Smoking and the Platelet Fibrinogen Receptor Glycoprotein IIb/IIIA PlA1/A2 Polymorphism Interact in the Risk of Lacunar Stroke and Midterm Survival

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Background and Purpose—Smoking, increased fibrinogen levels, and platelet activation are related to the risk of ischemic stroke. The platelet fibrinogen receptor glycoprotein (Gp) IIb/IIia PlA1/A2 polymorphism affects the binding of platelets to fibrinogen and is suggested to interact with smoking.

Methods—We explored the association of smoking and the PlA1/A2 polymorphism with ischemic stroke and survival in the Stroke Aging Memory cohort, comprising 486 consecutive patients (55 to 85 years old) who were analyzed 3 months after an ischemic stroke and followed up for 15 months. Stroke subtype determined by magnetic resonance imaging and GpIIb/IIa PlA1/A2 genotype data were available for 272 patients.

Results—In multivariate analysis, smoking was the only factor related to the risk of lacunar infarcts (odds ratio [OR] = 1.87, 95% CI = 1.05 to 3.31; P = 0.033), and it was also a predictor of death (n = 24, 8.8%) at 15 months (OR = 5.13, 95% CI = 1.61 to 16.36; P = 0.006), along with age (OR = 1.10, 95% CI = 1.01 to 1.19; P = 0.008). The GpIIb/IIa PlA1/A2 polymorphism alone showed no association with stroke subtype or survival. However, there was a smoking-by-genotype association with the risk of lacunar infarcts (OR = 2.10, 95% CI = 0.90 to 4.89; P = 0.087) and with survival (OR = 2.78, 95% CI = 0.89 to 8.61; P = 0.077). Among younger (55 to 69 years) stroke patients, smokers carrying the PlA2 allele were at a higher risk (OR = 5.81, 95% CI = 1.26 to 26.80; P = 0.024) risk of lacunar infarcts than noncarrier smokers (OR = 3.12, 95% CI = 1.06 to 9.24; P = 0.039). The effect of PlA2 and smoking combined on survival was also stronger (OR = 8.86, 95% CI = 1.68 to 46.55; P = 0.010) than the effect of smoking alone (OR = 5.06, 95% CI = 1.20 to 21.35; P = 0.027).

Conclusions—Our results indicate that prothrombotic genetic factors may interact with smoking by modifying the stroke phenotype and affecting midterm survival. (Stroke. 2007;38:50-55.)

Key Words: polymorphisms • smoking • stroke • survival

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Classic risk factors for stroke include smoking, heart failure, atrial fibrillation (AF), advanced age, dyslipidemia, hypertension, and diabetes.1–3 A dose-response relation between smoking and the risk of stroke was discovered in an occupational cohort.4 The role of genetic risk factors in ischemic stroke is unclear, because the link between proposed candidate gene polymorphisms and the development of stroke may be confounded by modifiable risk factors, such as smoking.

Cigarette smoking has been found to cause a transient increase in serum fibrinogen levels,5–6 and smoking has been demonstrated to constitute an independent predictor of poststroke survival.11,12 Previously, we have shown that carriers of the A allele of the fibrinogen −455GA polymorphism are predisposed to the development of multiple lacunar infarcts (LAs).13 This polymorphism has been shown to be functional and associated with serum fibrinogen levels.6 The available data indicate that smoking, fibrinogen, and genetic factors may interact with platelet aggregation and clot formation, which are crucial in the pathophysiology of atherothrombotic stroke.

Clot formation and subsequent thrombosis require the binding of fibrinogen and von Willebrand factor to platelet glycoprotein (Gp) IIb/IIa, a membrane integrin receptor.14 The PlA1/A2 polymorphism of GpIIb/IIa is characterized by a single point mutation in exon 2 of the GpIIa gene, leading to
the substitution of leucine (PlA1) for proline (PlA2), which in turn causes a change in the 3-dimensional configuration of the receptor.14 The presence of 1 or 2 PlA2 alleles is associated with increased binding affinity to fibrinogen as well as with platelet aggregate response to epinephrine, ADP, and collagen in vitro,15 and it has been implicated in the pathogenesis of acute coronary syndromes, especially in elderly middle age.16 It has also been suggested to be involved in the aspirin resistance syndrome in patients with acute coronary syndromes.16 The GpIIb/IIIa PlA1/A2 polymorphism has been shown to be associated with atherothrombotic stroke in young patients11 and in young white women in a rather small and limited study.17 In some studies, no association with ischemic stroke was detected.18,19 In patients with stable angina pectoris, however, it has been reported that only smokers with the PlA2 allele are at an increased risk of subsequent cardiac events.20

We hypothesized that smoking and genetic polymorphisms of the platelet GpIIb/IIIa fibrinogen receptor might predispose to ischemic stroke and thus modify the stroke phenotype and survival of patients who experience an ischemic stroke.

Subjects and Methods

Patients

The Stroke Aging Memory cohort13,21 comprises 486 consecutive patients 55 to 85 years of age who were recruited to the study 3 months after experiencing an ischemic stroke. Data on survival were collected during a 15-month period. A structured medical and neurological history was recorded as described elsewhere.21 Hypertension was defined as blood pressure ≥160/95 mm Hg. Smoking habit was scored as nonsmokers and smokers. Laboratory analyses included total and HDL cholesterol, triglycerides, and fasting blood glucose.

The study was approved by the ethics committee of the Department of Clinical Neurosciences, Helsinki University Central Hospital, Helsinki, Finland. The study was explained to the subjects, and informed consent was obtained.

General Clinical Assessment

A total of 383 patients (78.8%) of the Stroke Aging Memory cohort underwent a brain MRI investigation. Based on the MRI data, stroke subtypes were analyzed. Inclusion and exclusion criteria were used.22,23 The GpIIb/IIIa PlA1/A2 genotype was determined for 339 subjects (69.8%). Data on both genotype and MRI findings were available for 272 subjects (56.0%). The final study population did not differ from the remaining 214 excluded patients in terms of either vascular risk factors or stroke type.

Infarct Subtypes

Infarct subtypes were determined by MRI and defined as lacunar (ie, LAI) if the infarct was situated in the deep white or gray matter and had a diameter of 3 to 9 mm. Large-vessel infarct (LVI) was defined as an infarct located in the corticosubcortical layers of the cerebral hemispheres in (the territories of) the superficial branches of the anterior, middle, or posterior cerebral artery, with a diameter of ≥10 mm.22

DNA Procedures

DNA was separated from frozen blood samples according to standard procedures. Polymerase chain reaction for DNA amplification was carried out as described previously.24,25 The polymorphism in exon II of the GpIIa gene was detected by polymerase chain reaction and restriction digestion. The primer sequences and polymerase chain reaction protocol have been described in detail previously.24

Statistical Analysis

The investigation included the use of SPSS/WIN (version 12.0, SPSS Inc) software. The associations between single risk factors, stroke subtype, and survival were first evaluated by univariate statistical tests (Pearson χ2 and Student t test). Enter-mode logistic-regression analyses with sex, age, myocardial infarction, cardiac failure, arrhythmia, AF, hypertension, peripheral arterial disease, diabetes, total and HDL cholesterol, triglycerides, presence or absence of the PlA2 allele, or history of smoking as confounders were used to further explore the association of the PlA2 allele with LAIs and LVIs as well as survival. They were also used to examine the correlation between genotype and conventional risk factors. Interaction between smoking and genotype was analyzed by creating an interaction term within the logistic-regression analysis. To further study the possible interaction between smoking and the PlA2 allele, we created 4 new variables: (1) noncarriers with no history of smoking, (2) PlA2 allele carriers with no history of smoking, (3) noncarriers with a history of smoking, and (4) PlA2 allele carriers with a history of smoking. Group 1 was used as the reference category. To study the age dependence of the interaction, we subdivided the data into age groups of 55 to 69 years and 70 to 85 years.

Results

General Demographic Findings

The mean age of the patients was 70.5 years (range, 55 to 85 years). There were 133 men (48.9%) and 139 women (51.1%). Of the 272 patients, 57.3% (n = 156) had experienced an LVI, and 60.7% (n = 165), an LAI. Therefore, 18.0% of the patients (n = 49) had experienced both types of infarct. Of the 272 patients, 24 (8.8%) died within 15 months. The genotype distribution was 72.1% PlA1/A1, 27.6% PlA1/A2, and 0.4% PlA2/A2. The frequency of the PlA1 allele was thus 85.9%, and that of the PlA2 allele, 14.2%, corresponding to European population frequencies.16 The allele distribution was in Hardy-Weinberg equilibrium.

Phenotype of Stroke

In univariate analyses, significant associations were found between LVI and both arrhythmias (P < 0.001) and AF (P < 0.001), whereas smoking was the only significant predictor of LAI (P = 0.040). The PlA2 allele had no association with infarct phenotype. In logistic-regression analyses, smoking remained the only significant factor in the model to be associated with an increased risk of LAI (odds ratio [OR] = 1.87, 95% CI = 1.05 to 3.31; P = 0.033), whereas the association between LVI and cardiac arrhythmias was not significant (Table 1). There was a smoking-by-genotype interaction between the PlA1 polymorphism and a history of smoking affecting the risk for LAI (OR = 2.10, 95% CI = 0.90 to 4.89; P = 0.087) but not for LVI. In logistic-regression analysis with the aforementioned covariates, with 4 new subgroup forming the basis of the presence or absence of smoking and the PlA2 allele as a factor, smokers carrying the
TABLE 1. Effect of the Association Between Multiple Risk Factors and Platelet GpIIb/IIIa PlA1/PlA2 Fibrinogen Receptor Polymorphisms on Stroke Phenotype Among 272 Patients With Ischemic Stroke (Stroke Aging Memory Cohort)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valid n</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>272</td>
<td>71.0</td>
<td>7.6 SD</td>
<td>1.01</td>
<td>0.98</td>
<td>1.05</td>
<td>0.521</td>
</tr>
<tr>
<td>Female sex</td>
<td>139</td>
<td>74</td>
<td>53.2%</td>
<td>0.73</td>
<td>0.41</td>
<td>1.32</td>
<td>0.303</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>48</td>
<td>33</td>
<td>68.8%</td>
<td>1.51</td>
<td>0.70</td>
<td>3.25</td>
<td>0.296</td>
</tr>
<tr>
<td>Heart failure</td>
<td>56</td>
<td>34</td>
<td>60.7%</td>
<td>0.98</td>
<td>0.47</td>
<td>2.04</td>
<td>0.951</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>39</td>
<td>42</td>
<td>71.2%</td>
<td>1.80</td>
<td>0.55</td>
<td>5.86</td>
<td>0.330</td>
</tr>
<tr>
<td>AF</td>
<td>43</td>
<td>33</td>
<td>76.7%</td>
<td>1.65</td>
<td>0.41</td>
<td>6.55</td>
<td>0.479</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>37</td>
<td>23</td>
<td>62.2%</td>
<td>1.05</td>
<td>0.49</td>
<td>2.24</td>
<td>0.905</td>
</tr>
<tr>
<td>Hypertension</td>
<td>130</td>
<td>70</td>
<td>53.8%</td>
<td>0.83</td>
<td>0.48</td>
<td>1.42</td>
<td>0.493</td>
</tr>
<tr>
<td>Diabetes</td>
<td>61</td>
<td>34</td>
<td>55.7%</td>
<td>0.84</td>
<td>0.43</td>
<td>1.64</td>
<td>0.599</td>
</tr>
<tr>
<td>Smoking</td>
<td>145</td>
<td>86</td>
<td>59.3%</td>
<td>1.25</td>
<td>0.71</td>
<td>2.22</td>
<td>0.442</td>
</tr>
<tr>
<td>Chol, mmol/L</td>
<td>272</td>
<td>1.5</td>
<td>0.7 SD</td>
<td>1.01</td>
<td>0.67</td>
<td>1.53</td>
<td>0.950</td>
</tr>
<tr>
<td>HDL chol, mmol/L</td>
<td>272</td>
<td>1.2</td>
<td>0.6 SD</td>
<td>1.04</td>
<td>0.68</td>
<td>1.59</td>
<td>0.860</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>272</td>
<td>1.5</td>
<td>0.7 SD</td>
<td>1.01</td>
<td>0.67</td>
<td>1.53</td>
<td>0.950</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valid n*</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVI (n=156)</td>
<td>70.9</td>
<td>7.5</td>
<td>1.02</td>
<td>0.99</td>
<td>1.06</td>
<td>0.204</td>
<td></td>
</tr>
<tr>
<td>LAI (n=165)</td>
<td>83</td>
<td>59.7</td>
<td>0.90</td>
<td>0.49</td>
<td>1.63</td>
<td>0.727</td>
<td></td>
</tr>
</tbody>
</table>

The logistic regression model included sex, age, myocardial infarction, heart failure, arrhythmia, AF, hypertension, peripheral artery disease, diabetes, total and HDL cholesterol (chol), triglycerides, presence or absence of the PlA2 allele, and history of smoking as confounders.

*Eighteen percent of patients had both infarct types.

PiA2 allele had an increased risk of LAI (OR=2.50, 95% CI=0.95 to 6.60, P=0.064) when compared with nonsmokers who were not carriers of the PiA2 allele (Table 2). This effect was especially significant in younger stroke patients (55 to 69 years), among whom the interaction (OR=5.81, 95% CI=1.26 to 26.80; P=0.024) was greater than the effect of smoking alone (OR=3.12, 95% CI=1.06 to 9.24; P=0.039; Table 2).

Survival at 15 Months

In univariate analysis, age (P<0.001), smoking (P=0.030), and AF (P=0.040) predicted death at 15 months. In logistic-regression analysis adjusted for the confounding factors, age (OR=1.10, 95% CI=1.03 to 1.19; P=0.008) and smoking (OR=5.13, 95% CI=1.61 to 16.36; P=0.006) remained independent risk factors in the model for poststroke death (Table 3). In interaction analysis, there was a genotype-by-smoking effect on poststroke survival (OR=2.78, 95% CI=0.89 to 8.61; P=0.077). In logistic-regression analysis with the covariates mentioned earlier, and with the subgroups formed in varying combinations of smoking and the PiA2 allele as a factor, smokers carrying the PiA2 allele were at a higher risk of dying within 15 months after stroke (OR=8.86, 95% CI=1.68 to 46.55; P=0.010) than were smokers not carrying the PiA2 allele (OR=5.06, 95% CI=1.20 to 21.35; P=0.027; the Figure).

TABLE 2. Effect of the Interaction Between Smoking and Platelet GpIIb/IIIa PiA1/PiA2 Fibrinogen Receptor Polymorphisms on Stroke Phenotype Among 272 Patients With Ischemic Stroke (Stroke Aging Memory Cohort)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valid n</th>
<th>PiA2_ Smoking</th>
<th>PiA2_ Smoking</th>
<th>PiA2_ Smoking</th>
<th>PiA2_ Smoking</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole population</td>
<td>272</td>
<td>83</td>
<td>43</td>
<td>113</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVI</td>
<td>156</td>
<td>47</td>
<td>56.6%</td>
<td>0.79</td>
<td>0.33</td>
<td>1.87</td>
<td>0.58</td>
<td>1.08</td>
<td>0.56</td>
<td>2.11</td>
<td>0.812</td>
</tr>
<tr>
<td>LAI</td>
<td>165</td>
<td>45</td>
<td>54.2%</td>
<td>0.67</td>
<td>0.29</td>
<td>1.55</td>
<td>0.44</td>
<td>1.50</td>
<td>0.77</td>
<td>2.91</td>
<td>0.230</td>
</tr>
</tbody>
</table>

*The logistic regression model included sex, age, myocardial infarction, heart failure, arrhythmia, AF, hypertension, peripheral artery disease, diabetes, total and HDL cholesterol, and triglycerides as confounders.

*Forty-nine, †18, and ‡31 patients had both LAI and LVI strokes.
Discussion

We found that the effect of smoking on infarct phenotype and poststroke survival was modulated by the PI\textsuperscript{A1/A2} polymorphism of the GpIIIa gene encoding the fibrinogen receptor. We also found that the interaction between smoking and the PI\textsuperscript{A2} allele as a risk factor for LAIs was especially strong among younger stroke patients. The synergy between the PI\textsuperscript{A2} allele and smoking is most probably a consequence of an interaction between platelet aggregability, fibrinogen levels, and fibrinogen receptor binding affinity, which is modified by the presence of the PI\textsuperscript{A2} allele. Our study is the first to demonstrate an association between stroke and the GpIIb/IIIa PI\textsuperscript{A1/A2} polymorphism in smokers in a consecutive cohort of patients 55 to 85 years of age, who, in our opinion, represent the conventional clinical material available for research.

The prevalence of PI\textsuperscript{A2} allele carriers (PI\textsuperscript{A1/A2} or PI\textsuperscript{A2/A2}) was 28%. This prevalence is in line with observations made by Mikkelsson et al\textsuperscript{24,25} in Finnish patients who had had prehospital sudden cardiac death or who had died from unnatural causes. Previously, in a large case-control study on the association of PI\textsuperscript{A2} allele with myocardial infarction in Scandinavian patients, the prevalence of PI\textsuperscript{A2} allele carriers was 28% among controls and 35% among patients with myocardial infarction.\textsuperscript{26} Another previous finding for stroke patients was that the prevalence of PI\textsuperscript{A2} allele carriers was slightly higher among white women (case versus control, 36% versus 28%, respectively) when compared with black women (case versus control, 21% versus 22%), which suggests the existence of race-specific differences.\textsuperscript{17} Our population contained an equal number of men and women, and we found no sex difference. In the large Physicians’ Health Study consisting of a follow-up of 14 915 individuals, the frequency of the PI\textsuperscript{A2} allele among men was

![OR 8.66, CI 1.68 - 46.55, p=0.010](image)

The effect of smoking and platelet GpIIb/IIa PI\textsuperscript{A1/A2} fibrinogen receptor polymorphisms on poststroke survival at 15 months. The percentage of patients with different genotype combinations and history of smoking who died within 15 months is presented.

### Table 3: Association of Multiple Risk Factors and Platelet GpIIb/IIa PI\textsuperscript{A1/A2} Fibrinogen Receptor Polymorphisms for Survival at 15 Months Among 272 Patients With Ischemic Stroke (Stroke Aging Memory Cohort)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valid n</th>
<th>Alive at 15 Months (n=248)</th>
<th>Deceased at 15 Months (n=24)</th>
<th>OR</th>
<th>95% Cl</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>272</td>
<td>70.1 7.8 SD</td>
<td>75.3 6.6 SD</td>
<td>1.10</td>
<td>1.03-1.19</td>
<td>0.008</td>
</tr>
<tr>
<td>Female sex</td>
<td>139</td>
<td>126 90.6%</td>
<td>13 9.4%</td>
<td>2.00</td>
<td>0.69-5.77</td>
<td>0.201</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>48</td>
<td>40 83.3%</td>
<td>8 16.7%</td>
<td>1.72</td>
<td>0.60-4.97</td>
<td>0.315</td>
</tr>
<tr>
<td>Heart failure</td>
<td>56</td>
<td>47 83.9%</td>
<td>9 16.1%</td>
<td>1.34</td>
<td>0.46-3.91</td>
<td>0.587</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>59</td>
<td>50 84.7%</td>
<td>9 15.3%</td>
<td>0.77</td>
<td>0.08-7.75</td>
<td>0.826</td>
</tr>
<tr>
<td>AF</td>
<td>43</td>
<td>35 81.4%</td>
<td>8 18.6%</td>
<td>2.75</td>
<td>0.25-30.31</td>
<td>0.409</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>37</td>
<td>30 81.1%</td>
<td>7 18.9%</td>
<td>2.02</td>
<td>0.71-5.68</td>
<td>0.185</td>
</tr>
<tr>
<td>Hypertension</td>
<td>130</td>
<td>119 91.5%</td>
<td>11 8.5%</td>
<td>1.25</td>
<td>0.50-3.13</td>
<td>0.627</td>
</tr>
<tr>
<td>Diabetes</td>
<td>61</td>
<td>53 86.9%</td>
<td>8 13.1%</td>
<td>2.37</td>
<td>0.90-6.26</td>
<td>0.081</td>
</tr>
<tr>
<td>Smoking</td>
<td>145</td>
<td>127 87.6%</td>
<td>18 12.4%</td>
<td>5.13</td>
<td>1.61-16.36</td>
<td>0.006</td>
</tr>
<tr>
<td>Chol, mmol/L</td>
<td>272</td>
<td>5.6 1.2 SD</td>
<td>5.3 1.2 SD</td>
<td>0.77</td>
<td>0.49-1.21</td>
<td>0.257</td>
</tr>
<tr>
<td>HDL chol, mmol/L</td>
<td>272</td>
<td>1.2 0.6 SD</td>
<td>1.1 0.4 SD</td>
<td>0.92</td>
<td>0.32-2.58</td>
<td>0.869</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>272</td>
<td>1.5 0.7 SD</td>
<td>1.6 0.6 SD</td>
<td>1.32</td>
<td>0.67-2.59</td>
<td>0.424</td>
</tr>
<tr>
<td>PI\textsuperscript{A2} allele (A2/A1, A2/A2)</td>
<td>76</td>
<td>66 88.6%</td>
<td>10 13.2%</td>
<td>1.80</td>
<td>0.70-4.62</td>
<td>0.221</td>
</tr>
</tbody>
</table>

The logistic regression model included sex, age, myocardial infarction, heart failure, arrhythmia, AF, hypertension, peripheral artery disease, diabetes, total and HDL cholesterol, triglycerides, presence or absence of the PI\textsuperscript{A2} allele, and history of smoking as confounders.
15%,18 which equals the frequency of 14.2% found in our study.

To date, the role of the PI*2 allele of the GpIIb/IIIa fibrinogen receptor polymorphism in ischemic stroke has remained unclear, and contradictory results have been published. The Physicians’ Health Study found no evidence of an association between the PI*2 allele and myocardial infarction, stroke, or venous thrombosis.18 Those authors found no association with smoking, the PI*2 allele, or any vascular events, not even in subgroup analyses by age and smoking habit.18 However, the report did not differentiate between ischemic and hemorrhagic stroke, nor among ischemic stroke subtypes. The PI*2 allele frequency was double among previously healthy patients with their first LVI (23%) when compared with controls composed of neurological patients who had not experienced a stroke or transient ischemic attack (12%).27 That study did not, however, analyze the effect of the PI*2 allele on poststroke survival, nor did it address the effect of a history of smoking. In a 3-year follow-up study of 592 patients, only smokers with the PI*2 allele had a significantly increased incidence of the composite end point (cardiac death, myocardial infarction, or refractory angina requiring revascularization).20 This supports our finding of an interaction between the GpIIb/IIIa PI*2A2 polymorphism and smoking in stroke. In our study, MRI was performed 3 months after the stroke, and we did not have genotype data on the patients who died soon after arrival. A poor short-term outcome is more common in LVI than in LAI. Therefore, we cannot exclude the possibility of a survival bias, with the PI*2 allele affecting short-term survival among stroke patients and associating with LVI among patients who die soon after their stroke.

The strength of the present study is a thoroughly characterized cohort composed of consecutive stroke patients with an MRI-based infarct subtype classification. A significant weakness is that we do not have data on the fibrinogen levels of these patients, and we do not know the causes of death 15 months after stroke. It is obvious that the size of the study population resulted in wide CIs in some analyses, particularly with respect to analysis of survival, because the number of poststroke deaths in our population was rather small.

In a study comprising young white women <45 years of age, the PI*2 allele was associated with a 6.1-fold risk of stroke.17 Carter et al11 also demonstrated an association between the PI*2 allele and risk of atherothrombotic stroke only in a subgroup of patients aged <50 years. Another previous finding is that the PI*2 allele has been shown to be associated with coronary events, especially before the age of 60 years.28 These findings point to the fact that the PI*2 allele might be associated with ischemic stroke in younger patients, as was also found in our study. Interestingly, this association was no longer significant among older stroke patients.

Papp et al16 demonstrated that PI*2 allele prevalence was significantly higher in patients with acute coronary syndromes than in the control group (40% versus 25%). In their study, carriers of the PI*2 allele were at an increased risk of developing acute coronary syndromes (OR=5.74), and the occurrence of the PI*2 allele was significantly higher among patients with aspirin resistance than in patients with the appropriate response to aspirin.16 These authors found that patients homozygous for PI*2 did not respond to aspirin at all.16 They suggested that patients with PI*2 allele homozygosity might benefit from antiplatelet therapy based on ADP antagonists for prevention.16 After percutaneous angioplasty, patients who carried the PI*2 allele showed an increased risk of restenosis, which was halved among those who received cholesterol-lowering drugs, ie, statins, which are known to stabilize plaques. Statin therapy also significantly reduced the risk of coronary events in carriers of the PI*2 allele.29 There are no studies concerning the possible effect of statin therapy on survival among PI*2 allele–carrying stroke patients.

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Disclosures
None.

References
11. Carter AM, Catto AJ, Bamford JM, Grant PJ. Platelet GP IIIa PlA and GP Ib variable number tandem repeat polymorphisms and markers of platelet
1124–1131.


Smoking and the Platelet Fibrinogen Receptor Glycoprotein IIb/IIIa P1A1/A2 Polymorphism Interact in the Risk of Lacunar Stroke and Midterm Survival

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