)</th>
<th>3 (62.5–81.6 ng/mL)</th>
<th>4 (&gt;81.6 ng/mL)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude analysis*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk</td>
<td>1.0</td>
<td>1.3</td>
<td>1.2</td>
<td>2.2</td>
<td>0.02</td>
</tr>
<tr>
<td>95% CI</td>
<td>—</td>
<td>0.7–2.6</td>
<td>0.6–2.4</td>
<td>1.2–4.2</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>—</td>
<td>0.4</td>
<td>0.6</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Adjusted analysis†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk</td>
<td>1.0</td>
<td>1.3</td>
<td>1.3</td>
<td>2.2</td>
<td>0.03</td>
</tr>
<tr>
<td>95% CI</td>
<td>—</td>
<td>0.6–2.8</td>
<td>0.5–2.7</td>
<td>1.1–4.6</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>—</td>
<td>0.5</td>
<td>0.7</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

*Matched on smoking status and age and controlled for randomized treatment assignment.
†Matched on smoking status and age and controlled for randomized treatment assignment, body mass index (kg/m²), family history of premature coronary artery disease, history of hypercholesterolemia, history of hypertension, diabetes, and exercise frequency.
were obtained several years before the onset of first-ever vascular occlusion. By contrast, in our study, plasma samples obtained from P-selectin–deficient mice, it has been hypothesized that P-selectin may play an important role in the initiation of atherosclerosis.

In this prospective epidemiological evaluation of apparently healthy women, elevated baseline levels of soluble P-selectin were associated with increasing risks of future myocardial infarction, stroke, coronary revascularization, and cardiovascular death. This association was independent of age and smoking status and persisted after additional control for several lipid and nonlipid cardiovascular risk factors. In these data, the strongest correlates of P-selectin were smoking status and sICAM-1. However, the effects of P-selectin on risk were only minimally attenuated in analyses further controlling for these factors and for other traditional markers of cardiovascular risk. These data thus provide strong clinical support for the hypothesis that the very early inflammatory processes of leukocyte rolling, tethering, attachment, and transmigration across the vascular endothelium are critical initiating events in atherothrombosis. These data also provide a human extension of basic work demonstrating that P-selectin–deficient mice have delayed fatty streak formation and that anti–P-selectin antibodies inhibit cell adhesion in early atherogenesis, at least in apoE-deficient mice. Therefore, sex-specific findings for soluble P-selectin are possible; thus, care must be taken when generalizing these data to men. Finally, because soluble P-selectin derives from both platelets and endothelial cells, the present measurements cannot distinguish between these 2 potential sources of circulating soluble P-selectin. Furthermore, the plasma levels of soluble P-selectin could increase due to increased expression on the platelet or endothelial surface or be due to excessive shedding by as-yet poorly understood mechanisms.

In summary, the current report, together with prior data for other adhesion molecules, provides strong epidemiological support for the hypothesis that the very early inflammatory processes of leukocyte rolling, tethering, attachment, and transmigration across the vascular endothelium are critical initiating events in atherothrombosis. These data also provide a human extension of basic work demonstrating that P-selectin–deficient mice have delayed fatty streak formation and that anti–P-selectin antibodies inhibit cell adhesion in early atherogenesis, at least in apoE-deficient mice. Thus, accumulating data support the potential for adhesion molecules to serve as novel targets for the treatment and prevention of cardiovascular disorders.

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### Table 3. Age- and Smoking-Adjusted Relative Risks of Future Cardiovascular Events According to Baseline Plasma Concentration of Soluble P-Selectin Above the 50th, 75th, 90th, and 95th Percentile Cut Points of the Control Distribution

<table>
<thead>
<tr>
<th>Cut Point, %</th>
<th>Soluble P-Selectin, ng/mL</th>
<th>Controls, %</th>
<th>Cases, %</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>50th</td>
<td>&gt;62.8</td>
<td>50.0</td>
<td>58.3</td>
<td>1.4</td>
<td>0.9–2.2</td>
<td>0.1</td>
</tr>
<tr>
<td>75th</td>
<td>&gt;81.6</td>
<td>25.0</td>
<td>38.3</td>
<td>1.9</td>
<td>1.2–3.0</td>
<td>0.01</td>
</tr>
<tr>
<td>90th</td>
<td>&gt;112.2</td>
<td>10.0</td>
<td>18.3</td>
<td>2.0</td>
<td>1.1–3.8</td>
<td>0.03</td>
</tr>
<tr>
<td>95th</td>
<td>&gt;137.3</td>
<td>5.0</td>
<td>11.3</td>
<td>2.3</td>
<td>1.1–5.2</td>
<td>0.03</td>
</tr>
</tbody>
</table>

RR indicates relative risk; CI, confidence interval.
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References
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