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Elevated Plasma Lipoprotein(a) Is Associated With Coronary Artery Disease in Patients With Chronic Stable Angina Pectoris

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Objectives. **We sought to assess the relation between plasma lipoprotein(a) [Lp(a)] levels, clinical variables and angiographic coronary artery disease (CAD) in patients with chronic stable angina.**

Background. **The relation between plasma Lp(a) levels and the severity and extent of angiographic CAD has not been studied in well characterized patients with stable angina pectoris.**

Methods. **We investigated clinical variables, lipid variables and angiographic scores in 129 consecutive white patients (43 women) undergoing coronary angiography for chronic stable angina.**

Results. **Plasma Lp(a) levels were significantly higher in patients with than in those without significant angiographic stenoses (≥70%) (372 mg/liter [interquartile range 87 to 884] vs. 105 mg/liter [interquartile range 56 to 366], respectively, p = 0.002). This difference remained significant when patients with mild or severe angiographic disease were compared with those with completely normal coronary arteries (312 mg/liter [interquartile range 64 to 864] vs. 116 mg/liter [interquartile range 63 to 366], respectively, p = 0.02). However, subset analysis indicated that this difference achieved statistical significance only in women. Multiple logistic regression analysis indicated that Lp(a) concentration was independently predictive of significant angiographic stenoses (adjusted odds ratio [OR] 9.1, 95% confidence interval [CI] 2.0 to 42.1, p = 0.006) and remained true even after exclusion of patients receiving lipid-lowering treatment (n = 27) (OR 10.4, 95% CI 1.1 to 102.9, p = 0.05). Lp(a) also had independent predictive value in a similar analysis using mild or severe angiographic disease as the outcome variable (OR 11.8, 95% CI 1.5 to 90.8, p = 0.02).**

Conclusions. **Our results indicate that elevated plasma Lp(a) is an independent risk factor for angiographic CAD in chronic stable angina and may have particular significance in women.**

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Apolipoprotein(a) [apo(a)] is a hydrophilic glycoprotein that shows a remarkable homology with plasminogen (1). It acts as a competitive inhibitor of tissue-type plasminogen activator (2–4) and inhibits generation of the thrombolytic enzyme plasmin (5). Lipoprotein(a) [Lp(a)] is a macromolecular complex found in human plasma that is composed of low density lipoprotein (LDL) and apo(a). Some investigators (4) have proposed that Lp(a) may represent a link between the atherosclerotic and thrombotic manifestations of coronary artery disease (CAD). Lp(a) levels are highly heritable (6), and it has been shown (7) that excess plasma Lp(a) is the most frequent lipoprotein disorder in families with premature CAD. Raised plasma Lp(a) also correlates with a history of previous myocardial infarction (MI) (8,9) and is an independent risk factor for subsequent MI or cardiac death (10–14). Nevertheless, uncertainty still exists regarding the relation between plasma Lp(a) and angiographically defined CAD. Some studies have indicated an association between plasma Lp(a) levels and angiographic disease severity (15–18), but others have failed to confirm these findings (19,20). This controversy may be due to the lack of data regarding clinical status and coronary risk factors in many such studies. Furthermore, women have frequently been underrepresented, limiting the potential for analysis of potentially important gender-specific differences. In the present study, we measured plasma Lp(a) levels in a consecutive series of well characterized white men and women undergoing coronary angiography for the assessment of chest pain consistent with chronic stable angina. This approach enabled us to perform a careful investigation of the relation between Lp(a) levels, CAD severity and other clinical variables in men and women.

Methods

Patients. Over 4-month period (December 1995 through March 1996), we studied 129 white patients (43 women) from a consecutive series of 198 patients with chest pain undergoing diagnostic coronary angiography for investigation of chest pain consistent with chronic stable angina. *Chronic stable angina* was defined as typical exertional chest pain relieved either by rest or sublingual nitrates, or both, and with no change in symptoms in the preceding 3 months. Nonwhite patients were not

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Abbreviations and Acronyms

apo(a) = apolipoprotein(a)
CAD = coronary artery disease
CI = confidence interval
FATS = Familial Atherosclerosis Treatment Study
HDL = high density lipoprotein
LDL = low density lipoprotein
Lp(a) = lipoprotein(a)
MI = myocardial infarction
OR = odds ratio

included because of the potential confounding influence of interracial differences. Patients with the following characteristics were also excluded: significant valvular heart disease (n = 30); previous coronary artery bypass graft surgery (n = 17); MI within the previous 3 months (n = 6); cancer (n = 1); end-stage renal failure (n = 2); and participation in other research studies (n = 14). Clinical details, including previous MI, conventional risk factors for CAD (smoking, hypertension, family history of premature cardiovascular disease, diabetes, hyperlipidemia), menopausal status in women, drug therapy, blood pressure, height and weight were recorded for all patients. No patient was receiving niacin therapy, which has been shown (21) to significantly reduce Lp(a) levels.

Analysis of serum Lp(a) levels. Venous blood samples were collected from patients in the fasting state immediately before angiography. Plasma and serum were stored at −70°C (for <3 months) for subsequent analysis for Lp(a) levels and full lipid profile. Lp(a) was measured by a rate nephelometric method using the Beckman Array 360. The sample was diluted in Apodiluent and centrifuged before loading on the Array. The prediluted sample was mixed with rabbit anti-human antibody (Dako, Denmark). According to standard practice, the amount of light scattered is measured by nephelometry, and the scatter signal is converted to a maximal rate of light scatter or light units. As the antigen concentration increases, the maximal rate of light scatter increases. Lp(a) concentration was calculated from rate units by drawing a standard curve and interpolating the Lp(a) concentration. Within-match precision for the rate nephelometric method was 1.5% and 1.2% at Lp(a) values of 158 and 343 mg/liter, respectively (n = 10 in each case). Overall precision was 6% (mean 166 mg/liter, coefficient of variation 6.1% [n = 33]; mean 343 mg/liter, coefficient of variation 5.6% [n = 32], respectively). This precision is in accord with that reported for other automated nephelometric methods (22) and compares favorably with that recently reported for Lp(a) measurements using an ELISA method (23). The Lp(a) results from the Array method also agreed well with the results obtained by an immunozyme ELISA (Deming's regression: y [Array] = 0.96 [ELISA] −2.1, correlation coefficient 0.936 [n = 68]). Total cholesterol and triglyceride levels were measured by conventional enzymatic methods. High density lipoprotein (HDL) cholesterol was measured by dextran sulfate and magnesium chloride precipitation of LDL cholesterol, followed by cholesterol analysis of the supernatant using the model 12 Monarch centrifuge analyzer. LDL cholesterol was determined using the Friedewald formula.

Coronary angiographic analysis. Diagnostic coronary arteriography was carried out using the Judkins technique in all patients. The right and left coronary arteries were selectively imaged according to standard views with at least two orthogonal projections of any stenotic segments. Angiographic scoring (see later) of each vessel segment was based on the severity and extent of disease observed in the "most severe" projection, as is customary in such studies (24,25). Additional nitrate therapy was not administered routinely before imaging, although 70% of study patients were receiving oral nitrate therapy. Each angiogram was analyzed independently by two experienced cardiologists (R.S., J.C.K.) in blinded manner with regard to clinical and laboratory data. Analysis was performed according to the vessel and extent of disease scoring system previously described by Sullivan et al. (26) and utilized in other similar studies examining the role of Lp(a) in CAD (18). In summary, the severity and extent of CAD was assessed as follows.

Vessel score. Vessel score ranged from 0 to 3 according to the number of major epicardial vessels (left anterior descending, left circumflex and right coronary arteries) with significant stenoses (≥70% lumen diameter stenosis). The left main stem was regarded as one vessel. Stenosis of the left main stem and left anterior descending or left circumflex coronary artery, or both, was counted as two points.

Extent score. The length proportion (0 to 1.0) of each vessel segment involved by any angiographically visible atheroma was estimated and multiplied by a predefined weighting factor as follows: left main stem = 5; left anterior descending coronary artery = 20; main diagonal branch = 10; first septal perforator = 5; left circumflex coronary artery = 20; obtuse marginal and posterolateral vessels = 10; right coronary artery = 20 and main posterior descending artery = 10. If the major vessel supplying the lateral ventricular wall was a large obtuse marginal or intermediate vessel, a weighting factor of 20 was applied to the marginal/intermediate branch and 10 to the left circumflex artery. When a vessel was occluded and the distal segments were not filled by collateral flow, the mean extent score of the remaining vessel was assigned to the unvisualized segment or segments. The scores for each vessel or branch were added to give a total score up to a maximum of 100, representing the estimated percent of atheromatous involvement of the intimal coronary surface. For each scoring system, the mean of the scores from the two observers was used for analysis. For the purpose of analysis, the presence of angiographically detectable CAD was defined by an extent score >0. The interobserver variability (the standard deviation of the mean unsigned difference between paired estimates) for the extent score in this study was 4.7%.

Statistical analysis. Baseline characteristics of the study cohort were compared using the chi-square test. Lp(a) data were expressed as median (interquartile range) because of the known skewed distribution of these levels. Other data are

Table 1. Clinical Features of Study Groups

	Men (n = 86)	Women (n = 43)
Age (yr)	60 ± 10	62 ± 10
Previous MI	37%	14%
CCS class		
I	19%	10%
II	63%	64%
III	19%	26%
SBP (mm Hg)	135 ± 22	136 ± 22
DBP (mm Hg)	78 ± 13	77 ± 16
Hypertension	19%	22%
Family history of premature CAD	33%	62%
Smoking history		
Current smoker	12%	7%
Ex-smoker	70%	55%
Nonsmoker	19%	38%
Previous CVA or PVD	7%	9%
BMI (kg/m^2)	26.0 ± 3.5	27.0 ± 4.9

Data presented are mean value ± SD or percent of patients. BMI = body mass index; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; DBP = diastolic blood pressure; CVA = cerebrovascular disease; MI = myocardial infarction; SBP = systolic blood pressure.

expressed as mean value ± SD. The Mann-Whitney *U* test was used for two-group comparison of Lp(a), total cholesterol, LDL cholesterol and triglyceride concentrations. An overall test for differences between groups of patients classified according to coronary angiographic disease score was performed using the Kruskall-Wallis test; pairwise comparisons were not performed. Multivariate logistic regression analyses were performed using SAS Release 6.03. The same predictor variables (i.e., age, gender, hypertension, smoking and lipid parameters [Lp(a), LDL, HDL and triglycerides]) were used in all logistic models without stepwise selection. The dependent variable was either angiographic CAD or extent score (see earlier). The analysis was performed with inclusion of all patients (n = 129) and then repeated with inclusion of only patients not receiving lipid-lowering therapy (n = 102). The results of the multivariate analysis are expressed as odds ratios for the comparison of risk between the 10% and 90% percentiles (with 95% confidence intervals). Significance was defined as a p value <0.05 for the null hypothesis.

Table 2. Distribution of Coronary Scores

	No. (%) of Patients
Vessel score*	
0	48 (37.2%)
1	27 (20.9%)
2	29 (22.5%)
3	25 (19.4%)
Extent score*	
0	32 (24.8%)
1–20	54 (41.8%)
21–40	33 (25.6%)
>40	10 (7.8%)

*See Methods.

Results

Clinical variables at study entry. The baseline characteristics, including level of symptoms and conventional coronary risk factors of the study cohort, were similar in men and women in most respects (Table 1). However, previous MI was more common in men than in women (chi-square 6.4, p = 0.01), and family history of premature CAD was more prevalent in women than in men (chi-square 8.8, p = 0.003). All patients were receiving at least one antianginal medication, and 21% of the whole study group were receiving lipid-lowering treatment.

Distribution of angiographic scores and serum lipids. The distribution of angiographic scores in the study cohort is summarized in Table 2. Forty-eight patients (37%) had no significant coronary stenosis (≥70%), as defined by a vessel score of 0; 27 patients (21%) had single-vessel disease, and the remainder (42%) had double- or triple-vessel disease. Thirty-two patients (25%) had angiographically normal coronary arteries, as defined by an extent score of 0. Serum lipid and lipoprotein concentrations in the study cohort are summarized in Table 3. Overall, the median (interquartile range) Lp(a) level was 252 mg/liter (64 to 697) (i.e., within the normal range for healthy white subjects) (4). Twenty-six patients (19%) had plasma Lp(a) concentrations below the limit of detection for the assay (<50 mg/liter). There was no significant difference between Lp(a) levels in men and women (270 mg/liter [56 to 783] vs. 242 mg/liter [77 to 653], respectively, p = 0.94). Similarly there was no significant difference in LDL levels

Table 3. Serum Lipid and Lipoprotein Levels in Study Groups

	All Patients (n = 129)	Men (n = 86)	Women (n = 43)	No CAD (n = 48) (vessel score 0)	CAD (n = 81) (vessel score ≥1)	p Value
Total cholesterol (mmol/liter)	5.7 ± 1.0	5.7 ± 1.0	5.6 ± 1.0	5.6 ± 1.0	5.7 ± 1.0	0.35
HDL cholesterol (mmol/liter)	1.0 ± 0.4	0.9 ± 0.3	1.3 ± 0.4	1.2 ± 0.4	1.0 ± 0.4	0.01
LDL cholesterol (mmol/liter)	4.0 ± 0.9	4.1 ± 0.9	3.8 ± 0.9	3.7 ± 0.8	4.2 ± 1.0	0.03
TGs (mmol/liter)	1.6 ± 1.3	1.8 ± 1.5	1.2 ± 0.6	1.4 ± 0.8	1.7 ± 1.6	0.15
Lp(a) (mg/liter)	252 (64–697)	270 (56–783)	242 (77–653)	105 (56–366)	372 (87–884)	0.002

Data presented are mean value ± SD or median (interquartile range). CAD = angiographic coronary artery disease; HDL = high density lipoprotein; LDL = low density lipoprotein; Lp(a) = lipoprotein(a); TGs = triglycerides.

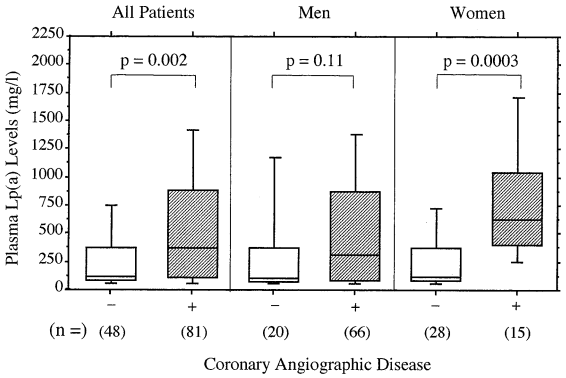

Figure 1. Plasma Lp(a) levels were significantly higher in patients with **(shaded boxes)** than in those without **(open boxes)** significant angiographic CAD. When patients were classified according to gender, this difference achieved statistical significance in women but not in men.

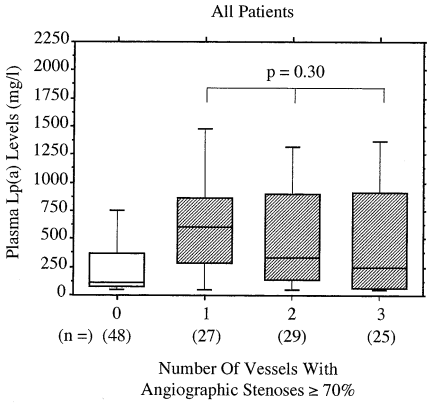

Figure 2. Subset analysis of patients with angiographic CAD according to vessel score did not indicate a significant difference between Lp(a) levels in patients with one-, two- or three-vessel disease.

between men and women. However, men had significantly higher levels of triglycerides and lower levels of HDL cholesterol than women ($p < 0.0001$ in both cases). Overall, the mean LDL level in our study group was only mildly elevated (4.0 ± 0.9 mmol/liter) but was significantly lower in patients who were receiving ($n = 27$) than in those not receiving ($n = 102$) lipid-lowering therapy (3.40 ± 0.83 vs. 4.18 ± 0.93 mmol/liter, respectively, $p = 0.0002$).

Relation between serum lipids and angiographic scores. Plasma Lp(a) levels were higher in patients with (vessel score ≥1) than in those without significant stenoses (372 mg/liter [87 to 884] vs. 105 mg/liter [56 to 366], respectively, $p = 0.002$) (Table 3, Fig. 1). Serum LDL cholesterol concentration was also significantly higher (4.2 ± 1.0 vs. 3.7 ± 0.8 mg/dl, respectively, $p = 0.03$) and HDL cholesterol levels significantly lower (1.0 ± 0.4 vs. 1.2 ± 0.4 mg/dl, respectively, $p = 0.01$) in patients with than in those without significant coronary stenosis. Further analysis using extent scores to include the effect of patients with mild angiographic disease yielded similar results. Plasma Lp(a) concentrations were significantly higher in patients with an extent score ≥1 ($n = 97$) than in those with an extent score of 0 ($n = 32$) (312 mg/liter [64 to 864] vs. 116 mg/liter [63 to 366], respectively, $p = 0.02$). Likewise, serum LDL cholesterol levels were significantly higher (4.1 ± 0.98 vs. 3.68 ± 0.84 mg/dl, respectively, $p = 0.04$) and HDL cholesterol concentrations significantly lower (0.99 ± 0.36 vs. 1.25 ± 0.46 mg/dl, respectively, $p = 0.01$) in patients with mild or severe CAD than in those with normal angiographic findings.

Gender differences in angiographic scores and plasma Lp(a) levels. The mean number of diseased vessels was higher in men than in women (1.5 ± 1.1 vs. 0.7 ± 1.0, $p < 0.0001$). Similarly, the average extent score was significantly higher in men than in women (15.5 [8 to 29] vs. 3.0 [0 to 14], respectively, $p < 0.0001$). The differences between plasma Lp(a) levels in patients with and without significant stenoses (defined by a vessel score ≥1 [Fig. 1]) appeared to be largely due to the difference observed in women (625 mg/liter [376 to 1,044] vs. 108 mg/liter [56 to 373], respectively, $p = 0.0003$). By comparison, the difference in Lp(a) levels observed in men alone failed to achieve statistical significance (320 mg/liter [60 to 875] vs. 103 mg/liter [54 to 366], respectively, $p = 0.11$). Further independent analysis of men and women using an extent score ≥1 to define the presence of angiographic CAD (i.e., including patients with mild angiographic disease) produced similar results. The difference observed in women was statistically significant (570 mg/liter [127 to 823] vs. 133 mg/liter [50 to 373], $p = 0.01$), whereas that observed in men was not (285 mg/liter [50 to 875] vs. 113 mg/liter [88 to 366], $p = 0.26$).

Extent of angiographic CAD, coronary occlusions and previous MI. Analysis of patients with significant stenoses according to vessel score (Fig. 2) demonstrated that Lp(a) levels did not differ significantly among patients with one-, two- and three-vessel disease ($p = 0.30$). Similarly, when patients with mild or severe disease (extent score ≥1) were classified into three groups according to extent of disease (1 to 20, 21 to 40, >40), there was no significant difference in Lp(a) levels between the groups ($p = 0.13$). In patients with significant angiographic CAD (vessel score ≥1), there was no significant difference in Lp(a) levels between those with ($n = 41$) and those without ($n = 40$) occlusions (415 mg/liter [109 to 1,019] vs. 350 mg/liter [76 to 785], respectively, $p = 0.63$). However, in patients with significant coronary stenoses (≥70%), a statistical trend appeared, suggesting that plasma Lp(a) levels were higher in those with ($n = 31$) than in those without ($n = 50$) a previous history of acute MI (415 mg/liter [199 to 1,023] vs. 330 mg/liter [60 to 720], respectively, $p = 0.12$). Furthermore, when angiographic CAD was defined by an extent score ≥1 (i.e., including patients with mild disease), the difference between patients with ($n = 34$) and without ($n = 63$) a previous MI achieved statistical significance (525 mg/liter [185 to 1,075] vs. 252 mg/liter [58 to 639], respectively, $p = 0.02$).

Multivariate analysis. Multiple logistic regression analysis including age, gender, hypertension, smoking and lipid variables [Lp(a), LDL, HDL and triglycerides] was performed using an extent score ≥1 to define the presence of angiographic CAD. When all patients were included in the model,

Table 4. Adjusted Odds Ratio for Risk of Patients Having Angiographic Coronary Artery Disease (extent score ≥1)*

Explanatory Variable	All Patients (n = 129)		Patients Not Receiving Lipid-Lowering Therapy (n = 102)	
	OR (CI)	p Value	OR (CI)	p Value
Lp(a)	11.8 (90.8–1.54)	0.02	4.76 (101–0.22)	0.33
TGs	0.24 (1.07–0.06)	0.06	0.12 (0.69–0.02)	0.02
LDL	2.75 (14.0–0.54)	0.23	9.99 (87.4–1.14)	0.04
HDL	0.28 (1.32–0.06)	0.11	0.20 (1.71–0.02)	0.14
Age	5.12 (25.8–1.01)	0.05	2.96 (21.2–0.41)	0.28
Female gender	0.16 (0.59–0.04)	0.01	0.10 (0.55–0.02)	0.01
Smoking	5.80 (23.0–1.46)	0.01	6.27 (29.4–1.34)	0.02
Hypertension	0.65 (2.34–0.18)	0.51	0.20 (1.21–0.03)	0.08

*Odds ratio (OR) (95% confidence interval [CI]) given to three significant figures; odds ratio for continuous variables defined according to ratio of risk between 10th and 90th percentiles.

Lp(a) concentration was the only lipid variable that achieved statistical significance as an independent predictor of CAD (Table 4). However, when patients receiving lipid-lowering therapy (n = 27) were excluded, both LDL cholesterol and triglyceride levels became significant independent predictors of CAD, and plasma Lp(a) concentration no longer achieved significance within the model. In both analyses, male gender and a history of smoking were independently predictive of CAD. A further multivariate analysis with CAD defined as the presence of any ≥50% stenosis (i.e., vessel score ≥1) yielded similar results. When all patients were included in this analysis, plasma Lp(a) concentration was the only lipid variable independently predictive for CAD [odds ratio [OR] 9.1, 95% confidence interval [CI] 2.0 to 42.1, p = 0.006). When patients receiving lipid-lowering treatment were excluded, Lp(a) concentration remained a significant predictor of CAD (OR 10.4, 95% CI 1.1 to 102.9, p = 0.05), whereas neither LDL (OR 5.3, 95% CI 0.8 to 33.4, p = 0.08) nor triglyceride level (OR 0.3, 95% CI 0.02 to 0.7, p = 0.12) achieved significance. HDL concentration was not significantly predictive of CAD as defined by vessel or extent score in any of the analyses.

Discussion

Many previous studies examining the relation between plasma Lp(a) levels and angiographic CAD have been limited because of the relative lack of clinical data and the underrepresentation of women. In the present investigation, we studied a consecutive series of well characterized white patients who had been admitted for routine coronary angiography for symptoms consistent with a diagnosis of chronic stable angina. Clinical variables, including conventional coronary risk factors, had been well characterized in all cases. Female patients were well represented (33%) in this series and had baseline clinical characteristics similar to those of the male patients.

Lp(a) and presence of angiographic CAD. The results of our study indicate that in patients with chronic stable angina, plasma Lp(a) levels are significantly higher in those with than in those without CAD. Analysis of all patients, including those receiving lipid-lowering therapy, was justified because the number of patients receiving lipid-lowering therapy in the study group was relatively small (21%), and the extent of their disease at angiography would tend to reflect the accumulated effects of their lipid environment before and after initiation of lipid-lowering therapy. Furthermore, Lp(a) levels are not substantially modified by standard lipid-lowering therapy (4). Our results are consistent with previous studies that have demonstrated an association between raised plasma Lp(a) and the presence of CAD (7,8,15–18,27–30) and highlights the atherogenic potential of Lp(a) (31). The mean LDL level in our study group was only mildly elevated but was significantly higher in patients with than in those without CAD. This difference remained significant before and after exclusion of those receiving lipid-lowering therapy. It is interesting to compare the results of our multiple regression analysis with the findings of the Familial Atherosclerosis Treatment Study (FATS) study (32), which assessed the effects of lipid-lowering interventions on angiographic disease progression in hypercholesterolemic men. The FATS results indicated that a >10% reduction of elevated plasma LDL levels offset the proatherogenic effects of raised Lp(a) levels, even when the latter remained unmodified. Conversely, plasma Lp(a) concentration remained strongly correlated with angiographic progression in patients with ≤10% reduction in plasma LDL levels. The mean LDL level in our study group was relatively low compared with that in the FATS study (4.0 ± 0.9 vs. 5.0 ± 1.2 mmol/liter, respectively) (32). In our study, plasma LDL levels were significantly lower in patients with (n = 27) than in those without (n = 102) lipid-lowering therapy (3.4 ± 0.8 vs. 4.2 ± 0.9 mmol/liter, respectively, p = 0.0002). Our multiple logistic regression analysis including all patients indicated that Lp(a) level was the only lipid variable that was an independent risk factor for the presence of any angiographic disease (extent score ≥1). This finding is consistent with a similar analysis of baseline disease severity performed in the FATS study (32). However, after exclusion of patients receiving lipid-lowering therapy, both LDL cholesterol and triglyceride levels became significant predictors of angiographic CAD within our model,

whereas Lp(a) was no longer significant. Although at first glance this finding appears to conflict with the results of the FATS trial, the outcome variable in our analysis was the presence or absence of angiographic disease compared with angiographic disease progression in the FATS trial. Furthermore, plasma LDL levels in our patients receiving lipid-lowering therapy had been elevated before the initiation of therapy, and most had been receiving lipid-lowering therapy for <1 year. With this in mind, our findings are consistent with the conclusion of the FATS investigators (32) that the proatherogenic potential of Lp(a) may be dependent on synergism with elevated plasma LDL cholesterol levels. Nevertheless, further multivariate analysis, including only those patients with angiographic stenoses ≥70% (i.e., excluding patients with mild disease), indicated that Lp(a) levels remain an independent predictor of CAD even after the exclusion of patients receiving lipid-lowering therapy. This finding suggests that high Lp(a) levels may independently contribute to the evolution of severe angiographic stenoses.

Plasma Lp(a), extent of angiographic CAD and presence of coronary occlusions. The results of our investigation did not indicate any significant difference between plasma Lp(a) levels in subsets of patients with significant CAD classified according to the number of diseased vessels or the extent of angiographic disease. These findings are in agreement with those of other investigators (19,20) who failed to demonstrate a correlation between Lp(a) levels and angiographic vessel score. We also found that in patients with ≥70% angiographic stenoses, there was no significant difference in Lp(a) levels between those with and without coronary occlusions. However, a strong statistical trend was demonstrated, suggesting that Lp(a) levels were higher in patients with CAD and a previous MI than in those with CAD but no previous MI. When this analysis was repeated using an extent score ≥1 to define CAD (i.e., including patients with mild disease), the difference between patients with and without an acute MI achieved full statistical significance ($p = 0.02$). These findings indicate that in addition to the positive relation between Lp(a) levels and angiographic CAD, a relation also exists between Lp(a) levels and the incidence of MI. This concept suggests that high Lp(a) levels may predispose to plaque disruption and thrombogenesis—the pathogenetic basis of MI. These findings are also in agreement with previous studies (8,15,16) that indicated that raised plasma Lp(a) levels correlate with a history of previous MI. Prospective studies have also suggested that elevated Lp(a) levels are a risk factor for subsequent MI (10–14), although other studies (33,34) have failed to confirm these findings.

Lp(a) as a risk factor in women. Our data indicated that the difference between Lp(a) levels in patients with and those without angiographic CAD was largely due to the difference observed in women. This finding is consistent with those of Stiel et al. (20) and supports the existence of important gender differences with regard to Lp(a) and CAD. Few other studies have analyzed the relation between CAD and Lp(a) levels in women. Interestingly, Labeur et al. (16) in a study of 1,054 patients, including 323 women, also observed a significant multivariable adjusted odds ratio for the presence of CAD in women but not men. Therefore, it appears that Lp(a) plasma levels may have particular significance with regard to the evolution of CAD in women.

Pathogenic mechanisms by which Lp(a) may contribute to the evolution of angiographic CAD and MI. Our findings suggest that high Lp(a) levels predispose to the evolution of CAD and MI, although the exact mechanisms remain speculative. Lp(a) can transverse the endothelium and accumulate in the arterial intima (35), where it may be taken up by macrophages (36). By virtue of its marked homology with plasminogen (2), apo(a) interacts directly with plasminogen binding sites, thereby interfering with the fibrinolytic process (3,37). Studies in transgenic mice models expressing apo(a) have demonstrated that apo(a) inhibits plasminogen activation in vivo (38). This result is consistent with the known association between high Lp(a) levels, clot formation and impaired spontaneous thrombolysis (1,3). Inhibition of plasminogen activation blocks the plasmin-dependent activation of transforming growth factor-beta (39), an autocrine inhibitor of vascular smooth muscle cell proliferation. These phenomena may represent the mechanisms whereby raised Lp(a) predisposes to atherosclerotic CAD and MI.

Conclusions. The results of our study indicate that elevated plasma Lp(a) is an independent risk factor for angiographic CAD and MI in patients with chronic stable angina and may have particular significance in women.

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