PlA Polymorphism of Platelet Glycoprotein IIIa and Risk of Restenosis After Coronary Stent Placement

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Background—Platelets play a central role in the process of restenosis after percutaneous coronary interventions. A polymorphism of platelet glycoprotein IIIa (PlA) has been associated with a higher risk of coronary thrombosis. We designed this prospective study to test the hypothesis that PlA polymorphism of glycoprotein IIIa is associated with an increased risk for restenosis after coronary stent placement.

Methods and Results—The study included 1150 consecutive patients with successful coronary stent placement and 6-month follow-up with coronary angiography. The end point of the study was the incidence of angiographic restenosis (≥50% diameter stenosis) at follow-up. Of the 1150 patients, 72.5% were homozygous for PlA1, 24.7% were heterozygous (PlA1/PlA2), and 2.8% were homozygous for PlA2. Patients with the PlA2 allele demonstrated a significantly higher restenosis rate than did those without (47% versus 38%; OR, 1.42; 95% CI, 1.09 to 1.84). The risk was highest in homozygous carriers of PlA2 (53.1% restenosis rate). After adjustment for several clinical and angiographic characteristics, the presence of the PlA2 allele remained a significantly independent risk factor for restenosis (adjusted OR, 1.35; 95% CI, 1.07 to 1.70). The influence of the PlA2 allele on restenosis was stronger in women. Women with PlA2 had a restenosis rate of 52% compared with the 33% incidence among women homozygous for PlA1 (OR, 2.21; 95% CI, 1.27 to 3.85).

Conclusions—This study showed a significant association between the PlA polymorphism of glycoprotein IIIa and the risk of restenosis after coronary stent placement. The risk was more pronounced in patients homozygous for PlA2 allele and in female patients. (Circulation. 1999;99:1005-1010.)

Key Words: platelets ■ glycoproteins ■ receptors ■ stents ■ genetics

Restenosis remains the main limitation of percutaneous coronary interventions. Despite technical advances and multiple pharmacological interventions, the incidence of angiographic restenosis remains in the range of 30% to 40%. Restenosis is a complex and multifactorial process that is not fully understood; however, platelets are thought to play an important role. In the cascade of events after balloon-induced vessel wall injury, platelet adhesion, secretion, and aggregation promote the migration and proliferation of smooth muscle cells and neointima formation. A relevant role is suggested for the platelet glycoprotein (GP)IIb/IIIa (αIibβ3 integrin) fibrinogen receptor based on experimental and clinical data with antagonists for this receptor. Part of the effect of these antagonists is, however, explained with the additional blockade of the vitronectin receptor (αvβ3 integrin), which shares the same GP IIIa with platelet fibrinogen receptor. These mechanisms may be even more active after the insertion of coronary stents, which elicit a major platelet activation and hyperplastic response, than after plain balloon angioplasty. GP IIIa, the constituent of both fibrinogen and vitronectin receptors, is a polymorphic protein with platelet antigens 1 (PlA1) and 2 (PlA2) as the most common allelic isoforms.15–17 In vitro18–20 and clinical21–25 studies have so far provided discordant data about the functional significance of this polymorphism.

We designed this prospective study to test the hypothesis that PlA polymorphism of GP IIIa is associated with increased risk for restenosis after coronary stent placement.

Methods

From April 1996 through June 1997, coronary stent implantation was attempted in 1559 consecutive patients with clinical symptoms or objective signs of ischemia. Exclusion criteria for the present study were an unsuccessful procedure (defined as the failure to place the stent at the desired position or to achieve a final diameter stenosis of <30% by visual inspection) and the occurrence of 1 or more major adverse cardiac events (death, myocardial infarction, coronary artery bypass graft surgery, and repeat balloon angioplasty) during the first month after the procedure. Based on these criteria, 37 patients (2.4%) with unsuccessful intervention and 58 patients (3.7%) with early cardiac events were excluded. All 1464 eligible patients were requested to undergo a follow-up angiography 6 months after the
procedure by attending physicians who were unaware of the patient’s PI\(^4\) genotype. Follow-up angiography was performed in 1150 patients (79%) at 184±63 days. These patients had 1665 coronary lesions treated with the insertion of stents and represent the study population. All patients included in this study gave written informed consent for the intervention and follow-up angiography.

All patients received heparin (15 000 units) and aspirin (500 mg) intravenously before the intervention. Stent implantation of various slotted-tube stents was performed as previously described.\(^{26}\) Short 7-mm or articulated 15-mm stents were hand-crimped on conventional angioplasty balloons and delivered under fluoroscopic guidance. The short 7-mm stent was used as the unit in the analysis. Standard 15-mm stents were counted as 2 stent units. The number of stents used were left to the operator’s discretion. After sheath removal and application of a pressure bandage, all patients received intravenous heparin for 12 hours. The standard postprocedural therapy consisted of aspirin (100 mg BID PO indefinitely) and ticlopidine (250 mg BID PO for 4 weeks; Tiklyd, Sanofi-Winthrop). Patients with suboptimal results due to residual thrombus or dissection with flow impairment after stent implantation received additional therapy with abciximab given as bolus injection during stent insertion with flow impairment after stent implantation received additional therapy with abciximab given as bolus injection during stent insertion procedure and as a 12-hour continuous infusion thereafter. The decision to give abciximab was at the operator’s discretion.

**Determination of PI\(^4\) Genotypes**

High-molecular-weight DNA was extracted from 200 μL of peripheral blood with use of the QIAamp blood kit (QIAGEN). PI\(^4\) genotypes were determined by allele-specific restriction enzyme analysis.\(^{27–29}\) Briefly, a 268-bp sequence containing exon 2 of the GP IIIa gene was amplified by polymerase chain reaction using specific oligonucleotide primers: the sense primer 5’-TCTGATGTCCTG-GACTTCTCTT-3’ and the reverse primer 5’-TCTCCTCCCATGTC-AAACAGT-3’. After allele-specific restriction enzyme digestion of the amplified DNA with MspI (Boehringer Mannheim), the PI\(^4\) genotype was identified on a 6% polyacrylamide gel.

**Angiographic Assessment**

Lesions were classified according to the modified American College of Cardiology/American Heart Association grading system.\(^{30}\) Lesions of grade B2 or C were considered to be complex. The diagnosis of reduced left ventricular function was established in presence of ≥2 hypokinetic segments in the contrast angiogram. Quantitative angiographic analysis was performed offline using the automated edge detection system CMS (Medics Medical Imaging Systems) by operators unaware of the patient’s PI\(^4\) genotype. Identical projections of the target lesion were used for all assessed angiograms. Minimum luminal diameter (MLD), reference diameter, percent diameter stenosis, and diameter of the maximally inflated balloon were compared by means of the unpaired, 2-sided \(t\) test. Expressions of reduced left ventricular function were assessed by means of the QIAamp blood kit (QIAGEN). Pl A genotype. Follow-up angiography was performed in 1150 patients (79%) at 1665 coronary lesions treated with the insertion of stents and represent the study population. All patients included in this study gave written informed consent for the intervention and follow-up angiography.

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**Study End Points**

The primary end point of the study was the angiographic restenosis. Patients with coronary stent placement in ≥1 lesion were considered to have restenosis if ≥1 of the dilated lesions was found to have restenosis at follow-up. The duration of the study period and the sample size of 1150 patients were chosen to provide the analysis with an 80% power for detecting an assumed 1.3-fold increase in the risk of restenosis in patients with PI\(^4\) polymorphism of GP IIIa.

**Statistical Analysis**

The main analysis consisted of comparing the incidence of restenosis between patients with and those without the PI\(^4\) allele in the GP IIIa gene. The analysis was repeated after exclusion of the patients with intervention in multiple coronary lesions. Discrete variables are expressed as counts and compared with the use of \(x^2\) or Fisher’s exact test. Continuous variables are expressed as mean±SD and compared by means of the unpaired, 2-sided \(t\) test. The independent association between the presence of the PI\(^4\) allele and restenosis was assessed after the adjustment for other potential confounding factors using a multiple logistic regression analysis. This analysis was performed on a per-lesion basis after correction for a possible patient-clustering effect by using the bootstrapping technique; this technique allows for the appropriate correction of the 95% CI of the OR derived from the regression analysis. As an additional measure, the multivariate analysis was repeated after exclusion of the patients with intervention in multiple coronary lesions. Specific interaction terms were included in the logistic regression model to evaluate whether the influence of the PI\(^4\) allele on restenosis varied between different groups of patients as defined by certain clinical and angiographic factors. All statistical analyses were performed using S-Plus software (Mathsoft). Statistical significance was assumed for \(P<0.05\).

**Results**

We assessed the genotype distribution of patients excluded from this study. Of the 95 patients not eligible for follow-up angiography (patients with procedural failure or major adverse cardiac events during the first month after the intervention), 73.7% had the PI\(^{A1/A1}\) genotype, 23.2% had the PI\(^{A1/A2}\) genotype, and 3.1% had the PI\(^{A2/A2}\) genotype. Of the 314 eligible patients without angiographic follow-up, 74.0% had the PI\(^{A1/A1}\) genotype, 24.0% had the PI\(^{A1/A2}\) genotype, and 2.0% had the PI\(^{A2/A2}\) genotype. Thirteen patients of this group died during the 1-year follow-up, 4 patients underwent bypass surgery, and no patient had a nonfatal myocardial infarction. According to the genotype, the adverse event rate among the 314 eligible patients without control angiography was 5.2% for PI\(^{A1/A1}\) carriers and 6.2% for PI\(^{A2}\) carriers (\(P=0.73\)).

The genotype distribution for the 1150 patients with angiographic follow-up, the study population, conformed to Hardy-Weinberg equilibrium: 72.5% of the patients had the PI\(^{A1/A1}\) genotype, 24.7% had the PI\(^{A1/A2}\) genotype, and 2.8% had the PI\(^{A2/A2}\) genotype. Table 1 shows no differences in baseline clinical characteristics between patients with the PI\(^{A1}\) allele and those homozygous for the PI\(^{A1}\) allele. Table 2 lists the angiographic and procedural characteristics of the lesions for patients with the PI\(^{A1}\) allele and those homozygous for the PI\(^{A1}\) allele. There were 2 characteristics for which there was a significant difference: lesions of carriers of the PI\(^{A2}\) allele were more complex (\(P=0.02\)) but slightly shorter (\(P=0.04\)) than lesions of patients homozygous for the PI\(^{A1}\) allele. Other

**TABLE 1. Baseline Clinical Characteristics of Patients**

<table>
<thead>
<tr>
<th></th>
<th>PI(^{A1/A2}) and PI(^{A1/A2}) (n=316)</th>
<th>PI(^{A2/A2}) (n=834)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.5±10.4</td>
<td>62.9±10.5</td>
<td>0.54</td>
</tr>
<tr>
<td>Women, %</td>
<td>23.1</td>
<td>21.1</td>
<td>0.46</td>
</tr>
<tr>
<td>Arterial hypertension, %</td>
<td>61.0</td>
<td>60.0</td>
<td>0.74</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>18.7</td>
<td>20.9</td>
<td>0.41</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>35.1</td>
<td>31.9</td>
<td>0.30</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>26.3</td>
<td>29.1</td>
<td>0.33</td>
</tr>
<tr>
<td>Acute myocardial infarction, %</td>
<td>16.8</td>
<td>19.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Unstable angina, %</td>
<td>23.7</td>
<td>21.3</td>
<td>0.38</td>
</tr>
<tr>
<td>Reduced left ventricular function, %</td>
<td>48.0</td>
<td>50.0</td>
<td>0.56</td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>72.2</td>
<td>71.1</td>
<td>0.73</td>
</tr>
</tbody>
</table>

n=1150.
Figure 1. Comparison of incidence of restenosis between patients with and those without PI A2 allele (left) and according to allelic genotype (right).

Figure 2. Association between presence of PI A2 allele and restenosis in women (left) and men (right).

TABLE 2. Lesion and Procedural Characteristics at Time of Intervention

<table>
<thead>
<tr>
<th>Lesion Parameters</th>
<th>PI A2/A2 (n=473)</th>
<th>PI A1/A1 (n=1192)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter stenosis, %</td>
<td>75.0±6.9</td>
<td>74.5±15.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>9.5±6.5</td>
<td>10.3±6.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Procedural data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal balloon pressure, atm</td>
<td>13.9±3.3</td>
<td>13.7±3.6</td>
<td>0.42</td>
</tr>
<tr>
<td>Balloon-to-vessel ratio</td>
<td>1.02±0.09</td>
<td>1.03±0.10</td>
<td>0.51</td>
</tr>
<tr>
<td>Stent units</td>
<td>2.25±1.26</td>
<td>2.35±1.40</td>
<td>0.17</td>
</tr>
<tr>
<td>Immediately after stenting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>5.8±8.3</td>
<td>5.8±7.9</td>
<td>0.90</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; complex lesions, ACC/AHA lesion types B2 and C. Values are percent of target lesions or mean±SD.

analyzed variables were comparable between the groups. Furthermore, the proportion of patients who received abciximab during the intervention was comparable between carriers of PI A2 allele and PI A1 homozygotes (17.7% versus 16.2%, P=0.53).

Follow-up angiography was carried out at very similar time intervals (185±65 days in patients with the PI A2 allele versus 184±62 days in those homozygous for the PI A1 allele). The restenosis rate at 6-month angiographic follow-up was significantly higher in patients with the PI A2 allele than in those homozygous for the PI A1 allele (47% versus 38%, P=0.009; Figure 1) with an OR of 1.42 (95% CI, 1.07 to 1.70). The presence of the PI A2 allele remained a significant factor (P=0.03) in the model confined to single-lesion patients. Additional independent risk factors for restenosis were ostial location, a greater lesion length and diameter stenosis before the intervention, a smaller vessel size, and a greater number of stents implanted.

Next, we assessed the possibility of significant interactions between PI A genotype and other clinical and angiographic factors. This assessment was made by entering separately into the multivariate model of restenosis the terms representing the interaction between the presence of the PI A2 allele on 1 side and age, sex, diabetes, hypercholesterolemia, acute myocardial infarction, and vessel size on the other side. The only significant interaction effect identified was that between the PI A2 allele and sex (P=0.048). This implies that the effect of PI A polymorphism on restenosis was different among men and women. Additional analyses were performed for men and women separately. The PI A genotype distribution was not significantly different. Figure 2 displays the sex-related difference in the association between the presence of the PI A2 allele and restenosis. The restenosis rate was significantly higher in women positive for the PI A2 allele (52% versus 33% in women homozygous for the PI A1 allele; OR, 1.42; 95% CI, 1.01 to 2.00). Using the test for trend, there was a significant difference in restenosis rate among the 3 PI A genotypes (53.1% in patients homozygous for the PI A2 allele, 46.1% in PI A1/A2 patients, and 38.4% in patients homozygous for the PI A1 allele, P=0.007; Figure 1). Thus, the risk of restenosis was highest in patients homozygous for the PI A2 allele and intermediate for PI A1/A2 heterozygotes.

The association found between the PI A2 allele and restenosis was assessed for independence by adjusting for several potential confounding factors. We embedded in the multivariate logistic regression model of restenosis all clinical, angiographic, and procedural factors enumerated in Tables 1 and 2 independently of the respective univariate probability value. The presence of the PI A2 allele constituted an independent risk factor for restenosis (P=0.01) with an adjusted OR of 1.35 (95% CI, 1.07 to 1.70). The presence of the PI A2 allele remained a significant factor (P=0.03) in the model confined to single-lesion patients. Additional independent risk factors for restenosis were ostial location, a greater lesion length and diameter stenosis before the intervention, a smaller vessel size, and a greater number of stents implanted.
similar path, regardless of the PI^A genotype (1.23±0.86 versus 1.22±0.86 mm, P=0.86).

Discussion

The major finding of this study was the significant association between the presence of the PI^A2 allele of the GP IIIa gene and the risk of restenosis after coronary stent placement. Because GP IIIa is a constituent of both fibrinogen and vitronectin receptors, it may be speculated that this polymorphism could enhance their impact on the restenosis process.8,31 The risk was more pronounced in patients homozygous for the PI^A2 allele. If a functional change of the receptors containing polymorphic GP IIIa is proved, a major risk for homozygous carriers of PI^A2 allele also is conceivable. In addition, results of the present study revealed that women present a stronger link between the PI^A2 allele and restenosis than do men. The responsible mechanism is not clear, but previous studies have shown that the activation of platelet fibrinogen receptors is more easily inducible in women than in men.32 Gender-related differences have also been noted in the treatment effect achieved with fibrinogen receptor antagonists; the recently published data from a large randomized trial of eptifibatide in patients with acute coronary syndromes show that women exhibit a lesser treatment effect than do men.33

These results are based on a large consecutive series of patients with coronary stent placement. This series presented frequently characteristics that are associated with increased risk for restenosis. It has been demonstrated that simple lesions fulfilling the Benestent and STRESS criteria constitute only a relatively small portion of those actually treated and a restenosis rate of 40% has been recorded for nonequivalent lesions.8,34 In a recent meta-analysis of studies on the association between the deletion allele of the ACE gene and myocardial infarction, Samani et al85 found that studies based on small series reported much higher average risk than did studies that included large numbers of patients; the authors attributed this difference to a possible publication bias. An analysis of samples of adequate size to discern true-positive effects is a statistical consideration that is crucial in genetic investigation into complex, polygenic, and multifactorial disorders.36 Our large series of patients presented with a PI^A2 allele frequency (15.1%) very similar to that usually reported in Europe24,28,29 and the United States,25 so our results are not attributable to any unusual frequency of this allele in the gene pool of the individuals of this study. Parallel with studies showing a link between PI^A polymorphism and atherosclerotic coronary artery disease,21,22 other studies have found no clinical significance for this form of polymorphism.24,25 The results of our study may not be viewed as in contrast with the negative findings of the latter studies24,25 because of the different pathophysiological mechanisms underlying the processes of atherosclerosis and restenosis.37 In a recent study carried out in 207 patients after plain coronary balloon angioplasty, Mamotte et al38 found a nonsignificant 4% difference in restenosis rate between PI^A2 carriers and PI^A1 homozygotes. The greater role of neointimal hyperplasia in the process of restenosis after stenting and our much larger sample size may serve as explanation for the significant effect of PI^A polymorphism observed in the present study. We have previously found that certain patients present a particularly high risk of restenosis after coronary stent placement.39 This risk could not be explained by conventional clinical or lesion characteristics.40 The results of present study show that a polymorphism of the GP IIIa protein may explain part of the increased risk in certain patients.

Study Limitations

This study showed an association between the presence of the PI^A2 allele and restenosis. Further studies are warranted to demonstrate its functional substrate. Complex processes in cardiovascular medicine are characterized by the concurrent interactive effects of multiple genetic and environmental factors.44 The possibility that a neighboring coinherited gene is responsible for such an association is not excluded.45,46 The assessment of the interaction between PI^A polymorphism and gender was not based on a strong prior hypothesis; hence, additional studies are required to corroborate these findings in larger female populations and to find an explanation for the major risk of restenosis the PI^A2 allele confers in women. Although we achieved a high repeat angiography rate of nearly 80% at 6 months after the procedure, we cannot fully exclude a potential bias related to the incomplete follow-up. This bias is unlikely to be of relevance because eligible patients without angiographic follow-up did not differ from the study patients with respect to genotype distribution; in addition, homozygous patients for the PI^A1 allele in this group showed even a slightly lower 1-year clinical event rate than did PI^A2 carriers. Patients who receive coronary stent implantation need potent antithrombotic therapy during the first weeks after the procedure to prevent stent vessel occlusion.44 The patients in this study were on combined therapy with ticlopidine and aspirin for 4 weeks. Although this combination neither interferes directly with the function of GP
IIb/IIIa inhibitors can reduce the excessive risk for restenosis of specific therapies intending to reduce restenosis. It would such as those identified in this study, may become the target agents, 46 we cannot exclude that this therapy might have the risk was more pronounced in patients homozygous for the IIb/IIIa– containing receptors 45 nor exerts any significant effect of restenosis after coronary stent placement. The assessment of this risk was more pronounced in patients homozygous for the homozygous for the platelet integrin $\alpha_{\text{IIb}}\beta_{3}$, the fibrinogen receptor. 479 – 484.

Conclusions
This study showed a significant association between the presence of the PI$^\text{A2}$ allele in the gene encoding for GP IIb and the risk of restenosis after coronary stent placement. The risk was more pronounced in patients homozygous for the PI$^\text{A2}$ allele and in female patients. These data suggest a new role for genetic factors in the development of restenosis after percutaneous coronary interventions. The assessment of this genetic predisposition may be a useful tool for better defining the risk of restenosis in individual patients before the intervention. Particularly high-risk patients with the PI$^\text{A2}$ allele, such as those identified in this study, may become the target of specific therapies intending to reduce restenosis. It would be of interest to evaluate in the future whether current GP IIb/IIIa inhibitors can reduce the excessive risk for restenosis after coronary stent implantation in this subset of patients.

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References


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