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Ö. Sirikci · V. Aytekin · I.C.C. Demiroglu
C. Demiroglu · S.M. Marcovina

Association of lipoprotein(a) concentration and apo(a) isoform size with restenosis after percutaneous transluminal coronary angioplasty

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Abstract Lp(a) is a unique class of lipoprotein particles that exhibits a considerable size heterogeneity resulting from the size polymorphism of apo(a), its unique protein component. An elevated level of Lp(a) in plasma has been proposed to be a risk factor for premature development of coronary artery disease. To evaluate the relationship between Lp(a) concentration and apo(a) isoform size with restenosis after percutaneous transluminal coronary angioplasty, Lp(a) levels and apo(a) phenotypes were determined in 204 patients who underwent a successful coronary angioplasty procedure and stent implantation. The patients were followed with clinical examinations and exercise tests at 1, 3, and 6 months, and a control coronary angiography was performed after 6 months to evaluate restenosis. Lp(a) levels were determined with an ELISA that is insensitive to the size heterogeneity of Lp(a), and the apo(a) isoforms were determined by a high-resolution agarose gel electrophoresis method followed by immunoblotting with a specific monoclonal antibody. Of the 146 patients who underwent angiographic evaluation, 57 (39%) had restenosis, whereas 89 (61%) did not. Lp(a) levels and the distribution of the expressed apo(a) phenotypes were compared in these two groups of patients. Although the mean and median Lp(a) levels were higher in the restenosed group, the difference was not statistically significant. However, a significant difference in Lp(a) values was found in women (P=0.043), even though, because of the small number of women in the study (n=35), no sound conclusions can be reached on the predictive role of Lp(a) in restenosis. There also was no difference in the distribution of apo(a) phenotypes between the two groups. Because of their wide distribution, Lp(a) values and apo(a) isoforms do not seem to be a useful indicator of risk of restenosis after percutaneous transluminal coronary angioplasty in our study cohort.

Key words Lipoprotein(a) · Apo(a) size · Restenosis · Risk factor

Ö. Sirikci
Department of Biochemistry, Marmara University School of Medicine, Istanbul, Turkey

V. Aytekin · C. Demiroglu
Kadir Has University Faculty of Medicine, Florence Nightingale Hospital, Istanbul, Turkey

I.C.C. Demiroglu
Florence Nightingale Hospital, Istanbul, Turkey

S.M. Marcovina (✉)
Department of Medicine, University of Washington, Northwest Lipid Research Laboratories, 2121 N. 35th Street, Seattle, WA 98103, USA

Introduction

Lipoprotein(a) [Lp(a)] is a unique lipoprotein discovered by Berg in 1963 [1]. Lp(a) is formed by a lipoprotein particle very similar in lipid and protein composition to low-density lipoprotein (LDL) and by a specific protein, apo(a), linked by a covalent bond to apo B-100 of LDL. The apo(a) molecule contains multiple copies of kringle 4, one copy of kringle 5, and an inactive protease domain, all showing a high degree of structural homology to the equivalent regions of plasminogen [2], a zymogen of the coagulation cascade. Ten different types of kringle 4 are present in apo(a), each as a single copy except the kringle 4 type 2. The number of kringle 4 type 2 repeats varies within and between individuals, imparting a wide range of size heterogeneity to apo(a) and consequently to Lp(a) [3, 4]. The different number of kringle 4 type 2 repeats results in the expression of 35 different apo(a) isoforms in human plasma [5]. There is an inverse relationship between the size of the expressed apo(a)

isoform and the level of Lp(a) in plasma [6], even though the molecular mechanism of this relationship is not completely understood. Apo(a) size cannot entirely explain the variations observed in plasma Lp(a) levels, and the strength of this relationship varies in different populations [7, 8].

In numerous case-control studies, Lp(a) levels were found to be higher in coronary heart disease (CHD) and myocardial infarction cases, and thus an elevated Lp(a) level was considered as an additional risk factor for CHD and myocardial infarction. However, prospective studies and some large-scale epidemiological studies have reported conflicting results, with some of the studies confirming high levels of Lp(a) to be a risk factor for CHD [9, 10], while others did not. Conflicting results have also been presented regarding the association of Lp(a) and restenosis after percutaneous transluminal coronary angioplasty (PTCA). Few studies have evaluated the relationship of apo(a) isoform size and CHD, and recently evidence has been presented that small apo isoforms are a powerful predictor of advanced atherosclerosis, particularly when associated with high Lp(a) levels [11, 12]. The association between apo(a) isoform size and restenosis after PTCA has not been investigated to date in clinical studies. The aim of our study was to evaluate prospectively the association between Lp(a) levels and apo(a) isoform size with restenosis after PTCA and stent implantation.

Materials and methods

Patients

Between January and December 1997, 204 patients who underwent a coronary intervention because of stable or unstable angina pectoris were enrolled in this prospective clinical trial. The criteria for coronary intervention included the angiographically documented stenosis of ≥70% in at least one of the major branches of the coronary tree and accompanying ischemic changes in electrocardiograms (ECG) at rest or with provocative tests. Because it has been suggested that Lp(a) levels may change in an acute-phase reaction [13], patients who had a myocardial infarction, PTCA, or by-pass surgery in the previous month were not included in the study. Before the intervention, the patients underwent a complete blood count, ECG, and chest X-rays evaluation, in addition to the determination of glucose level, lipid profile, liver and renal function parameters. Overnight fasting blood samples were also obtained before PTCA for the determination of Lp(a) level and apo(a) isoform size, and 1-ml plasma aliquots were stored at –80°C until analyses were performed. An informed consent was obtained from each patient and this study was approved by the ethical committee of the Marmara University School of Medicine.

Procedure and follow-up

PTCA procedures and stent implantations of the scheduled patients were performed in the Catheterization Laboratory of Florence Nightingale Hospital (Kadir Has University Faculty of Medicine). The angioplasty procedures were performed via the femoral approach with an 8-Fr guiding catheter, according to the standard PTCA technique as originally described by Grüntzig et al. [14]. The angiographic criteria of a successful angioplasty were defined as an increase of greater than 50% in luminal diameter with a final stenosis of less than 30% in luminal diameter and no major complications. A stent was implanted in bail-out situations and in cases where a suboptimal result was obtained with conventional PTCA. All patients who did not have a history of previous gastrointestinal bleeding were on aspirin (100–300 mg/day) before and after the intervention. The patients also received intravenous bolus heparin (10,000 U in PTCA and 15,000 U in stent patients), which was continued for 24 h after the procedure. As adjunctive medical therapy, the patients also received ticlopidine for 6 weeks (stent patients), calcium channel blockers and nitroglycerin for 6 months. Intensive medical therapies were prescribed for any of the present risk factors such as hypercholesterolemia, hypertension, and diabetes. No patients were taking lipid-lowering drugs known to affect Lp(a) concentrations. The patients were followed with clinical examinations and exercise tests at 1, 3, and 6 months after the intervention. A coronary angiogram was scheduled after 6 months to evaluate restenosis. Coronary angiograms performed between 3 and 6 months were considered adequate for angiographic control. In coronary arteriographic evaluation, patients with greater than 50% stenosis in luminal diameter at the angioplasty site were considered to have restenosis. Both angioplasty and control angiographies were recorded with cineangiography for documentation.

Determination of Lp(a)

Serum Lp(a) levels were determined by a double monoclonal antibody-based ELISA that has been demonstrated to be insensitive to the size heterogeneity of Lp(a) [15]. The Lp(a) particles were captured on microtiter plates with a monoclonal antibody (mAb a-6) specific for an epitope on kringle 4 type 2. The captured Lp(a) was determined with a peroxidase-conjugated monoclonal antibody (mAb a-40) specific for an epitope on kringle 4 type 9, which is present as a single copy per molecule. The Lp(a) concentrations were expressed in nanomoles per liter of Lp(a) protein.

Apo(a) phenotyping

Expressed apo(a) isoforms were separated with high-resolution sodium dodecyl sulfate-agarose gel electrophoresis and transferred onto nitrocellulose membranes as previously reported [5]. The membranes were incubated with apo(a)-specific monoclonal antibody (a-5) and were visualized using an enzyme-linked second antibody and a chemiluminescent substrate. A standardized nomenclature proposed by Marcovina et al. [16] that relies on a consistent relationship between the number of kringle 4 repeats and the relative migration of apo(a) isoforms in agarose gel was used to define the isoforms. Thus each apo(a) isoform was designated according to the respective number of kringle 4 repeats. Of the two isoforms expressed in heterozygous individuals, the one that was predominantly expressed was used in statistical analyses.

Data analysis

The difference in the distribution of dichotomous characteristics in outcome groups was explored with the chi-square test. The difference among numerical parameters exhibiting a normal distribution was explored with the *t*-test. The comparison of groups for Lp(a) and apo(a) distributions was performed with the Mann-Whitney U test. The statistical tests were performed using Complete Statistical System Software and SPSS for Windows 5.0 software.

Results

Of the 204 patients included in the study, 146 (72%) had a control angiography performed at the end of the follow-up period. The mean time interval for control angiography was 6.9±3.6 months. The mean age of these 111 males (76%) and 35 females (24%) was 56±10 years. To avoid the problem that asymptomatic restenosis may not have been detected, the statistical evaluations were performed only on the 146 patients who underwent a follow-up coronary angiogram. According to the angiographic evaluation, 57 of the patients (39%) were diagnosed to have restenosis, whereas 89 patients (61%) did not. The mean and median Lp(a) values were 57.8 nmol/l and 27.5 nmol/l respectively. These values are very similar to those determined in a large group (n=2,060) of white Americans [17] by the same enzyme immunoassay used in the present study (mean=47.9 nmol/l and median=20.0 nmol/l). Upon phenotype analysis, 70.3% of the patients were found to be heterozygous for apo(a) isoform size, while 29.7% expressed a single apo(a) isoform. The proportion of heterozygous subjects in this cohort is only slightly lower (70.3% vs. 75.7%) than that observed in a population-based study of white Americans [17].

The homogeneity of the restenosis and non-stenosis groups was analyzed with the chi-square test for the distribution of gender, number of lesions, or type of intervention (PTCA vs. stent), and the number of diabetic, hypertensive, and smoking patients. The distribution of these characteristics was not significantly different between the restenosis and the non-stenosis group, except for smoking, which was significantly associated with restenosis (P=0.044). The application of PTCA, with or without stent implantation, to patients having one, two, or three lesions also was not significantly different (P=0.622). The age and blood lipid parameters of the restenosis and non-stenosis groups are presented in Table 1. The mean age (P=0.133), total cholesterol (P=0.280), LDL-cholesterol (P=0.438), HDL-cholesterol (P=0.377), and triacylglycerol (P=0.660) levels of patients prior to PTCA were not significantly different in the restenosis and non-stenosis groups with the *t*-test. Other than smoking status, none of these risk factors were found to be associated with restenosis outcome with univariate analyses.

The frequency distribution of Lp(a) levels in restenosis and non-stenosis patients is presented in Fig. 1. Because the Lp(a) distribution was highly skewed (skewness=1.539, n=146), the median Lp(a) values of restenosis and non-stenosis groups were compared by non-parametric tests (Table 2). Although the median Lp(a) level in the restenosis group was higher than in the non-stenosis group, the difference was not statistically significant with the Mann-Whitney U test (45 vs. 24.4 nmol/l, P=0.093). When the Lp(a) levels were compared according to gender, men had a statistically non-significant elevation in the restenosis group (36.3 vs. 25.0 nmol/l, P=0.237), whereas Lp(a) values were significantly different in women (106.6 vs. 16.9 nmol/l, P=0.043).

The median Lp(a) values of restenosis and non-stenosis groups were also compared among subsets according to the type of intervention (PTCA vs. stent), and according to patients having single or multiple lesions. The Lp(a) levels of patients with conventional PTCA (P=0.105), stent (P=0.578), and patients with single lesions (P=0.565) did not differ significantly in their respective restenosis and non-stenosis groups. Patients with multiple lesions had a significantly elevated median Lp(a) level in the restenosis group compared with those in the non-stenosis group (50.7 vs. 16.7 nmol/l, P=0.042).

The frequency distribution of apo(a) isoforms in restenosis and non-stenosis patients is presented in Fig. 2. Again, the distribution is very similar to that previously reported in white Americans [17]. In contrast to Lp(a), the distribution of apo(a) isoforms in the restenosis and non-stenosis groups were very similar, with identical median values of 24 kringles (Table 2), and there was no significant difference either when compared all together (P=0.392) or according to

Table 1 Age and blood lipid parameters of the restenosis and non-stenosis groups (*HDL* high-density lipoprotein, *LDL* low-density lipoprotein)

	Restenosis (n=57)					Non-stenosis (n=89)				
	Mean	Median	Min.	Max.	SD	Mean	Median	Min.	Max.	SD
Age (years)	57.2	58	38	76	9.8	54.8	55	32	78	9.5
Total cholesterol (mg/dl)	212.5	213	122	313	45.4	221.1	220	123	399	45.6
Triacylglycerols (mg/dl)	200	171	60	690	130.3	208.6	184	61	573	100.1
HDL-cholesterol (mg/dl)	46.4	48	30	56	5.5	45.5	47	24	58	6.1
LDL-cholesterol (mg/dl)	127.9	125.9	51.2	238	43.3	133.9	134	42.6	313.2	44.7

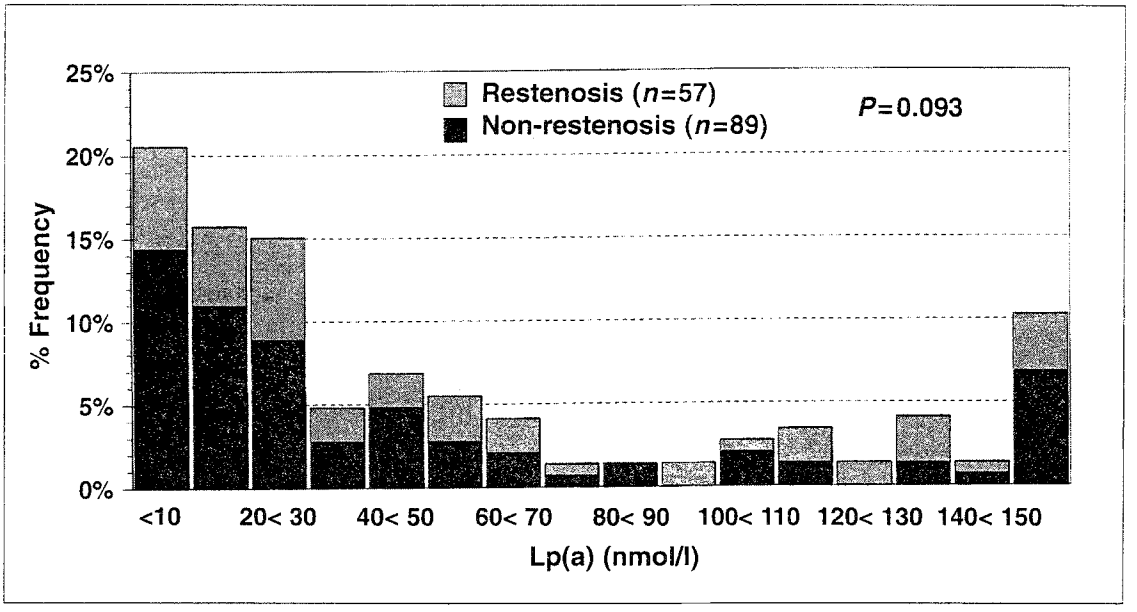

Fig. 1 Frequency distribution of lipoprotein(a) [Lp(a)] values in patients with and without restenosis after coronary angioplasty

Table 2 Distribution of lipoprotein(a) [Lp(a)] levels and apo(a) phenotypes in restenosis and non-stenosis groups (*PTCA* percutaneous transluminal coronary angioplasty)

	MedianLp(a) values (nmol/l)			Median of the predominantly expressed apo(a) isoforms (number of kringle 4 repeats)		
	Restenosis	*P* value	Non-stenosis	Restenosis	*P* value	Non-stenosis
Whole group	45.0	NS	24.4	24.0	NS	24.0
Male	36.3	NS	25.0	24.0	NS	24.5
Female	106.6	0.043	16.9	20.5	NS	24.0
PTCA	45.0	NS	24.4	24.0	NS	25.0
Stent	38.7	NS	23.4	24.0	NS	24.0
Single lesion	32.5	NS	24.4	24.0	NS	24.0
Multiple lesion	50.7	0.042	16.7	24.0	NS	25.0

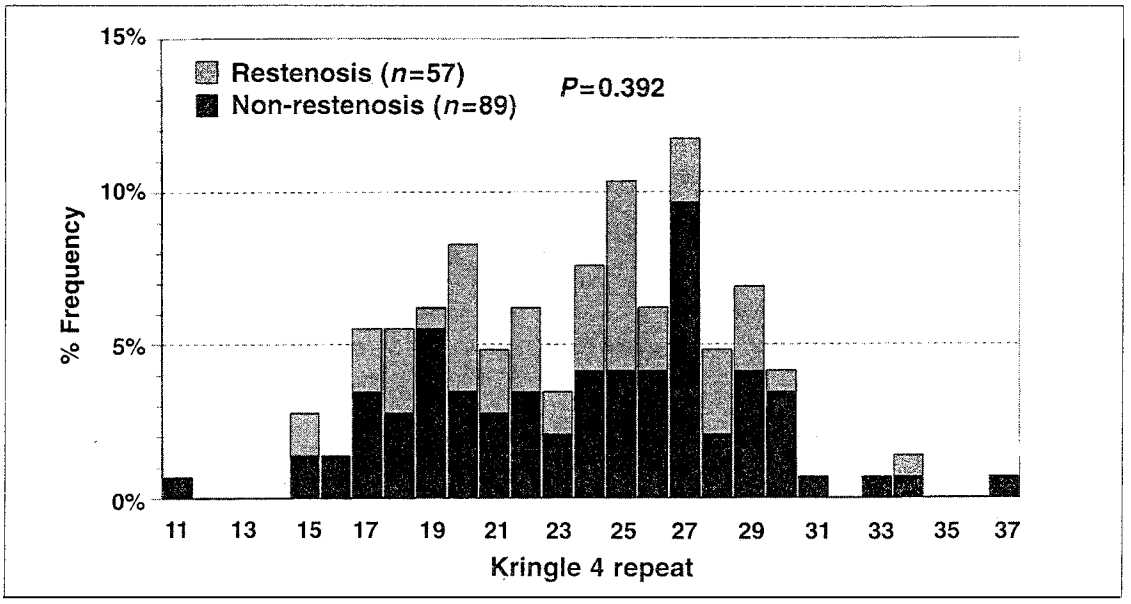

Fig. 2 Frequency distribution of the predominantly expressed apo(a) isoform size in patients with and without restenosis after coronary angioplasty

gender (men, P=0.475; women, P=0.097). The predominantly expressed apo(a) isoform was not significantly different in restenosis and non-stenosis patients who underwent conventional PTCA (P=0.214) or stent (P=0.857), or in patients with single (P=0.508) or multiple lesions (P=0.536).

There was a significant inverse correlation between the predominantly expressed apo(a) isoforms and serum Lp(a) levels with Spearman's rank correlation in the patient group as a whole (R_s –0.618, P<0.0001). This relationship was also observed in the restenosis and non-stenosis groups and in their subsets by gender. The Lp(a) values were also weakly but significantly correlated with total cholesterol (R_s 0.193, P=0.022) and LDL-cholesterol (R_s 0.227, P=0.007) values.

Discussion

Lp(a) is a complex lipoprotein particle of undefined function. The presence of the LDL component and the structural homology of apo(a) to plasminogen impart both atherogenic and thrombogenic potential to the Lp(a) molecule. However, the structural complexity, the extreme size polymorphism, and the lack of knowledge of the physiological role render very complex the assessment of the pathological role of Lp(a) and its mechanisms of action. The numerous case-control studies and, more recently, a variety of prospective studies have generated a huge amount of data but, because of the discordance in the conclusions, the studies have not provided a clearly defined role of Lp(a) in CHD [10]. The same discordant conclusions have also been obtained from studies which investigated the role of Lp(a) in restenosis after PTCA. Several studies have reported a 6-month restenosis rate of 30%–40% [18]. While the pathogenesis of restenosis has not been fully elucidated, the migration of smooth muscle cells from the media to the intima and the consequent proliferation in the intima are considered one of the primary mechanisms of restenosis. Lp(a) has been found to be ubiquitous in coronary atheroma specimens and a correlation was reported between plaque α-actin (a marker for smooth muscle cells) and the area of Lp(a) deposition [19]. A number of studies have suggested that Lp(a) may inhibit fibrinolysis by competing with plasminogen for binding to fibrin and to cell surfaces, thus promoting thrombotic events [10]. Because thrombus formation is considered to contribute to restenosis after PTCA, Lp(a) may be directly involved in the process by inhibiting fibrinolysis. However, while several studies have found an association between high Lp(a) level and restenosis after PTCA [10], others have not [20, 21]. Additionally, two large studies involving 2,223 and 325 patients respectively have found no relationship between Lp(a) levels and restenotic events after coronary stent [22, 23].

In addition to Lp(a) levels, the size of apo(a) has also been found to play a role in atherogenesis, and there are recent results suggesting that high Lp(a) concentration and small apo(a) size can act synergistically in predicting advanced atherosclerosis [11]. Because no studies have been performed on the combination of the two factors as indicators of restenosis, we have evaluated Lp(a) levels and apo(a) isoforms in 146 patients undergoing PTCA with or without stent implantation. Although an elevated median Lp(a) value was observed in the patients with restenosis (45.0 nmol/l vs. 24.4 nmol/l obtained in the non-stenosis group), the widespread and skewed distribution of Lp(a) levels (skewness=1.539, kurtosis=1.889) prevented this difference from being statistically significant. When analyses were performed according to gender, again no statistically significant difference in Lp(a) levels was found between restenosis and non-stenosis male patients. However, in female patients, we observed a significantly higher median Lp(a) value in the restenosis group (106 nmol/l vs. 16.9 nmol/l), but the small size of the female patient group (10 in the restenosis group and 25 in the non-stenosis), coupled with a P value of 0.043, renders it difficult to strongly support the significance of Lp(a) levels in predicting restenosis in female patients. The median Lp(a) level was also higher in restenosis but did not reach statistical significance when analyses were performed according to the type of intervention (PTCA with or without stent) or according to the number of lesions. Only in patients with multiple lesions was there a modestly significant difference in Lp(a) values between restenosis and non-stenosis groups (P=0.042).

Because the level of circulating Lp(a) is genetically determined and there is an inverse correlation between Lp(a) concentration and apo(a) size [6], we also determined the apo(a) isoform size and evaluated whether there is an association between apo(a) size and restenosis. The described inverse correlation between Lp(a) concentration and apo(a) size was also present in our patient cohort (R_s=0.618, P<0.001). Unlike the Lp(a) levels, the predominantly expressed apo(a) isoforms of the restenosis group (mean 22.9, median 24) and the non-stenosis group (mean 23.8, median 24) were nearly identical. The fact that we observed different Lp(a) distributions in restenosis and non-stenosis groups, whereas the predominantly expressed apo(a) isoforms were almost identically distributed, indicates that more information is needed to understand the factors regulating circulating Lp(a) levels in CHD or after coronary interventions.

Because risk factors such as hypercholesterolemia, diabetes, hypertension, and high triglyceride levels (as determined before the coronary intervention) were controlled with appropriate medical therapies during the follow-up period, these characteristics were not associated with the restenosis outcome. However, smoking was associated with restenosis, possibly because of the failure of smokers to quit smoking.

Thus, neither Lp(a) levels nor apo(a) isoforms were predictive of restenosis in this prospective study of 146 patients who underwent PTCA and stent implantation. Differences in

experimental design (number of subjects, inclusion/exclusion criteria, duration of follow-up, etc.), sample processing and storage, analytical method used for the determination of Lp(a) levels, and the statistical procedures used in the evaluation of the data have all played a potential role in the accumulation of conflicting results in the role of Lp(a) as a risk factor for CHD [10]. One important factor contributing to the lack of comparability of data obtained in different studies is the influence of apo(a) size on the immunochemical determination of Lp(a) values [15]. The strength of our study is that we have used a well-characterized ELISA to measure Lp(a) values that has been demonstrated to be unaffected by apo(a) size polymorphism, thus enabling us to report the results in nanomoles per liter [15]. Another strength is that apo(a) isoforms were also determined in our cohort using a high-resolution phenotyping method [5]. Therefore, it is unlikely that technical artifacts played a role in our study. Additionally, the rate of restenosis in our population (39%) was very similar to that reported in the literature [18], and both the distribution of Lp(a) concentration and the distribution of apo(a) isoforms were very similar to those observed in a large white American cohort [24]. thus minimizing the likelihood of patient selection bias.

In addition to the list of factors [10] that may explain the conflicting results on the predictive role of high Lp(a) levels in atherosclerosis and in thrombotic events, it needs to be added, as postulated by Scanu [25], that the action of Lp(a) at the cell surface may be related to focal events rather than to the Lp(a) level in plasma. Owing to the retention of Lp(a) in the intima, the effective concentration of apo(a) in localized regions of vascular injury may be manyfold higher than in plasma. This may explain why several studies have failed to demonstrate a relationship between plasma Lp(a) levels and various fibrinolytic parameters [26].

In conclusion, based on the results of our study, Lp(a) levels and apo(a) size do not appear to be useful parameters for identifying individuals who are at increased risk for restenosis after PTCA. To elucidate the relationship between Lp(a), thrombosis, and atherosclerosis, further studies are required using approaches which assess specifically the role of apo(a)/Lp(a) in the intimal milieu and which also address the role of apo(a) size heterogeneity in these processes.

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