Plasma Lipoprotein(a) Is Not a Predictor for Restenosis After Elective High-Pressure Coronary Stenting

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Background—Lipoprotein(a) is a risk factor for coronary artery disease. Although it has been implicated in restenosis after balloon angioplasty, its role in restenosis within coronary stents is unknown. The aim of the study was to assess the role of plasma lipoprotein(a) as a predictor for restenosis after elective coronary stenting.

Methods and Results—Elective, high-pressure stenting of de novo lesions in native coronary arteries with Palmaz-Schatz stents was performed in 325 consecutive patients. Clinical, angiographic, and biochemical data were analyzed prospectively. Angiographic follow-up was performed at 6 months. Lipoprotein(a) levels were compared in patients with and without restenosis. Angiographic follow-up was obtained in 312 patients (96%); recurrence was observed in 67 patients (21.5%). No clinical or biochemical variable was associated with restenosis. Lipoprotein(a) level was 37.81±49.01 mg/dL (median, 22 mg/dL; range, 3 to 262 mg/dL) in restenotic patients and 36.95±40.65 mg/dL (median, 22 mg/dL; range, 0 to 244 mg/dL) in nonrestenotic patients (P=NS). The correlations between percent diameter stenosis, minimum luminal diameter, and late loss at follow-up angiography and basal lipoprotein(a) plasma level after logarithmic transformation were 0.006, 0.002, and 0.0017, respectively. Multiple stents were associated with a higher incidence of restenosis (P=0.006), but biochemical data in these patients were similar to those treated with single stents.

Conclusions—The basal plasma level of lipoprotein(a) measured before the procedure is not a predictor for restenosis after elective high-pressure coronary stenting. (Circulation. 1998;98:1172-1177.)

Key Words: stents ■ restenosis ■ lipoprotein(a)

Although the plasma level of lipoprotein (Lp) (a) has been proposed to be a major independent risk factor for atherosclerosis and progression of coronary artery disease,1-3 the pathogenetic role of Lp(a) remains unclear.4,5 Numerous case-control studies that have compared Lp(a) levels in patients with known coronary artery disease and in control subjects have demonstrated higher Lp(a) concentrations in the former. In prospective studies, however, results are uncertain, probably because of the potential importance of Lp(a) heterogeneity in this process.6

Lp(a) is involved in lipid metabolism, the coagulation and fibrinolytic systems, and the stimulation of smooth muscle cell proliferation.7,8 Plasma concentration of Lp(a) in humans ranges from <1 mg/dL to >100 mg/dL, with risk for cardiovascular disease associated with levels >25 to 30 mg/dL.9-11 According to epidemiological studies, this threshold corresponds to the 75th12 or 90th13 percentile.

Most initial studies designed to assess the correlation between the serum level of Lp(a) and restenosis after percutaneous transluminal coronary angioplasty (PTCA) have been limited to small groups of patients and have considered restenosis as a simple binary phenomenon, with incomplete angiographic follow-up; results of these studies are inconsistent.14-21 A larger, more recent study confirmed the association between recurrence after PTCA and Lp(a), suggesting that its action may be crucial in the arterial healing process after balloon injury.21

Restenosis occurs less frequently after coronary stenting than after balloon PTCA, with in-stent tissue proliferation playing a key role in the former and negative remodeling in the latter.22 The function of Lp(a) in recurrence after balloon PTCA is open to new interpretations on the basis of this understanding,22 and its role after coronary stenting has not been studied previously. This prospective study investigates the association between Lp(a) and angiographic restenosis after elective, high-pressure stent implantation in patients with de novo lesions of the native coronary circulation.

Methods

From December 1993 to July 1997, 325 consecutive white patients who had coronary artery disease treated with PTCA and elective coronary stenting with Palmaz-Schatz stents and complete assess-
ment of factors associated with restenosis were enrolled in this study. These patients are part of a larger prospective study of biochemical and genetic risk factors for restenosis that is ongoing in our institution. All patients fulfilled the following criteria: patients of both sexes <80 years old with single-vessel or multivessel disease of native coronary arteries, a new lesion successfully treated with elective placement of 1 or 2 Palmaz-Schatz stents, no contraindication to the administration of ticlopidine, and agreement to undergo protocol follow-up coronary angiography at 6 months. Clinical and angiographic exclusion criteria were as follows: coronary atherectomy followed by stenting, primary or rescue PTCA, PTCA within 1 month of acute myocardial infarction, acute or chronic inflammatory disease, renal insufficiency, liver dysfunction, treatment with steroids, insulin-dependent diabetes, a severe comorbid status, ostial lesions of the right coronary artery or the left main stem, total coronary obstructions >2 weeks old, and lesions >30 mm long. Thirteen patients included in the study were not considered in the final analysis for the following reasons: 1 patient died, 2 developed subacute stent thrombosis (within 1 month of the procedure), and 10 did not undergo follow-up angiography. Angiographic follow-up at 6 months, or earlier when recurrence of angina or ischemia was suspected, was thus available in 312 patients (96%).

Coronary intervention, angiographic assessment, and quantitative coronary analysis were performed as previously described. Immediate angiographic success was considered to be the deployment of the stent(s) in the target lesion, with a Thrombolysis in Myocardial Infarction grade 3 coronary flow and a residual stenosis <20%. Restenosis was defined as a percent diameter stenosis ≥50% at the site of the lesion treated with the stent(s) in at least 1 of 2 orthogonal incidences, 1 of these always including the “worst view” of the segment being analyzed: only in-stent restenosis was considered.

Analysis of Conventional Clinical and Laboratory Risk Factors
Data for all patients were recorded as to age, sex, body mass index, family history of coronary artery disease, current smoking habits (>10 cigarettes/d), hypertension (diastolic blood pressure >90 mm Hg or systolic blood pressure >160 mm Hg), and non-insulin-dependent diabetes.

Biochemical Determination
Blood samples obtained in the morning before PTCA, after a 12-hour fast, were used to measure levels of plasma glucose, total cholesterol, HDL cholesterol, and triglycerides with enzymatic-colorimetric methods. Apolipoprotein B was measured with a nephelometric method. Lp(a) level was measured with a quantitative latex method for nephelometric Lp(a) assay [N-latex Lp(a) and Behring Nephelometric Analyzer, Behring Diagnostic Inc]. The N-latex Lp(a) reagent consists of a rabbit polyclonal anti-human Lp(a) antiserum as antibody for the nephelometric assay. The Lp(a) used in the preparation of the antiserum is a mixture of Lp(a) isoforms; the specificity of the antibody from Behring has been tested by immunoelectrophoresis and Western blotting as reported elsewhere. The method has intra-assay and interassay coefficients of variation of 1.5% to 3.0% and 1.7% to 3.2%, respectively. The nephelometric method using a reagent consisting of a polyclonal antibody is likely to recognize all of the many genetic isoforms of Lp(a); the antibody is also specific, because it does not precipitate plasminogen or any other apolipoprotein as tested by immunoelectrophoresis; thus, this method should be largely insensitive to variations related to the number of kringle 4 repeats. Its excellent precision and accuracy, the good correlation with the electroimmunodiffusion method, and the quick and easy use for the study of normal and pathological concentrations are well suited for use in clinical and research studies. All frozen assays were analyzed within 1 week to avoid underestimation secondary to prolonged freezing.

Study Sample Size Calculation
The number of patients included in this analysis was tailored to achieve a statistical significance as to the incidence of restenosis in subjects with high (>30 mg/dL) or low Lp(a) levels, with an expected frequency of restenosis of 30% in the whole population and 49% in subjects with high Lp(a) levels, with α=0.5 and β=0.20.

Statistical Analysis
Data are expressed as mean±SD or as median with ranges. Student’s t test was used to compare differences between continuous variables. The χ² statistic with Yates’s correction or Fisher’s exact test when appropriate was used to test associations of categorical data. Linear regression analysis with logarithmic transformation was used to correlate Lp(a) plasma level and angiographic parameters of restenosis. For variables with nonnormal distribution, a nonparametric test (Mann-Whitney U test) was used. Recurrence rates were also calculated for each quintile of Lp(a) concentration.

A value of P<0.05 was considered significant. SPSS release 5.0.1 for Windows was used to perform all statistical analysis.

This investigation was approved by the review committee of our institution, and all patients gave informed consent for inclusion in the study.

Results
Of 312 patients who had 6-month angiographic follow-up, 268 were male and 44 female, and all were between 31 and 78 years old (60.3±9.5 years). Follow-up angiography was performed at 6.3±1.7 months after coronary stenting for the whole cohort (range, 1.8 to 12 months). Angiographic restenosis was present in 67 patients (21.5%) and absent in 245 patients at 5.4±1.4 and 6.5±1.6 months after the procedure, respectively (P=0.0001). Lp(a) concentrations and recurrence rates were not different in 45 patients (14.4%) receiving lipid-lowering therapy; none were using drugs known to affect Lp(a) level.

No significant difference was present between patients with and without restenosis as to demographic, clinical, and biochemical variables or reference diameter before the procedure, after the procedure, and at 6-month follow-up (Table 1). Quantitative coronary analysis data before angioplasty and after coronary stenting were also similar in restenotic and nonrestenotic patients except for the higher incidence of restenosis among patients treated with multiple stents (P=0.0006). Multiple stents were used to treat patients with more diffuse forms of coronary artery disease. However, levels of Lp(a) in this subgroup were not significantly different between patients with and without restenosis (37.8±33.06 mg/dL [median, 23.0 mg/dL; range, 3.8 to 111.6 mg/dL] in 16 patients with restenosis versus 36.93±28.03 mg/dL [median, 22.6 mg/dL; range, 5.2 to 190 mg/dL] in 27 patients without restenosis, P=NS).

A separate analysis of 6-month angiographic results was performed considering subgroups of patients divided according to conventional cutoff values of Lp(a) known to be associated with ischemic events or coronary artery disease (Table 2), but no difference was found in the recurrence rate of patients with low or high plasma levels of Lp(a). Analysis of the recurrence rates studied according to Lp(a) concentration by quintile also demonstrated similar restenosis rates in patients with the lowest and highest concentrations (Figure).

Further analysis was performed considering restenosis as a continuous variable; the correlation between plasma level of Lp(a) and percent diameter stenosis, minimum luminal diam-

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eter, and late loss at follow-up was not statistically significant ($r = 0.006$, $r = 0.002$, and $r = 0.0017$, respectively).

**Discussion**

Our results show that the basal serum level of Lp(a) assessed by nephelometry is not a predictor for angiographic restenosis after elective, high-pressure coronary stenting using Palmaz-Schatz stents in patients with de novo lesions of native coronary arteries.

These results cannot be compared with others aimed at studying the role of Lp(a) in the recurrence of lesions after balloon PTCA, mainly because of the different mechanism of restenosis after coronary stenting. In fact, classic concepts of restenosis after balloon dilatation consist of immediate recoil,
platelet deposition, and thrombus formation, followed by smooth muscle cell proliferation and matrix formation, a mechanism analogous to wound healing after balloon injury, in which Lp(a) may be involved. Following this line of evidence, Desmarais et al found that the basal level of Lp(a) is a strong predictor of restenosis, suggesting that the link between the structural and physiological properties of Lp(a) and the mechanisms controlling fibrinolysis, coagulation, and cellular mitogenesis, which occur at sites of deep arterial injury after balloon dilatation, may be responsible for this effect. More recently, Horie et al described a higher basal Lp(a) level and a significant reduction after balloon PTCA in patients who developed restenosis at 4 months, elaborating the hypothesis of a most important inhibition of thrombolysis and promotion of thrombus formation that may contribute to restenosis in these patients.

Studies with intracoronary ultrasound have demonstrated that recurrence after balloon PTCA is mainly due to a process of negative arterial remodeling in response to balloon injury, accounting for >70% of late lumen loss. On the other hand, stents create a larger final lumen cross-sectional area and practically abolish arterial remodeling because the metallic scaffold does not recoil. Neointimal hyperplasia is therefore the main factor responsible for in-stent restenosis after coronary stenting, offering a pure proliferative model for the study of restenosis. A neointimal proliferative effect has been attributed to Lp(a), and evidence of this action has been obtained in vitro. Although neointimal proliferation after coronary stenting may be activated or stimulated by many biochemical mediators, our results suggest that the basal level of Lp(a) does not play a leading role in this setting.

Our study was designed to minimize interference by the variables that might affect the incidence of restenosis after coronary stenting or might influence basal levels of Lp(a). The nephelometric assay used in this study is sensitive to all the isoforms of Lp(a), which adds uniformity to the values found in our patients and limits problems that arise from the spectrum of isoforms.

In agreement with other series of white subjects, Lp(a) concentrations were not distributed normally in our population but rather were skewed toward lower values. Bearing in mind that pathological effects of Lp(a) occur in patients with high levels (>30 mg/dL), the relatively small number of patients “at risk” is apparent when the usual distribution is respected; therefore, our study was sized to detect a difference in the recurrence rate of 19% among patients with low or high Lp(a) levels.

From univariate analysis, no relationship was observed between clinical variables and restenosis after coronary stenting. Unstable angina and diabetes are among the strongest predictors of recurrence after balloon PTCA; however, the restenosis rate in unstable patients treated with elective high-pressure implantation of Palmaz-Schatz stents is uncertain. Diabetes seems to be related to restenosis after coronary stenting as well; this was not observed in our population or in a recently published series of diabetic patients. The exclusion of insulin-dependent diabetic patients and the strict metabolic control exerted by drug or dietary treatment in our patients may have blunted the effect of this variable.

From the analysis of angiographic characteristics, a higher restenosis rate was observed in patients treated with multiple stenting. Multiple stents were used to treat patients with more diffuse forms of coronary disease, and the degree of coronary artery disease is known to be correlated with serum levels of Lp(a). This was also apparent in our population, although the difference did not reach statistic significance: Lp(a) levels in patients with focal versus diffuse disease were 33.29±36.18

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**TABLE 2. Restenosis Rate According to Basal Plasma Levels of Lp(a).**

<table>
<thead>
<tr>
<th>Quantitative Coronary Analysis</th>
<th>Lp(a), mg/dL</th>
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<tbody>
<tr>
<td></td>
<td>≤30 (n=213)</td>
</tr>
<tr>
<td>D-ref, mm</td>
<td></td>
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<tr>
<td>Before PTCA</td>
<td>2.88±0.62</td>
</tr>
<tr>
<td>After CS</td>
<td>3.10±0.41</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2.80±0.58</td>
</tr>
<tr>
<td>MLD, mm</td>
<td></td>
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<tr>
<td>Before PTCA</td>
<td>0.62±0.45</td>
</tr>
<tr>
<td>After CS</td>
<td>2.79±0.44</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1.84±0.81</td>
</tr>
<tr>
<td>%DS</td>
<td></td>
</tr>
<tr>
<td>Before PTCA</td>
<td>77.15±16.28</td>
</tr>
<tr>
<td>After CS</td>
<td>10.29±7.53</td>
</tr>
<tr>
<td>Follow-up</td>
<td>34.76±24.74</td>
</tr>
<tr>
<td>Acute gain, mm</td>
<td>2.16±0.61</td>
</tr>
<tr>
<td>Late loss, mm</td>
<td>0.89±0.74</td>
</tr>
<tr>
<td>Net gain, mm</td>
<td>1.27±0.88</td>
</tr>
<tr>
<td>Stenosis&gt;50%, n (%)</td>
<td>47/213 (22.1)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

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mg/dL (median, 22 mg/dL) versus 46.33 ± 43.87 (median, 22 mg/dL), respectively (P = 0.22). Therefore, Lp(a) concentration was not significantly different among patients with single or multiple stents (37.12 ± 43.16 mg/dL [median, 22 mg/dL] and 37.26 ± 38.63 mg/dL [median, 22 mg/dL], respectively), but because of the small number of patients in the latter subgroup, a statistical error cannot be excluded (Table 1).

None of the biochemical variables tested were related to restenosis (Table 1), and the analysis of a subgroup of patients with elevated Lp(a) levels yielded negative results (Table 2). Furthermore, no correlation was found between Lp(a) and restenosis as a continuous variable analyzing the recurrence rate for each quintile of Lp(a) concentration (Figure 1) or using regression analysis after logarithmic transformation.

The link between Lp(a) and coronary artery disease as an independent risk factor is still not straightforward. Most of the discrepancies observed in prospective studies may be in part secondary to a large number of confounding variables that are still unknown about the “mysteries of Lp(a).”

Furthermore, no studies have been performed to evaluate the impact of method inaccuracy on the interpretation of clinical data, and this may explain why results are not consistent.

Although the present study does not address the potential role of different isoforms of Lp(a) in restenosis after stent implantation, our negative data strongly suggest that the basal serum level of Lp(a) screened with a simple, reliable, and quick nephelometric method is not a valuable predictor of 6-month outcome after coronary stenting. Additional studies could be useful to validate this observation.

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References


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