

ORIGINAL ARTICLE

Lp(a) Lipoprotein, Vascular Disease, and Mortality in the Elderly

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ABSTRACT

BACKGROUND

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As compared with what is known about predictors of vascular events in middle-aged persons, less is known about these events in the elderly. Lp(a) lipoprotein, which plays an important part in atherothrombogenesis, has been associated with an increased risk of vascular disease. We investigated this relation among older U.S. adults.

METHODS

In a prospective study of 5888 community-dwelling older adults (65 years of age or older) in the United States, 2375 women and 1597 men who were free of vascular disease provided base-line serum samples for analysis for levels of Lp(a) lipoprotein. These 3972 subjects were followed for a median of 7.4 years to evaluate the development of stroke and to track deaths from vascular causes and all causes. The men and women were divided into quintile groups according to the Lp(a) lipoprotein level at base line.

RESULTS

Using Cox proportional-hazards models, we determined the risk associated with each quintile level of Lp(a) lipoprotein, with the lowest quintile serving as the reference group. As compared with those in the lowest quintile, men in the highest quintile had three times the unadjusted risk of stroke (relative risk, 3.00; 95 percent confidence interval, 1.59 to 5.65), almost three times the risk of death associated with vascular events (relative risk, 2.54; 95 percent confidence interval, 1.59 to 4.08), and nearly twice the risk of death from all causes (relative risk, 1.76; 95 percent confidence interval, 1.31 to 2.36). Adjustment for age; sex; the levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides; carotid-wall thickness; smoking status; the presence or absence of diabetes and systolic and diastolic hypertension; body-mass index; and other traditional risk factors had little effect on the final assessments. Similar analyses for women, which also included adjustment for estrogen use or nonuse, revealed no such relation.

CONCLUSIONS

Among older adults in the United States, an elevated level of Lp(a) lipoprotein is an independent predictor of stroke, death from vascular disease, and death from any cause in men but not in women. These data support the use of Lp(a) lipoprotein levels in predicting the risk of these events in older men.

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LESS IS KNOWN ABOUT PREDICTORS OF vascular events among the elderly than about predictors among middle-aged people. Several studies^{1,2} have suggested that some traditional risk factors for cardiovascular diseases are not adequate predictors of vascular events in this older age group, underscoring the need for continued research on this topic.

Lp(a) lipoprotein is a low-density lipoprotein particle in which apolipoprotein B-100 is linked by a single interchain disulfide bridge to a unique glycoprotein, apoprotein(a).³⁻⁶ Basic research indicates that Lp(a) lipoprotein has a vital role in atherothrombogenesis.^{3,4} Although investigators have demonstrated its presence in atherosclerotic plaques in the vascular tree, including the aorta and cerebral arteries,⁷ prospective studies of Lp(a) lipoprotein and the risk of vascular disease in middle-aged populations have yielded inconclusive results.⁵⁻¹⁸ Data on the relation between Lp(a) lipoprotein and the risk of vascular disease in the elderly are unavailable; however, emerging evidence suggests that the atherogenic effects of Lp(a) lipoprotein may be age- and sex-specific.¹⁹ Therefore, we investigated the hypotheses that an elevated level of Lp(a) lipoprotein is associated with an increased risk of vascular events in older persons and that there are sex-specific differences in the atherogenicity of Lp(a) lipoprotein within this group.

METHODS

SUBJECTS AND STUDY DESIGN

The participants were enrolled in the Cardiovascular Health Study,¹ a prospective, multicenter study of risk factors and cardiovascular consequences in men and women 65 years of age or older, sponsored by the National Heart, Lung, and Blood Institute. The study was started in 1987 with an initial cohort of 5201 participants, the majority of whom (approximately 95 percent) were white; an additional ethnic-minority cohort of 687 persons was enrolled in the period from 1992 to 1993, bringing the total cohort to 5888. These participants were recruited on the basis of random sampling of Medicare beneficiaries listed by the Health Care Financing Administration at four participating centers: Johns Hopkins University (Washington County, Md.), Wake Forest University (Forsyth County, N.C.), the University of Pittsburgh (Allegheny County, Pa.), and the University of California–Davis (Sacramento County, Calif.). The institutional review boards of all four sites and of the

coordinating center at the University of Washington in Seattle approved the study. The subjects were non-institutionalized persons who gave informed consent to enter and to remain in the study.

Participants were eligible for enrollment whether or not they had a history of vascular disease. The full details of the recruitment process have been published elsewhere.²⁰ In brief, the participants underwent an initial evaluation that consisted of a detailed medical history, a physical examination, laboratory tests, and an assessment of health status that included any evidence of vascular disease. Blood samples were collected at base line from participants in the initial cohort for analyses, including measurement of Lp(a) lipoprotein. The analyses of blood samples from the subsequent minority cohort did not include measurement of Lp(a) lipoprotein, and thus that component was not available for this study.

ASCERTAINMENT OF EVENTS

The vascular events studied were stroke, coronary heart disease, and death (from vascular disease and from all causes). Stroke was defined as either a cerebrovascular accident or a transient ischemic attack. Coronary heart disease was defined by the occurrence of angina, myocardial infarction, coronary angioplasty, or bypass surgery. Deaths due to vascular disease were defined as those from cerebrovascular events, atherosclerosis (including peripheral vascular disease), coronary heart disease, and other cardiovascular causes.

All events were assessed semiannually. The full details of the surveillance and ascertainment of events in the Cardiovascular Health Study have been published elsewhere.²¹ In brief, all events that occurred after the base-line clinic visit were classified as new events. These were classified with use of the coding system of the *International Classification of Diseases, 9th Revision, Clinical Modification*.²² Information about deaths was obtained from reviews of medical records, death certificates, autopsy reports, and coroner's reports. The rate of ascertainment with respect to mortality in the Cardiovascular Health Study is 100 percent. All provisional diagnoses of events were reviewed and adjudicated at periodic meetings of the study's morbidity and mortality subcommittee, which comprised investigators from each center, from the coordinating center, and from the project office of the National Heart, Lung, and Blood Institute. The events in this report are those that were adjudicated from 1989 through June 1997.

MEASUREMENT OF Lp(a) LIPOPROTEIN

Analysis of Lp(a) lipoprotein was performed on the base-line samples within the year of collection. Thus, prolonged storage, an important factor that could affect the measurement of Lp(a) lipoprotein,

would not be expected to affect our results. Lp(a) lipoprotein was measured with a monoclonal antibody-based enzyme-linked immunosorbent assay. The assay is very sensitive, reacts to all isoforms of Lp(a) lipoprotein, and is highly specific, with less than 1 percent cross-reactivity for either low-density lipoprotein or plasminogen. The reagents were obtained from Genentech. Results are expressed in terms of the Lp(a) lipoprotein protein concentration (excluding lipid), with reference to a purified standard calibrated by quantitative amino acid analysis. The overall coefficient of variation for Lp(a) lipoprotein measurements in this study was 7.5 percent. Low-density lipoprotein was calculated according to the Friedewald formula. A detailed description of the method of Lp(a) lipoprotein measurement in the Cardiovascular Health Study has been published elsewhere.²³

STATISTICAL ANALYSIS

The distribution of Lp(a) lipoprotein values was stratified into quintiles, with the cutoff points chosen so that each quintile group would contain approximately 20 percent of the full cohort. Incidence rates were calculated as the number of events per 1000 person-years at risk. Curves for overall survival or event-free survival were estimated by the Kaplan-Meier method.²⁴ Using Cox proportional-hazards models,²⁵ we assessed the relative risks associated with the vascular events for each quintile of Lp(a) lipoprotein, relative to the first quintile. A test for trend was performed by treating the quintile of Lp(a) lipoprotein as a continuous variable in the model. Because previously published data showed a sex-specific vascular effect of Lp(a) lipoprotein,¹⁹ all Cox regressions were stratified according to sex. However, if sex-stratified results were similar, the analysis was repeated for men and women combined.

Potential confounders were defined as traditional risk factors or variables that were significantly associated with Lp(a) lipoprotein (Table 1). Because the frequency distribution of Lp(a) lipoprotein was highly skewed, the associations between the log of the Lp(a) lipoprotein levels and continuous variables were assessed with use of Pearson's correlation coefficients, and the associations between the log Lp(a) lipoprotein level and categorical variables were assessed with use of a t-test or analysis of variance. P values for all tests were two-tailed, and differences were considered to be significant at the 0.05 level. Statistical analyses and plots were conducted with SAS²⁶ and S-Plus²⁷ software, respectively.

Table 1. Base-Line Characteristics of the Study Cohort.*

Variable	Entire Cohort (N=3972)	Women (N=2375)	Men (N=1597)
Age (yr)	72.6±5.6	72.2±5.4	73.2±5.8
White race (%)	94.7	94.5	95.0
Glucose (mg/dl)	108.9±33.0	106.7±32.8	112.1±33.2
Blood pressure (mm Hg)			
Diastolic	70.6±11.4	69.4±11.3	72.4±11.3
Systolic	136.1±21.2	135.9±21.3	136.3±21.1
Cholesterol (mg/dl)			
Total	214.8±38.6	224.1±37.7	201.1±35.8
LDL (mg/dl)	132.5±35.2	137.1±35.9	125.7±33.1
HDL (mg/dl)	55.1±15.8	59.7±15.9	48.3±12.9
Triglycerides (mg/dl)	139.4±75.3	139.8±72.9	138.6±78.9
Body-mass index	26.4±4.6	26.4±5.0	26.4±3.8
Family history of MI (%)	30.4	31.7	28.3
Former or current smoking (%)	51.0	42.4	66.0
Hypertension (%)	38.1	38.9	36.9
Diabetes status (%)†			
Normal	73.1	76.7	67.8
Impaired glucose tolerance	13.5	11.7	16.0
Diabetes	13.4	11.6	16.2
History of stroke (%)	3.0	2.0	4.4
COPD (%)	7.7	7.5	7.9
History of cancer (%)	14.6	14.6	14.7
Maximal common carotid-wall thickness (mm)	1.0±0.2	1.0±0.2	1.0±0.2
Maximal internal carotid-wall thickness (mm)	1.4±0.7	1.4±0.6	1.6±0.7
Depression score‡	4.3±4.3	4.8±4.5	3.5±3.8
Estrogen use(%)		13.3	
Lp(a) lipoprotein (mg/dl)§	4.2 (5.8)	4.4 (6.0)	3.9 (5.6)

* Plus-minus values are means ±SD. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, MI myocardial infarction, and COPD chronic obstructive pulmonary disease. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert values for glucose to millimoles per liter, multiply by 0.05551; to convert values for cholesterol to millimoles per liter, multiply by 0.02586; and to convert values for triglycerides to millimoles per liter, multiply by 0.01129.

† Diabetes status was classified according to the criteria of the American Diabetes Association.

‡ Depression was scored on the Center for Epidemiological Studies Depression Scale (modified version); scores range from 0 to 30, with 30 representing the most depression, and 0 the least.

§ Values are medians, with the difference between the 75th percentile and the 25th percentile given in parentheses.

RESULTS

Of the 5888 subjects enrolled, 5166 had their Lp(a) lipoprotein levels measured at base line. Of these subjects, the 1006 who had established coronary heart disease, the 184 who were taking lipid-lowering medications, and the 4 with Lp(a) lipoprotein levels greater than or equal to 50 mg per deciliter were excluded. Table 1 shows the base-line characteristics of the 3972 subjects in the current analysis. The age range at entry was 65 to 100 years, with a mean of 72 years for women and 73 for men. Whites made up approximately 95 percent of the cohort. Men were more likely than women to be current or former smokers and to have diabetes at study entry. Women had higher total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels than men, on average, and were more likely to have a family history of myocardial infarction.

The percentages of subjects in each quintile of Lp(a) lipoprotein are shown in Figure 1. Women had a higher median Lp(a) lipoprotein level than men (4.4 vs. 3.9 mg per deciliter), and a higher proportion of women than of men were in the top quintile (21 percent vs. 17 percent). Incidence rates for each event (the number of events per 1000 person-years

at risk) were roughly the same for women in all the Lp(a) lipoprotein quintiles (Table 2). The same trend was seen for men in relation to coronary heart disease. The incidence of stroke was 6.33 per 1000 person-years for men in the lowest Lp(a) lipoprotein quintile, roughly twice as high for men in quintiles 2 through 4, and three times as high (18.99 per 1000 person-years) for men in the highest quintile. The overall mortality rate increased to 57.31 for men in the highest quintile, as compared with that in the lower four quintiles (range, 33.47 to 37.00).

Overall, no significant association was seen between levels of Lp(a) lipoprotein and any of the vascular outcomes among women (Table 3). Nor was any significant association seen in men in relation to coronary heart disease. For men in the highest quintile of Lp(a) lipoprotein, the unadjusted risk of stroke was tripled (relative risk, 3.00; 95 percent confidence interval, 1.59 to 5.65), the unadjusted risk of death from vascular causes was almost tripled (relative risk, 2.54; 95 percent confidence interval, 1.59 to 4.08), and the unadjusted risk of death from all causes was nearly doubled (relative risk, 1.76; 95 percent confidence interval, 1.31 to 2.36), as compared with men in the lowest quintile. After adjustment for other vascular risk factors that are correlated with Lp(a) lipoprotein, these risks re-

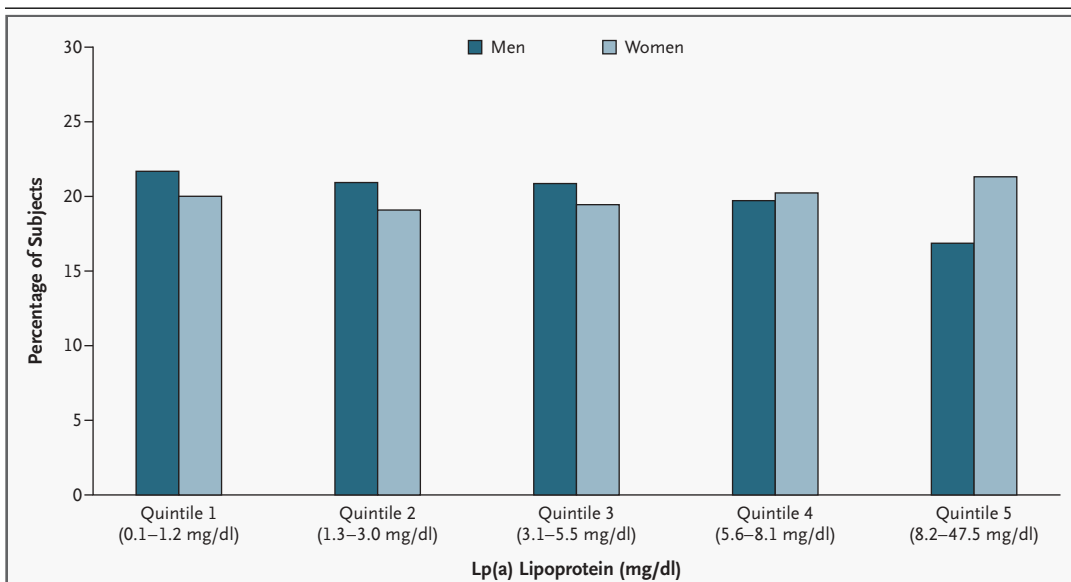


Figure 1. Percentages of Study Participants in Quintiles of Lp(a) Lipoprotein.

Each quintile group comprises approximately 20 percent of the total cohort, which included 1597 men (median Lp(a) lipoprotein level, 3.9 mg per deciliter) and 2375 women (median, 4.4 mg per deciliter).

Table 2. Incidence of Vascular Events According to Sex and the Quintile of Lp(a) Lipoprotein at Base Line.*

Lp(a) Lipoprotein Quintile	Women			Men		
	Death	CHD	Stroke	Death	CHD	Stroke
	<i>no. of events/1000 person-years</i>					
1	22.92	19.87	11.38	33.47	36.15	6.33
2	18.69	17.05	11.44	37.00	33.01	12.26
3	25.38	18.21	10.34	34.96	41.58	13.43
4	20.53	20.31	9.23	36.97	42.41	12.18
5	23.06	22.22	13.41	57.31	45.39	18.99
Total	22.14	19.60	11.06	38.01	39.30	12.44

* CHD denotes coronary heart disease.

mained significant. The estimates of survival were similar among men in the first four quintiles, but the estimates were remarkably lower among men in the highest quintile (Fig. 2). We observed no interactions between Lp(a) lipoprotein and other lipid particles.

DISCUSSION

The results of our large study of older persons in the United States suggest that elevated levels of Lp(a) lipoprotein independently predict an increased risk of stroke, death from vascular disease, and death from all causes in men but not in women. Our findings provide new, relevant evidence of risk among elderly men and comprehensive information on the dichotomous relation of Lp(a) lipoprotein and sex. This prospective study helps to clarify the role of Lp(a) lipoprotein in the prediction of vascular disease in older adults, in whom the applicability of some traditional risk factors has been questioned.^{1,2}

Among men, we found a robust association between Lp(a) lipoprotein and vascular events, with a magnitude of risk similar to that among middle-aged persons in other studies.⁸⁻¹⁸ In a meta-analysis¹⁸ of all the prospective studies addressing this issue, excluding those that enrolled participants with renal disease or diabetes, 12 of the 14 studies reported higher levels of Lp(a) lipoprotein among the subjects in whom vascular disease subsequently developed than in the controls. Nine of these 12 studies provided information on dose-response relations, and 6 of the 9 showed a positive relation between Lp(a) lipoprotein and the risk of vascular dis-

ease, lending further credibility to the notion that Lp(a) lipoprotein significantly contributes to the development of these vascular events.

Our findings are similar to those of two other studies involving elderly subjects.^{28,29} Although in both studies correlations were found between Lp(a) lipoprotein and vascular disease, there are differences between our study and the other two. First, unlike the other two, our cohort provided blood samples before the occurrence of events. Second, our study had a much larger sample, and we are therefore able to provide detailed information on sex-specific associations in our cohort.

Most,²⁸⁻³¹ but not all,³² prospective studies of Lp(a) lipoprotein and stroke have found positive associations, including studies involving the elderly.^{28,29} We found a threefold risk of stroke in the highest Lp(a) lipoprotein quintile among men, but not among women. Nguyen et al.¹⁵ reported a similarly strong association between Lp(a) lipoprotein and the risk of stroke among men but not among women. The explanation for the absence of an association between Lp(a) lipoprotein and the risk of vascular events in women, despite the higher Lp(a) lipoprotein levels among women than among men in our study, is unclear.

Several plausible mechanisms have been proposed to explain the association between Lp(a) lipoprotein and vascular disease. First, it has been suggested that Lp(a) lipoprotein plays a part in the initiation, progression, and subsequent rupture of atherosclerotic plaque.³⁻¹⁸ Second, because of the structural homology of apoprotein(a) and plasminogen, Lp(a) lipoprotein may compete with, bind, and inhibit the thrombolytic activity of tissue plasminogen; Lp(a) lipoprotein could therefore have a thrombogenic effect by its interference with intrinsic fibrinolysis.³⁻¹² Third, Lp(a) lipoprotein has been associated with endothelial dysfunction.³³ Fourth, Lp(a) lipoprotein activates monocytes, colocalizes with plaque macrophages, stimulates smooth-muscle cells, and could induce inflammation.³⁴

The strength of our study lies in the fact that our participants are apparently healthy elderly men and women who were randomly selected from the community in which they live and are therefore representative of the average older person in the United States. The prospective nature of our study, and the exclusion of those with vascular disease at base line, helped reduce possible confounding by factors with the potential to affect our outcomes, since Lp(a) lipoprotein is an acute-phase reactant, and levels

Table 3. Hazard Ratios for Vascular Events and Death According to the Quintile of Lp(a) Lipoprotein.*

Event and Lp(a) Lipoprotein Quintile	Women		Men	
	Unadjusted	Adjusted† <i>hazard ratio (95 percent confidence interval)</i>	Unadjusted	Adjusted†
Stroke				
1	1.00	1.00	1.00	1.00
2	0.93 (0.59–1.48)	0.99 (0.61–1.61)	2.07 (1.10–3.92)	1.76 (0.92–3.35)
3	0.91 (0.56–1.47)	0.82 (0.48–1.38)	2.13 (1.11–4.05)	1.87 (0.97–3.61)
4	0.81 (0.50–1.31)	0.79 (0.48–1.34)	1.94 (1.00–3.74)	1.69 (0.86–3.30)
5	1.18 (0.76–1.81)	1.11 (0.70–1.78)	3.00 (1.59–5.65)	2.92 (1.53–5.57)
P value	0.71	0.97	0.002	0.003
Death from vascular causes				
1	1.00	1.00	1.00	1.00
2	0.67 (0.39–1.15)	0.62 (0.35–1.09)	1.05 (0.62–1.77)	0.88 (0.51–1.53)
3	0.90 (0.53–1.50)	0.70 (0.40–1.24)	1.17 (0.70–1.98)	1.12 (0.65–1.92)
4	0.62 (0.35–1.08)	0.48 (0.26–0.90)	1.25 (0.74–2.10)	1.01 (0.58–1.76)
5	1.08 (0.67–1.73)	0.87 (0.52–1.40)	2.54 (1.59–4.08)	2.09 (1.27–3.47)
P value	0.78	0.58	0.01	0.004
Death from all causes				
1	1.00	1.00	1.00	1.00
2	0.78 (0.56–1.09)	0.77 (0.53–1.07)	1.11 (0.82–1.50)	1.04 (0.76–1.44)
3	1.16 (0.85–1.58)	1.09 (0.77–1.50)	1.03 (0.75–1.41)	1.04 (0.74–1.44)
4	0.90 (0.65–1.24)	0.96 (0.67–1.33)	1.10 (0.81–1.50)	1.10 (0.79–1.54)
5	1.01 (0.74–1.37)	0.96 (0.67–1.30)	1.76 (1.31–2.36)	1.60 (1.16–2.19)
P value	0.77	0.84	0.002	0.01
Coronary heart disease				
1	1.00	1.00	1.00	1.00
2	0.86 (0.59–1.24)	0.79 (0.54–1.16)	0.91 (0.66–1.26)	0.86 (0.62–1.21)
3	0.92 (0.64–1.31)	0.87 (0.60–1.27)	1.15 (0.85–1.57)	1.14 (0.83–1.57)
4	1.03 (0.73–1.45)	0.92 (0.64–1.33)	1.17 (0.86–1.60)	1.09 (0.79–1.52)
5	1.12 (0.80–1.56)	1.02 (0.71–1.46)	1.26 (0.91–1.74)	1.19 (0.84–1.67)
P value	0.29	0.63	0.11	0.29

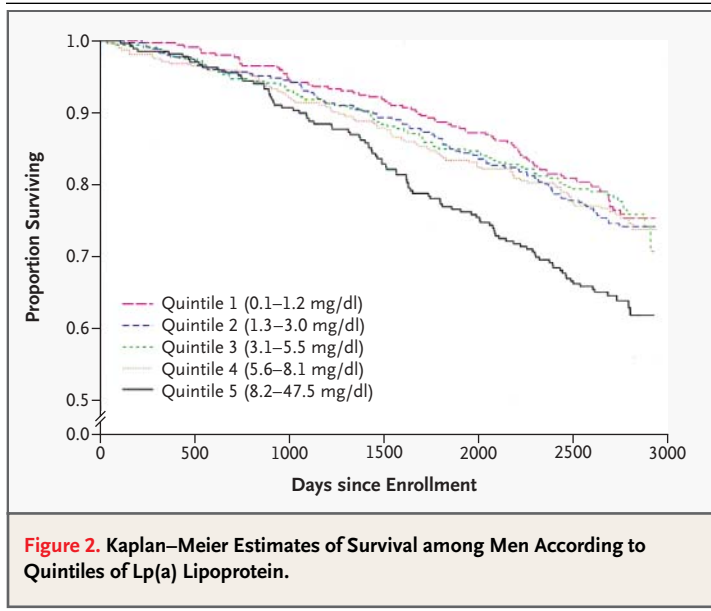
* Hazard ratios are from Cox proportional-hazards models. Subjects in the first quintile served as the reference group. P values are for the trend across quintiles.

† Hazard ratios have been adjusted for age, race (white vs. nonwhite), glucose and triglyceride levels, the presence or absence of hypertension, the ankle–arm index (≤ 0.9 vs. > 0.9), smoking status (ever vs. never), the level of total and low-density lipoprotein cholesterol, the minimal internal carotid-wall thickness, the body-mass index, estrogen use or non-use (women only), and diabetes status (normal vs. increased glucose tolerance or diabetes).

may go up after an event. Furthermore, the large sample size, our method of ascertaining events, the adequacy of our follow-up, and the fact that there was no need for prolonged storage of blood samples make chance less likely to be the sole explanation for our findings.

The limitations of this study include the fact that analyses of Lp(a) lipoprotein results vary according to race, ethnic origin, and age. Our data are limited

to persons 65 years of age or older, almost all of whom were white; therefore, the data are not applicable to the general population. Second, because our study was originally designed to determine risk factors for vascular disease, but not to determine the risk of death, our data cannot adequately control for all potential variables that contribute to mortality. We could and did control for variables that are known to affect vascular events.



The inherent value of this study is suggested by current data on aging, which indicate that persons

older than 85 years constitute the fastest-growing segment of our population. By the year 2030, one in four persons in the United States will be 65 years of age or older.³⁵ Although the elderly are the most vulnerable of all age groups to the effects of vascular diseases, including death, predictors of vascular events in the elderly are poorly understood. Thus, the finding that, in men, elevated levels of Lp(a) lipoprotein are associated with a risk of vascular disease higher than that associated with known traditional risk factors may highlight a subgroup of men for whom aggressive risk-factor management should be explored. Our findings support the consideration of the measurement of serum Lp(a) lipoprotein as a screening tool for the risk of vascular outcomes in elderly men. Whether such screening will aid in reducing these risks is unknown and may be a useful subject for further investigation.

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