High Concentrations of Soluble P-Selectin Are Associated with Risk of Venous Thromboembolism and the P-Selectin Thr715 Variant

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Background: The cell adhesion molecule P-selectin has an important role in the pathophysiology of thrombosis. The effect on venous thromboembolism (VTE) of increased circulating concentrations of soluble P-selectin (sP-selectin) and their association with the P-selectin variant Thr715Pro is still uncertain.

Methods: This study was a case-control study of 116 patients with confirmed recurrent VTE and at least 1 event of unprovoked deep venous thrombosis or pulmonary embolism, and 129 age- and sex-matched healthy individuals. We measured sP-selectin by ELISA and P-selectin gene (SELP) variation by genotyping and sampled blood after a mean interval of 2.55 years after the most recent VTE event.

Results: The mean (SD) sP-selectin concentration was higher in patients than in controls: 47.3 (15.0) μg/L vs 36.8 (11.0) μg/L, P < 0.001. The unadjusted odds ratio (OR) for sP-selectin > 55.1 μg/L, representing the 95th percentile for controls, was 8.5 (95% CI, 3.7–23.3; P < 0.001) and increased after adjustment for factor V Leiden, the prothrombin G20210A variant, increased factor VIII, and hyperhomocysteinemia (OR, 10.6; 95% CI, 4.1–31.2; P < 0.001). Pro715 carriers were more prevalent among controls than patients (21.7% vs 14.7%). sP-selectin concentrations were lower in this subgroup than in noncarriers: 31.3 (7.9) μg/L vs 44.1 (14.1) μg/L; P < 0.001).

Conclusions: Increased sP-selectin concentrations are associated with VTE and genotype status. sP-selectin concentrations are lower in individuals carrying the P-selectin Pro715 variant than in those without this variant.

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In the past decade, many studies have investigated the role of the cell adhesion molecule P-selectin in blood coagulation and thrombosis. P-selectin [also known as granule membrane protein 140 (GMP-140), platelet activation-dependent granule-external membrane protein (PADGEM), and CD62] is a 140-kDa transmembrane glycoprotein (1, 2) found in the α-granules of platelets (3) and the Weibel–Palade bodies of endothelial cells (4). During cell activation P-selectin is translocated to the cell surface, where part of it is released into the plasma in soluble form (sP-selectin)5 (5, 6). P-selectin is responsible for leukocyte rolling and leukocyte adhesion to stimulated endothelial cells and platelets (7). P-selectin may also have an important role in the association of inflammation with thrombosis.

Interaction between P-selectin and its main counterreceptor on leukocytes, P-selectin glycoprotein ligand 1 (PSGL-1), leads to neutrophil and macrophage recruit-
ment and, along with other mediators, induces leukocytes to generate procoagulant microparticles (8). Furthermore, P-selectin triggers increased expression of tissue factor on monocytes (9) and mediates the transfer of tissue factor to platelets (10). Tissue factor, the main initiator of coagulation in vivo, causes activation of the extrinsic pathway of the coagulation cascade. A recent study revealed that P-selectin induces phosphatidylserine exposure and increases surface-dependent thrombin generation on monocytes (11). This property may represent an additional prothrombotic mechanism.

Possible roles for P-selectin in the pathogenesis of thrombosis were explored in several in vivo studies. Myers et al. (12, 13) demonstrated significantly lower thrombus weights in genetically modified animals that were deficient in P- and E-selectin compared with wild-type control animals and showed that high circulating concentrations of P-selectin caused larger thrombi. Interestingly, inhibition of the interaction between P-selectin and PSGL-1 was associated with a strong antithrombotic effect, reduced the extent of an experimentally induced venous thrombosis, and facilitated thrombus lysis (14-17).

High sP-selectin concentrations have been observed in ischemic heart disease (18), atherosclerosis (19), and acute ischemic stroke (20). Patients with venous thromboembolism (VTE) have demonstrated increased sP-selectin concentrations immediately after an acute event (21, 22) and at several months after VTE (23).

A number of P-selectin gene (SELP)(6) variants that affect the protein sequence have been described (24). One such variant, a single nucleotide polymorphism that produces the amino acid substitution Thr715Pro, has consistently been associated with lower sP-selectin concentrations in plasma (25-27), but the data on the effect of this variant on myocardial infarction and stroke are conflicting (25-29).

The data for an association between sP-selectin concentration and VTE have been limited, and no studies on the role of the Thr715Pro P-selectin variant in VTE are available. We investigated sP-selectin and the Thr715Pro variant in a high-risk population of patients with a history of confirmed recurrent VTE.

**Materials and Methods**

**Participants**

One hundred forty-six consecutive patients with a history of confirmed recurrent VTE and who had experienced at least 1 event of unprovoked deep venous thrombosis (DVT) or pulmonary embolism (PE) visited our department between January 2003 and December 2004 for an assessment of thrombosis risk factors. In 2005, we invited these patients to participate in this study and recruited 116 (79%) of the patients between January 2005 and February 2006.

Unprovoked VTE was defined as thrombosis without a triggering event (i.e., surgery, trauma causing immobilization, pregnancy, delivery, or malignancy). Events that occurred while the patient was taking oral contraceptives or undergoing hormone-replacement therapy were also considered as unprovoked because such treatments had continued for a long time and were probably not the direct trigger for VTE. VTE diagnosis was confirmed in all cases and events with at least 1 of the following methods: duplex ultrasonography or venography for DVT diagnosis, and angiography, spiral computed tomography, or combined ventilation/perfusion scan for PE diagnosis. Only patients with an interval of >3 months between the 1st and the recurrent thrombotic events were eligible. Exclusion criteria were thromboembolic events in the 3 months before enrollment and underlying disorders such as malignancy, overt infection, and autoimmune diseases.

The Ethics Committee of the Medical University Vienna approved the study. We informed every patient of the details of the study in individual interviews, and all patients provided written informed consent. We obtained patients’ medical histories from the responses to a standardized questionnaire and from medical records. Postthrombotic syndrome was diagnosed when a patient had continuous edema of the leg or crural ulcer after DVT. We invited all patients for a follow-up investigation after 3 months. We obtained blood samples for a 2nd sP-selectin measurement from 102 (88%) of the patients.

As controls, we chose 129 unrelated healthy individuals who were from the same geographic region and ethnic background as the patients and who had no medical history of VTE or arterial thrombosis. We interviewed the control group regarding any history of arterial or venous thrombosis or PE and ruled out a previous thrombotic event when the medical history was undoubtedly negative for such an event. We obtained written informed consent from all participating control individuals, all of whom had to be unrelated to the patients. These individuals were spouses or acquaintances of patients, hospital staff, or their friends or relatives. Control group individuals were not related. The control group was matched to the patient group by sex and age in a whole-group—not a pair-wise—manner.

**Blood Sampling and Laboratory Analysis**

At the day of study entry and after the individuals had fasted overnight, we drew venous blood samples byatraumatic and sterile antecubital venipuncture into plasma vacuum tubes (Vacuette®; Greiner Bio-One) containing 1/10 volume sodium citrate stock solution at 0.129 mmol/L. We obtained platelet-poor plasma by centrifuging citrated blood (ROTANTA/TRC®; Hettich) at 1500g for 15 min and obtained platelet-free plasma with a 2nd centrifugation step (Eppendorf) at 13 400g for 2 min.

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We centrifuged each sample within 1 h of blood sampling and froze each sample within 1 h of centrifugation. Plasma aliquots were stored at −80 °C for a mean (SD) of 6.5 (3.1) months until they were assayed in series. Patient and control samples were treated the same. We blinded samples by coding them before laboratory analyses. We measured sP-selectin by means of a highly sensitive sandwich ELISA technique and a commercially available test reagent set (Human sP-Selectin/CD62P ELISA reagent set; R&D Systems) according to the manufacturer’s instructions. We carried out duplicate measurements with 100-μL aliquots of plasma diluted 20-fold into sample diluent included in the ELISA reagent set and measured the absorbance at 450 nm with a microplate reader (MR7000; Dynex Technologies/Dynatech Laboratories). We read the sP-selectin concentration from a calibration curve generated with Revelation™ software (version G 3.2) from Dynex Technologies.

We routinely evaluated risk factors for VTE (protein C, protein S, and antithrombin deficiency; lupus anticoagulant; homocysteine concentration; factor V Leiden; prothrombin G20210A variation) in every patient and control individual as previously described (30). Factor VIII activity (upper limit of the reference interval, 230%) and high-sensitivity C-reactive protein (hs-CRP) were measured as described elsewhere (31).

PCR ANALYSIS OF THE P-SELECTIN THR715PRO VARIANT
We isolated DNA from citrated blood with the MagNA Pure DNA-isolation system (Roche Diagnostics) and used the principle of mutagenically separated PCR as previously described (32) to detect the Thr715Pro variant.

STUDY DESIGN AND STATISTICAL ANALYSIS
The study was designed as a case-control study. Our calculations before patient enrollment indicated that a sample size of 110 patients and 110 control individuals would have 96% power to detect an effect of 0.5 SD (assuming comparable variances for the 2 groups) with a Student t-test and a 2-sided significance level of 0.05.

To describe the imprecision of repeated sP-selectin measurements, we measured the sP-selectin concentration twice for each patient and calculated the mean difference between the 1st and 2nd sP-selectin measurements. We used the mean of the 2 sP-selectin values for all further analyses.

We compared continuous variables with the unpaired Student t-test and evaluated variables with a nongaussian distribution with the unpaired Mann-Whitney U-test. We used the χ2 and the Fisher exact tests to evaluate differences in dichotomous variables and described the correlation between continuous variables with the Pearson correlation coefficient. Variables with a skewed distribution were log-transformed.

We used univariate and multiple logistic regression models (33) to describe the unadjusted and adjusted effects on VTE of sP-selectin (≥55.1 μg/L vs ≤55.1 μg/L), factor V Leiden (heterozygous or homozygous vs wild type), prothrombin G20210A variation (heterozygous or homozygous vs wild type), factor VIII activity (>230% vs ≤230%), hyperhomocysteinemia (yes vs no), and the SELP Pro715 allele (heterozygous or homozygous vs wild type). The 55.1-μg/L cutoff for sP-selectin represents the 95th percentile of the sP-selectin distribution in our controls. We used odds ratio (OR) estimates and the 95% CI to describe the strength of each prognostic factor.

To compare the importance of sP-selectin with respect to other established thrombosis risk factors, we calculated sensitivity and specificity for all of the risk factors considered in the regression model. We used ROC curves as estimated in the univariate and multiple logistic regression models to describe the discriminatory importance of sP-selectin. We used these curves, which show the sensitivities and specificities produced by all possible cutoff values, to distinguish patients and controls.

All P values are the results of 2-sided tests, and values <0.05 are considered statistically significant.

Results
Table 1 summarizes the demographic characteristics of the patients and control individuals, laboratory variables, and data on established risk factors for VTE. Table 1 also lists the triggering events and the sites of thrombotic events for the 1st and 2nd VTE episodes. Two VTE episodes occurred in 87 patients (75%), and 29 cases (25%) had ≥3 episodes. Seven patients also had a history of arterial thrombosis (2 of peripheral artery disease, 4 of myocardial infarction, and 1 of stroke). At the time of study inclusion, 78 patients (67%) were receiving oral anticoagulant (OAC) therapy. We documented statin therapy in 8 patients and 4 control individuals, antihypertension therapy in 27 patients and 19 controls, and antidiabetes therapy in 5 patients and 2 controls. The median interval between the last VTE event and study entry was 2.55 years [interquartile range (IQR), 1.58–5.36 years] and that between the 1st VTE episode and study entry was 11.45 years (IQR, 6.54–20.23 years).

Basal sP-selectin concentrations were significantly higher in patients [mean (SD), 47.3 (15.0) μg/L] than in control individuals [36.8 (11.0) μg/L; P < 0.001; Fig. 1A]. Thirty-four patients (29.3%) had sP-selectin concentrations greater than the 55.1-μg/L cutoff. We measured sP-selectin again 3 months after study entry in 102 of the 116 patients. sP-selectin concentrations at study entry [46.3 (15.8) μg/L] and after 3 months [47.8 (15.4) μg/L] were not significantly different. The mean difference between the 2 sP-selectin values was 2.2 (10.2) μg/L. The 1st and 2nd sP-selectin measurements were markedly correlated (r = 0.8). We detected no differences in sP-selectin concentration between patients receiving OAC therapy (n = 78) and those without OAC therapy (n = 38) [47.1 (15.1) μg/L vs 47.7 (15.0) μg/L; P = 0.83]. We also
noted no significant differences between the patients with isolated DVT (1st and recurrent episodes; n = 68) and the patients with PE (1st or recurrent episode, n = 48), which included patients with both DVT and PE. The sP-selectin concentrations in these groups were 48.8 (16.1) µg/L and 45.1 (13.2) µg/L, respectively (P = 0.19).

We evaluated the correlation coefficients between some key variables of the patient group and compared them with the corresponding coefficients in the control group. Because the results were broadly similar, we present the correlation coefficients for the entire study population (Table 2: partial correlation coefficients adjusted for case/control status). We found no significant correlation between sP-selectin concentration and platelet count, leukocyte count, hs-CRP concentration, body mass index (BMI), fibrinogen concentration, factor VIII activity, or age [see Table 1 (Complete Table 2) in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol53/issue7]. Likewise, we found no correlation between sP-selectin concentration and the time from the 1st VTE event to study entry (r = 0.12), the time from the last VTE event to study entry (r = 0.03), postthrombotic syndrome (r = 0.06), or current smoking status (r = 0.07).
The SELP Pro715 allele was more prevalent in the control group (21.7%) than in the patients (14.7%); however, the difference did not reach statistical significance ($P = 0.19$). All carriers were heterozygous except for 1 patient who was homozygous for the SELP Pro715 allele. The genotype distribution for the 2 SELP alleles (i.e., wild type and Thr715Pro) did not deviate significantly from the Hardy–Weinberg equilibrium in the entire study population ($P = 0.38$), the patient group ($P = 0.70$), or the control group ($P = 0.17$). Carriers of the SELP Pro715 allele had sP-selectin concentrations that were significantly lower than those of noncarriers (Table 3; Fig. 1B). Interestingly, the difference in sP-selectin concentration between the patient and control groups for carriers of the Pro715 allele was not statistically significant.

Univariate and multivariable ORs for VTE with respect to sP-selectin concentration and established risk factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Leukocyte count</th>
<th>hs-CRP concentration</th>
<th>Fibrinogen concentration</th>
<th>BMI</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count</td>
<td>0.33</td>
<td>0.29</td>
<td>0.22</td>
<td>-0.06</td>
<td></td>
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<tr>
<td>hs-CRP concentration</td>
<td>0.63</td>
<td>0.39</td>
<td>0.30</td>
<td>0.19</td>
<td></td>
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<tr>
<td>Fibrinogen concentration</td>
<td>0.39</td>
<td>0.30</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.06</td>
<td>0.19</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.30</td>
<td>0.10</td>
<td></td>
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</table>

* Correlation coefficients between 0.3 and 0.6 (moderate correlation) and >0.6 (strong correlation) are shown.

* $P$ values for $|r| \geq 0.20$ (in absolute value) are strongly statistically significant.

* For log-transformed data.
are presented in Table 4. The unadjusted OR for increased sP-selectin concentration was significantly associated with VTE (OR, 8.5; 95% CI, 3.7–23.3; \( P < 0.001 \)). Multiple logistic regression analyses then tested the independent association of increased sP-selectin concentration with VTE. After adjustment for factor V Leiden, prothrombin G20210A variation, increased factor VIII concentration, and hyperhomocysteinemia, the association of increased sP-selectin concentration with VTE increased in the multiple regression model (OR, 10.6; 95% CI, 4.1–31.2; \( P < 0.001 \)). The ROC curves for sP-selectin (univariate model; Fig. 2A), the multiple regression model without sP-selectin (Fig. 2B), and the multiple regression model including sP-selectin (Fig. 2C) indicate a considerable improvement when sP-selectin is included in the multiple regression model. This result is in accord with the significant influence of sP-selectin on thrombosis risk revealed in the OR estimates.

Additional adjustments for the SELP Pro715 allele, BMI, hs-CRP concentration, and fibrinogen concentration in the multiple regression model still revealed a very strong association between sP-selectin concentration and VTE (OR, 10.4; 95% CI, 3.8–32.3; \( P < 0.001 \)). Considering sP-selectin as a continuous independent variable likewise revealed statistically significant unadjusted and adjusted ORs of sP-selectin (per 10-\( \mu \)g/L increase in concentration) for VTE: 1.9 (95% CI, 1.5–2.4; \( P < 0.001 \)) and 2.0 (95% CI, 1.5–2.6; \( P < 0.001 \)), respectively.

The OR of the SELP Pro715 allele for VTE was not statistically significant, either in a univariate analysis or in a multivariate analysis adjusted for factor V Leiden, the prothrombin G20210A variant, increased factor VIII concentration, hyperhomocysteinemia, and BMI: 0.6 (95% CI, 0.3–1.2; \( P = 0.16 \)) and 1.2 (95% CI, 0.5–2.6; \( P = 0.64 \)), respectively. We also found no statistically significant interaction (\( P = 0.20 \)) in the logistic regression analysis between sP-selectin and the SELP Pro715 allele with respect to the effect on VTE.

**Discussion**

We have found sP-selectin concentrations in patients with a history of recurrent VTE to be significantly higher than those of control individuals. The unadjusted OR of an increased sP-selectin concentration for VTE was significantly increased and remained high after adjustment for established risk factors. In these patients, an increased sP-selectin concentration had a role similar to or even more important than an increased factor VIII concentration, hyperhomocysteinemia, and the factor V Leiden mutation.

Only a few publications have considered the relationship of sP-selectin to VTE. In the Leiden thrombophilia study, measurements of sP-selectin in a subgroup of 89 patients revealed significantly higher blood concentrations in patients ≥6 months after DVT than in control individuals (23). Other studies have also investigated sP-selectin as a marker for predicting acute thrombosis, but the results have been inconsistent. Whereas one study showed no increase in sP-selectin concentration in patients with acute VTE compared with patients with sus-

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<tr>
<th>Table 3. Distribution of the SELP Pro715 allele and sP-selectin concentrations in carriers and noncarriers among patients, controls, and the entire study population.</th>
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<tbody>
<tr>
<td>Patients (n = 116)</td>
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<td></td>
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<tr>
<td>Controls (n = 129)</td>
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<tr>
<td>Patients + controls (n = 245)</td>
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</table>

\( ^a \) All individuals heterozygous except for 1 homozygous patient.

\( ^b \) Data are presented as the mean (SD).

<table>
<thead>
<tr>
<th>Table 4. Univariate and multivariable ORs and 95% CIs in absolute values for VTE (dependent variable) for increased sP-selectin concentration and established thrombosis risk factors (all independent variables).</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Increased sP-selectin concentration</td>
</tr>
<tr>
<td>Factor V Leiden (heterozygous or homozygous)</td>
</tr>
<tr>
<td>Prothrombin G20210A variation (heterozygous or homozygous)</td>
</tr>
<tr>
<td>Increased factor VIII concentration</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
</tr>
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</table>

\( ^a \) Adjusted for all listed parameters.

\( ^b \) Estimated probability: \( \text{prob}(\text{VTE} = 1) = 1 / [1 + \exp(1.4 - 2.4 \times \text{sP-selectin} - 1.8 \times \text{Factor V} - 1.9 \times \text{Factor II} - 1.9 \times \text{Factor VIII} - 2.4 \times \text{hyperhomocysteinemia})] \). All risk factors are coded as 0 = absent or not elevated, 1 = present or elevated.
pected but unverified thrombosis (34), a more recent study identified increased sP-selectin concentration to be of predictive value in confirming acute DVT (21). We can exclude a direct effect of an acute thrombotic event in our study, because we enrolled our patients at least 3 months after the acute episode. The median interval between the most recent VTE event and sP-selectin measurement was 2.55 years. In addition, the median values for the 1st sP-selectin measurements and the 2nd set of measurements 3 months later were almost identical for the 102 patients. Presumably, an increased sP-selectin concentration is not due to a previous thrombotic event, and we suppose that sP-selectin concentration is not related to a current VTE episode. sP-selectin concentration was not sufficiently correlated with other established VTE risk factors (such as increased factor VIII concentration, hyperhomocysteinemia, or inflammation markers such as fibrinogen concentration, leukocyte count, or hs-CRP) to explain the association of VTE with sP-selectin. Furthermore, sP-selectin concentration did not correlate with

Fig. 2. ROC curves for the probability of VTE as estimated by use of (A) sP-selectin in a univariate model, (B) the multiple logistic regression model without sP-selectin, and (C) the multiple regression model including sP-selectin.
the platelet count or BMI. Previous reports have described a weak effect of smoking on sP-selectin concentration (23, 35); however, we could not confirm this finding. These data suggest that the baseline sP-selectin concentration is independently related to an individual’s propensity to develop VTE.

Several studies have demonstrated the prothrombotic effect of P-selectin, as we have outlined in the Introduction (12, 13). P-selectin–deficient mice were reported to exhibit a prolonged bleeding time and defects in hemostasis in a local Shwartzman reaction (36). Injection of P-selectin immunoglobulins improved hemostasis in a mouse model of hemophilia A with a bleeding diathesis (37).

Inhibition of P-selectin decreased thrombosis risk without adverse anticoagulation effects (17) and could therefore represent a new target for therapeutic intervention in patients with VTE. One consequence is the inhibition of the interaction between P-selectin and its receptor, which occurs on different cell types, including platelets and leukocytes. Inhibiting the interaction between P-selectin and PSGL-1 with P-selectin antagonists (recombinant soluble PSGL-immunoglobulin), intravenously administered soluble ligands, or an orally administered nonprotein inhibitor (PSI-697) markedly attenuated the prothrombotic effect in a mouse model (13–17). Statin medication has recently been reported to reduce sP-selectin concentrations significantly (38–40), and sP-selectin concentration was inversely correlated with the progression of coronary heart disease (38). Oral anticoagulation therapy with vitamin K antagonists does not seem to influence sP-selectin concentration, because we found no differences in sP-selectin concentration in our study between patients who underwent OAC therapy and those who did not receive such treatment.

We observed a higher proportion of carriers of the SELP Pro715 allele among the control individuals than among patients; however, the difference was not statistically significant. Our results suggest the possibility that other alleles have a major influence on sP-selectin concentration. A comparison of the patients and control individuals revealed a major difference in sP-selectin concentrations, even when we compared individuals without the SELP Pro715 allele (Fig. 1B). Carriers of the SELP Pro715 allele had significantly lower sP-selectin concentrations (Table 3), a finding that is concordant with every study that has investigated the association of sP-selectin concentration with the SELP Thr715Pro allele (25–27). We assume that the ELISA used in our study is equally sensitive to both variants (Thr715 and Pro715). We did not specifically evaluate this assumption, however, so we cannot completely exclude a difference in sensitivity between the 2 variants. Three different case-control studies of patients with coronary heart disease found the Pro715 allele to be associated with decreased risk, suggesting a protective effect of this variant (24, 25, 29); however, the prospective observational Atherosclerosis Risk in Communities study did not find the Pro715 allele to be predictive of future coronary events or ischemic stroke, although the investigators did identify a clear association with sP-selectin concentration (26).

The limitations of our study are the relatively small number of study participants and the retrospective case-control design; however, we note that the frequency of established thrombosis risk factors in the patients and control individuals was in the expected range and that the effect of sP-selectin concentration on thrombosis risk was very strong. We cannot completely exclude the possibility that increased sP-selectin concentrations were due to previous thrombotic events; however, the fact that neither the period between the 1st and the most recent event nor the presence of symptoms of a postthrombotic syndrome was associated with sP-selectin concentration is an argument against this possibility.

In conclusion, our findings are compatible with the following hypothesis: (a) an increased sP-selectin concentration is a fairly stable characteristic that induces a susceptibility to VTE; (b) this susceptibility may be independent of other biochemical risk markers; and (c) the Pro715 allele may be protective by providing a defense against increases in sP-selectin concentration that are commonly seen in Thr715 homozygotes.

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