

Role of Lipoprotein(a) and Apolipoprotein(a) Phenotype in Atherogenesis

Prospective Results From the Bruneck Study

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Background—Experimental studies have suggested both atherogenic and thrombogenic properties of lipoprotein(a) [Lp(a)], depending on Lp(a) plasma concentrations and varying antifibrinolytic capacity of apolipoprotein(a) [apo(a)] isoforms. Epidemiological studies may contribute to assessment of the relevance of these findings in the general population.

Methods and Results—This study prospectively investigated the association between Lp(a) plasma concentrations, apo(a) phenotypes, and the 5-year progression of carotid atherosclerosis assessed by high-resolution duplex ultrasound in a random sample population of 826 individuals. We differentiated early atherogenesis (incident nonstenotic atherosclerosis) from advanced (stenotic) stages in atherosclerosis that originate mainly from atherothrombotic mechanisms. Lp(a) plasma concentrations predicted the risk of early atherogenesis in a dose-dependent fashion, with this association being confined to subjects with LDL cholesterol levels above the population median (3.3 mmol/L). Apo(a) phenotypes were distributed similarly in subjects with and without early carotid atherosclerosis. In contrast, apo(a) phenotypes of low molecular weight emerged as one of the strongest risk predictors of advanced stenotic atherosclerosis, especially when associated with high Lp(a) plasma concentrations (odds ratio, 6.4; 95% CI, 2.8 to 14.9).

Conclusions—Lp(a) is one of the few risk factors capable of promoting both early and advanced stages of atherogenesis. Lp(a) plasma concentrations predicted the risk of early atherogenesis synergistically with high LDL cholesterol. Low-molecular-weight apo(a) phenotypes with a putatively high antifibrinolytic capacity in turn emerged as one of the leading risk conditions of advanced stenotic stages of atherosclerosis. (*Circulation*. 1999;100:1154-1160.)

Key Words: atherosclerosis ■ apolipoproteins ■ lipoproteins ■ genetics ■ carotid arteries

Lipoprotein(a) [Lp(a)] consists of 2 components, an LDL particle and an attached apolipoprotein(a) [apo(a)]. The complex structure may explain its atherogenic and thrombogenic properties.¹ Lp(a) is believed to contribute to lipid-induced atherogenesis similarly to LDL particles.² Compared with LDL, however, it contains lower amounts of antioxidants and exhibits a high affinity to extracellular matrix and fibrin(ogen),³⁻⁵ which prolongs residence time in the subintima. Both properties of Lp(a) facilitate its oxidative modification and may enhance its capacity to cause injury.

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Effects on coagulation in turn derive from a high sequence homology of apo(a) with plasminogen.⁶ Lp(a) competes with plasminogen for binding to plasminogen receptors, fibrinogen, and fibrin,^{4,5} as well as other cellular binding sites,^{7,8} but lacks plasmin-like activity. Furthermore, it interferes with

plasminogen activation by inhibition of the tissue plasminogen activator⁹ and by itself enhances the expression of plasminogen activator inhibitor 1.¹⁰ In vitro studies on the thrombogenic nature of Lp(a) suggested that this property is defined primarily by the particle size of apo(a) and only secondarily by the Lp(a) concentration.¹¹⁻¹³ In other words, the same Lp(a) concentrations may be associated with a markedly different atherothrombotic risk, depending on the apo(a) isoform.

Epidemiological studies may help to assess the relevance of these in vitro findings in vivo and for the general population. The current prospective population study attempts to clarify the complex association between Lp(a) and carotid atherosclerosis, with special attention directed to possible differential effects of the apo(a) components of various sizes on different stages of atherosclerotic disease. Interpretation of most previous surveys on this issue is

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complicated by highly selected study populations, cross-sectional study design, and/or lack of consideration of apo(a) phenotypes.

Methods

Study Population

The study design and survey area have been described in detail previously.¹⁴ At study entry (year 1990), the study population was composed of an age- and sex-stratified random sample of all inhabitants of Bruneck (Bolzano Province, Italy) 40 to 79 years old (125 women and 125 men in each of the fifth to the eighth decades). There was a participation of 93.6% among individuals invited and complete data assessment in 919 subjects. During the 5-year follow-up period between summer 1990 and summer 1995, 62 individuals died and 1 subject moved away and could not be traced. Follow-up rate was 99.9% with regard to clinical end points ($n=918$) and 96.5% for sonographic reassessment of survivors ($n=826$). All participants gave informed consent before enrollment in the study.

Scanning Protocol and Definition of Ultrasound End Points

The internal (bulbous and distal segments) and common (proximal and distal segments) carotid arteries were scanned by ultrasound on either side with a 10-MHz imaging probe and a 5-MHz Doppler probe.¹⁴ Atherosclerotic lesions were identified by 2 ultrasound criteria: (1) wall surface (protrusion into the lumen or roughness of the arterial boundary) and (2) wall texture (echogenicity). The maximum radial diameter of plaques was assessed in each of the 8 vessel segments, with the ultrasound beam directed through the center of the vessel (for details see References 15 through 19). Scanning was performed twice, namely in 1990 and 1995, by the same experienced sonographer, who was blinded to the subjects' clinical and laboratory characteristics. On the basis of the follow-up evaluation, 2 epidemiologically and etiologically different stages of atherogenesis were differentiated: (1) early atherogenesis was defined by the occurrence of new plaques in previously normal segments, and (2) advanced atherogenesis was assumed whenever the relative increase in the maximum plaque diameter between 1990 and 1995 exceeded the double measurement error of the method (distal internal carotid artery, 35%; bulbous, 30%; common carotid artery, 20%) and a narrowing of the lumen (stenosis) >40% occurred. As detailed elsewhere,^{18,19} the cutoff of 40% appeared to be a biological threshold in our population, at which marked changes in the growth kinetics of plaques, in the risk profiles, and in the vascular remodeling process occurred.

Our ultrasound progression model (person-based approach) was developed and validated before the present study was carried out.^{18,19}

Clinical Evaluation and End Points

All participants underwent a complete clinical examination, with cardiologic and neurological priorities described recently in detail.¹⁴ Cardiovascular disease (CVD) end points during follow-up were fatal and nonfatal myocardial infarction according to the World Health Organization criteria for definite disease status²⁰ and ischemic stroke and transient ischemic attack according to the criteria of the National Survey of Stroke.²¹ Self-reported data were verified from hospital records, death certificates, and information from general practitioners and supplemented by a thorough screening of the regional hospital database for diseases of interest.

Laboratory Measurements

At the 1990 baseline investigation, blood samples were taken from the antecubital vein after subjects had fasted and abstained from smoking for ≥ 12 hours. Lp(a) was measured by a double-antibody ELISA (Immuno) using a polyclonal anti-apo(a) for capture and a monovalent anti-apo(a) Fab fragment coupled with peroxidase for detection. The interassay coefficients of variation were 3.5%, 4.6%,

and 6.3% for Lp(a) concentrations of 5, 16, and 54 mg/dL, respectively.

Apo(a) phenotyping was performed by sodium dodecyl sulfate-agarose gel electrophoresis (SDS agarose)²² under reducing conditions, as previously outlined.²³ Laboratory investigators were unaware of patient histories and outcomes.

As for most of the Lp(a) assays, we cannot rule out that the assay we used measured apo(a) isoform-dependently. To test whether this could have influenced our major findings, we repeated the same calculations as presented in the Results section simulating "corrected" Lp(a) levels. Because we used as a reference standard a plasma sample with the same apo(a) isoform as a recent study comparing an isoform-dependent with an isoform-independent assay,²⁴ we were justified in correcting the Lp(a) level of each subject by dividing it by the ratio of these 2 assays (see Reference 24) for each single apo(a) isoform group. In the case of subjects expressing 2 apo(a) isoforms, we first estimated the relation of the 2 isoforms in the SDS agarose electrophoresis and calculated the corresponding amount of Lp(a) for each isoform. These 2 concentrations were divided by the published ratios²⁴ and then finally added again.

LDL cholesterol was calculated by the Friedewald formula, correcting for the contribution of Lp(a) cholesterol.²⁵

Statistical Procedures

Strength and type of association between Lp(a) plasma concentration/apo(a) phenotype and progression of atherosclerosis were assessed by logistic regression analysis. To assess distinct effects of Lp(a) on various stages in atherogenesis, separate equations were fitted for subjects without carotid atherosclerosis at the 1990 baseline (no atherosclerosis versus incident atherosclerosis during follow-up) and in those with preexisting lesions (no change versus incidence of stenotic atherosclerosis). Multivariate regression models were built with a forward stepwise selection procedure that allowed for all variables listed in Table 1. On the basis of experiences from previous cross-sectional analyses in this cohort,²⁵ Lp(a) concentrations were dichotomized [$Lp(a) \leq 32$ versus >32 mg/dL] or treated as a continuous variable. Likewise, apo(a) phenotypes were divided into 2 subgroups a priori according to the molecular weight of the smaller apo(a) isoforms. In analogy to all of our own and some other previous work,²⁶⁻²⁹ the low-molecular-weight (LMW) group included subjects with ≥ 1 apo(a) isoform with 11 to 22 kringle (K)-IV repeats,²³ and the high-molecular-weight (HMW) group comprised all subjects who had only isoforms with >22 K-IV repeats. In an attempt to confirm the appropriateness of these preselected categorizations, separate analyses were fitted with 6 equally sized categories of Lp(a) concentrations (range, 8 mg/dL each) or K-IV repeats (steps, 3 repeats each) (scale fitting). Separate equations that excluded subjects receiving aspirin, anticoagulation, or antihypertensive or lipid-lowering therapy (in all, $n=280$) or adjusted for lifestyle variables confirmed the results of the original analysis (data not presented). Statistical interaction between Lp(a) and other variables (eg, LDL cholesterol) was assessed by comparing the relation between Lp(a) and atherosclerosis progression at different levels of exposure to the variable of interest. Finally, crude and adjusted hazard ratios of incident CVD were calculated by Cox models. The proportional hazard assumptions were satisfied.

Results

The median Lp(a) level in this white population was 8.8 mg/dL (range, 0.1 to 143.2 mg/dL). Plasma concentrations were similar in men and women except for a slight divergence in the postmenopausal period. Lp(a) plasma concentration emerged as independent of all other vascular risk factors and lifestyle variables.²⁵

Early Atherogenesis

Five hundred individuals were free of carotid atherosclerosis at the 1990 baseline examination. A quarter of these individ-

TABLE 1. Baseline Age- and Sex-Adjusted Characteristics of the Study Population According to 5-Year Changes of Carotid Atherosclerosis

Characteristic	No Atherosclerosis at 1990 Baseline (n=500)		Preexisting Atherosclerosis at 1990 Baseline (n=326)	
	Early Atherogenesis		Advanced Atherogenesis	
	No (n=375)	Yes (n=125)	No (n=234)	Yes (n=92)
Age, y	51.4±8.8	57.4±9.7‡	64.9±9.2	67.8±8.0*
Male sex, n (%)	156 (41.6)	73 (58.4)‡	125 (53.4)	60 (65.2)
Diabetes mellitus, n (%)	10 (2.7)	8 (6.4)	19 (8.1)	21 (22.8)‡
Systolic blood pressure, mm Hg	137.4±17.7	144.5±20.1*	151.7±21.7	158.0±22.4*
Hypertension, n (%)	61 (16.3)	47 (37.6)‡	89 (38.0)	47 (51.1)*
Cigarette smoking, n (%)				
Lifelong nonsmoker	227 (60.5)	63 (50.4)	132 (56.4)	35 (38.0)‡
Ex-smoker	63 (16.8)	30 (24.0)	59 (25.2)	23 (25.0)
Current smoker	85 (22.7)	32 (25.6)	43 (18.4)	34 (37.0)
Regular alcohol intake, n (%)				
Abstainer	197 (52.5)	50 (40.0)†	114 (48.7)	42 (45.7)*
1–50 g/d	134 (35.7)	37 (29.6)	60 (25.6)	15 (16.3)
51–99 g/d	33 (8.8)	29 (23.2)	37 (15.8)	17 (18.5)
≥100 g/d	11 (3.0)	9 (7.2)	23 (9.8)	18 (19.6)
Fibrinogen, g/L	2.44±0.52	2.65±0.69	2.70±0.60	2.93±0.63†
Antithrombin III, %	98.7±12.7	98.8±14.2	96.3±13.0	92.8±16.4*
Factor V Leiden mutation, n (%)	14 (3.7)	2 (1.6)	5 (2.1)	7 (7.6)*
Ferritin, μg/L	109.9±115.4	190.1±195.0‡	165.8±178.2	208.9±222.8
Total cholesterol, mmol/L	5.54±0.94	5.95±1.04‡	5.87±1.08	6.21±1.28
HDL cholesterol, mmol/L	1.48±0.34	1.41±0.34*	1.46±0.35	1.39±0.40
LDL cholesterol, mmol/L	3.59±0.90	3.75±0.97‡	3.71±1.01	3.98±1.21*
Lp(a), median (IQR), mg/dL	7.6 (4.0–19.6)	9.1 (4.8–25.9)*	7.9 (4.3–24.4)	10.7 (4.8–25.3)†

Values are mean±SD except for Lp(a), which is presented as median (interquartile range, IQR).

* $P<0.05$, † $P<0.01$, ‡ $P<0.001$ are age- and sex-adjusted P values for comparison of subjects with vs without early atherogenesis (incident plaques) and with vs without advanced atherogenesis (incident stenosis).

uals (n=125) developed atherosclerotic lesions during the 5-year follow-up period. These patients with incident atherosclerosis (early atherogenesis) were older, more often male, hypertensive, smokers, and heavy drinkers and had higher ferritin and total and LDL cholesterol concentrations than those who remained free of atherosclerosis (Table 1).

Lp(a) plasma concentrations were higher in subjects who developed new atherosclerotic lesions (Table 1). After adjustment for other vascular risk factors and potential confounders, Lp(a) was significantly associated with early atherogenesis in subjects with LDL cholesterol concentrations above the median of 3.3 mmol/L (Table 2) but not in the low-LDL-cholesterol group ($P<0.05$ for effect modification). The risk of early atherogenesis in the high-LDL-cholesterol group increased gradually with increasing Lp(a) concentration (dose-response relation, Figure 1). In contrast, apo(a) phenotype expressed as the absolute number of K-IV repeats did not show a significant association with early atherogenesis, nor did predefined categories of LMW and HMW apo(a) types. This finding applied to subjects with LDL cholesterol concentrations ≥ 3.3 mmol/L and < 3.3 mmol/L (Figure 1 and Table 2).

Exclusion of patients with a neoplasm, renal failure, or manifest CVD yielded results almost identical to those of the original analysis. Use of Lp(a) levels corrected for a simulated apo(a) isoform-dependent measurement of Lp(a) revealed nearly the same odds ratios as described in Table 2.

TABLE 2. Association of Lp(a) Plasma Concentrations and Apo(a) Phenotypes With Early Atherogenesis (Incident Atherosclerosis)

Variable	n	OR (95% CI)	P
Lp(a)*	500	1.06 (0.96–1.17)	0.240
Lp(a)			
LDL ≥ 3.3 mmol/L*	248	1.21 (1.03–1.41)	0.019†
LDL < 3.3 mmol/L*	252	0.95 (0.81–1.10)	0.497†
LMW/HMW apo(a) phenotype	500	1.16 (0.71–1.89)	0.886
Number of K-IV repeats	500	1.01 (0.96–1.07)	0.595

ORs were derived from stepwise multivariate logistic regression analysis (selected covariates: age, ferritin, LDL cholesterol, hypertension, smoking, and alcohol consumption). This analysis focused on subjects free of carotid atherosclerosis at the 1990 baseline.

*ORs were calculated for an 8-mg/dL increase in Lp(a) concentration.

† $P<0.05$ for effect modification.

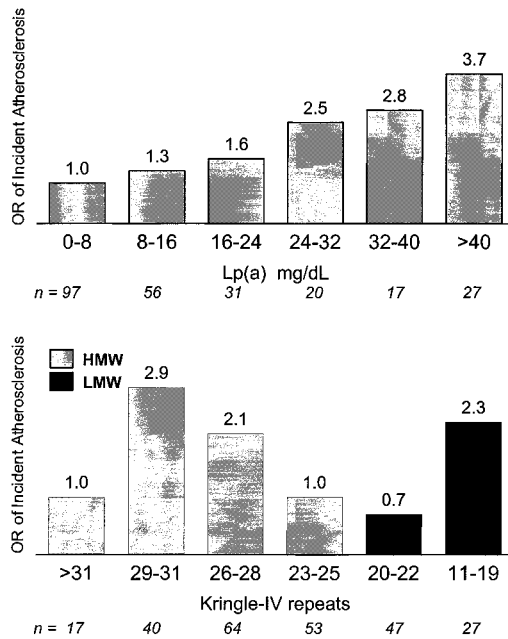


Figure 1. Risk of incident atherosclerosis (early atherogenesis) according to categories of Lp(a) concentrations and apo(a) phenotypes in subjects without atherosclerosis at 1990 baseline and LDL cholesterol levels ≥ 3.3 mmol/L ($n=248$). Graph demonstrates a linear-type association for Lp(a) concentrations ($P=0.01$ for linear trend), whereas apo(a) phenotypes were unrelated to risk of incident atherosclerosis. ORs were derived from multivariate logistic regression analysis (adjusted for covariates age, ferritin, LDL, hypertension, smoking, and alcohol consumption). n indicates number of subjects in each category.

Advanced Atherogenesis

Of 326 subjects with preexisting carotid artery disease at the 1990 baseline examination, 92 (28.2%) developed carotid stenosis $>40\%$ (advanced atherogenesis) during follow-up. These subjects were more often diabetic, smokers, and carriers of the factor V Leiden mutation and had higher fibrinogen and lower antithrombin III than those who remained free of advanced atherosclerosis (Table 1). Lp(a) plasma concentrations were significantly elevated in those with advanced atherogenesis (Table 1), and LMW apo(a) phenotypes were markedly overrepresented (50% versus 32.9%, $P<0.01$; Table 3).

Stepwise logistic regression analysis revealed a binary-type association between advanced atherogenesis and high Lp(a) plasma concentrations. Analogous results were obtained for LMW apo(a) phenotypes (Figure 2). These associations were not modified by LDL cholesterol levels. When both Lp(a) concentration and apo(a) phenotype were considered in a single regression equation, excess risk of stenosis was confined to the LMW apo(a) phenotype and was most pronounced in those with both LMW apo(a) phenotype and high Lp(a) plasma concentrations (OR, 6.4; 95% CI, 2.8 to 14.9; Figure 3 and Table 4). The risk profile of advanced atherogenesis further included diabetes, smoking, low antithrombin III, high fibrinogen level, factor V mutation, alcohol consumption, and age. Again, the above results remained virtually unchanged after subjects with neoplasms, renal failure, and CVDs had been excluded. Using Lp(a) levels corrected for a simulated apo(a) isoform-dependent measure-

TABLE 3. Apo(a) Size Polymorphism of the Study Population According to the 5-Year Incidence of the Carotid Stenosis $>40\%$ (Advanced Atherogenesis)

Characteristic	Incident Stenosis in Subjects With Preexisting Atherosclerosis	
	No ($n=234$)	Yes ($n=92$)
Apo(a) alleles, n (%) [*]		
11–19 K-IV repeats	23 (9.8)	12 (13.0)
20–22 K-IV repeats	54 (23.1)	34 (37.0)
23–25 K-IV repeats	38 (16.2)	8 (8.7)
26–28 K-IV repeats	57 (24.4)	21 (22.8)
29–31 K-IV repeats	39 (16.7)	8 (8.7)
>31 K-IV repeats	23 (9.8)	9 (9.8)
Apo(a) phenotypes [†]		
LMW apo(a) phenotypes, n (%)	77 (32.9)	46 (50.0)
HMW apo(a) phenotypes, n (%)	157 (67.1)	46 (50.0)

^{*}Likelihood ratio χ^2 test comparing the frequencies of apo(a) alleles of patients with and those without carotid atherosclerosis: $\chi^2=11.3$, $df=5$, $P<0.05$.

[†]Pearson's χ^2 test comparing the frequencies of LMW apo(a) phenotypes of patients with and those without carotid atherosclerosis: $\chi^2=8.2$, $df=1$, $P<0.01$.

ment resulted in only minor changes of the odds ratios without changing the quintessence.

Cardiovascular Disease

What has been described for advanced carotid atherosclerosis applied equally to clinical CVD ($n=64$). Lp(a) concentrations conferred an increased risk of fatal and nonfatal CVD only in subjects with LMW apo(a) phenotypes. Within this group, the risk for incident CVD increased further when Lp(a) concentration exceeded the cutoff of 32 mg/dL (Table 4).

Discussion

The present population study may well be the first to systematically and prospectively investigate the influence of Lp(a) plasma concentrations and apo(a) phenotypes on carotid atherosclerosis. The study design permits us to differentiate early from advanced (stenotic) stages of atherogenesis. Notably, the latter process did not rely on conventional risk factors but emerged as a domain of procoagulant risk attributes and most likely arises from plaque thrombosis.^{18,19} This 2-stage hypothesis is substantiated by pathoanatomic and epidemiological observations.^{18,19,30}

Lp(a) plasma concentrations predicted the risk of early atherogenesis in a dose-dependent fashion, with this association being confined to subjects with LDL cholesterol levels ≥ 3.3 mmol/L (median). Apo(a) phenotype, in contrast, distributes similarly in subjects with and without early carotid atherosclerosis. A cross-sectional evaluation of the ARIC study yielded analogous results in that Lp(a) was significantly elevated in subjects with high intima-media thickness, without any differences observed in the apo(a) phenotype distribution.³¹ Synergistic effects of different lipoproteins [LDL and Lp(a)] have been observed previously in studies aimed at investigating risk profiles of coronary artery disease:

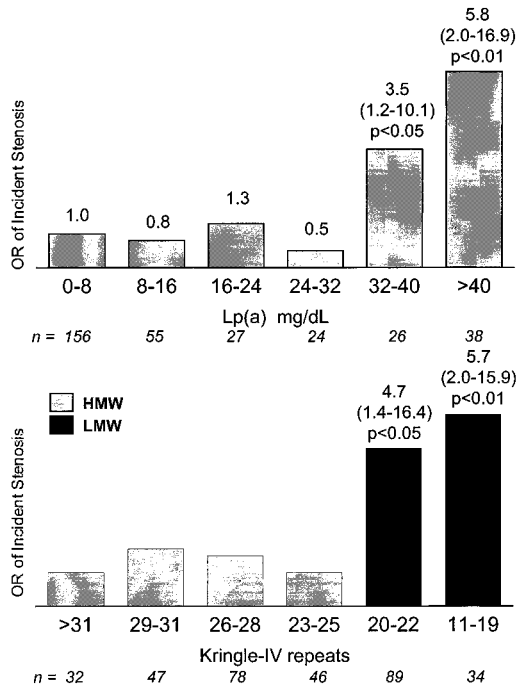


Figure 2. Risk of advanced atherogenesis (incident stenosis >40%) according to categories of Lp(a) concentrations and apo(a) phenotypes. Graph demonstrates a binary type of association with a clear cutoff at 32 mg/dL of Lp(a) concentration and 22 K-IV repeats. This analysis focused on subjects with pre-existing atherosclerosis (n=326). ORs were derived from multivariate logistic regression analysis (covariates age, antithrombin III, fibrinogen, diabetes mellitus, smoking, alcohol consumption, and factor V Leiden mutation). n indicates number of subjects in each category.

Armstrong and colleagues³² reported that the combination of high Lp(a) plasma concentrations and LDL cholesterol levels above the group median amplified the risk of coronary artery disease 6-fold. Therapeutic lowering of LDL cholesterol by ≥10% was found to dilute the predictive value of high Lp(a) for coronary artery disease.³³ Finally, a recent study revealed high Lp(a) plasma concentrations to increase the risk of familial coronary artery disease only if the total/HDL chole-

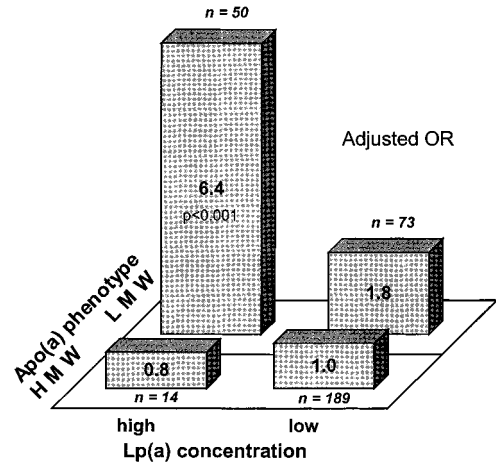


Figure 3. Risk of advanced atherogenesis (incident stenosis >40%) according to 4 categories built by low and high Lp(a) plasma concentrations (cutoff, 32 mg/dL) with HMW and LMW apo(a) phenotypes (cutoff, 22 K-IV repeats). ORs were derived from multivariate logistic regression analysis (covariates age, antithrombin III, fibrinogen, diabetes mellitus, smoking, alcohol consumption, and factor V Leiden mutation). n indicates number of subjects in each category.

sterol ratio was elevated.³⁴ Apparently, the interaction of Lp(a) with other lipoproteins triggers or enhances its atherosclerotic properties.

In addition to the lipid pathway, several other mechanisms have been proposed by which Lp(a) may promote early atherosclerosis. High Lp(a) impairs activation of transforming growth factor-β by downregulation of plasmin generation, thereby contributing to smooth muscle cell proliferation.³⁵ These in vitro findings were confirmed in apo(a) transgenic mouse experiments³⁶ and found an in vivo equivalent in markedly depressed serum concentration of active transforming growth factor-β in advanced human atherosclerosis.³⁷ Two recent studies demonstrated that Lp(a) induces chemotactic activity to human monocytes in a dose-dependent fashion.^{38,39} Lp(a) enhances the expression of intercellular adhesion molecule-1.⁴⁰ Because Lp(a) accumulates in the subendothelial space of the vessel wall, it may act

TABLE 4. Association of Lp(a) Plasma Concentration and Apo(a) Phenotype With Advanced Atherogenesis and CVD

Outcome	HMW Apo(a) Type		LMW Apo(a) Type		P
	Low Lp(a)	High Lp(a)	Low Lp(a)	High Lp(a)	
Advanced atherogenesis					
Cases, n (%)	44 (23.3)	2 (14.3)	21 (29.2)	25 (49.0)	
OR (95% CI), univariate	1.0	0.6 (0.1–2.6)	1.4 (0.7–2.5)	3.2 (1.7–5.9)‡	0.003
OR (95% CI), multivariate§	1.0	0.8 (0.2–4.5)	1.8 (0.9–3.7)*	6.4 (2.8–14.9)‡	<0.001
Incident CVD					
Cases, n (%)	29 (4.9)	2 (6.3)	16 (8.7)	17 (14.8)	
HR (95% CI), univariate	1.0	1.3 (0.3–5.6)	1.8 (1.0–3.5)†	3.3 (1.8–6.2)‡	0.003
HR (95% CI), age/sex adjusted	1.0	1.0 (0.2–4.6)	1.8 (1.0–3.5)†	3.4 (1.7–6.5)‡	0.003

HR indicates hazard ratio.

*P<0.1, †P<0.05, ‡P<0.001.

§Adjusted for covariates age, antithrombin III, fibrinogen, diabetes mellitus, smoking, alcohol consumption, and factor V Leiden mutation.

as a potent chemoattractant for monocytes in human atherosclerosis. Preliminary data suggest this property to be independent of apo(a) size.³⁹

Previous cross-sectional reports on effects of Lp(a) on advanced stages of atherosclerosis are sparse, and most of these did not consider apo(a) phenotypes. In our study, the apo(a) phenotype emerged as a particularly strong risk predictor of incident carotid stenosis >40% (advanced atherogenesis). Notably, excess risk of advanced atherogenesis was confined to LMW apo(a) phenotypes, especially when associated with high Lp(a) plasma concentrations (Figure 3). This finding is consistent with the theory that plaque-induced thrombosis probably reflects the main pathogenic mechanism of advanced atherogenesis; consequently, attenuated fibrinolysis is crucial in stabilizing atheroma-attached fibrin thrombi. Hervio and colleagues^{11,12} observed that the apo(a) size polymorphism influences the effect of Lp(a) on fibrinolysis in that only LMW apo(a) isoforms showed high-affinity binding to fibrin surfaces, thereby acting as a prominent competitive antagonist to plasminogen. These in vitro findings suggest that high concentrations of Lp(a) of LMW size should have the most pronounced influence on fibrinolysis, which is in close agreement with our results.

Cross-sectional^{27,41} and prospective^{28,29,42} studies revealed strong associations between the apo(a) size polymorphism and CVD.²⁹ A higher frequency of LMW apo(a) phenotypes was observed in men but not in women who experienced incident myocardial infarction or coronary death in the Stanford Five-City Project.²⁸ Two further prospective studies found that LMW apo(a) phenotypes were significantly associated with CVD in men <60 years old²⁹ and in hemodialysis patients.⁴² In analogy to advanced stenotic atherosclerosis, the risk for incident fatal and nonfatal CVD in our survey was markedly elevated in subjects with LMW apo(a) phenotypes combined with high Lp(a) concentrations.

Conclusions

In this exclusively white study cohort, Lp(a) appears to be involved in both early and advanced stages of atherosclerosis, although in distinct ways. On the one hand, plasma concentration of Lp(a) dose-dependently predicted early atherosclerosis in subjects with high LDL cholesterol levels. This effect was independent of the apo(a) size polymorphism. Conversely, apo(a) polymorphism emerged as one of the strongest risk predictors of advanced stenotic atherosclerosis. Only LMW apo(a) phenotypes with high antifibrinolytic capacity appeared to be involved in this clinically relevant stage of arterial disease.

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