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Lipoprotein (a) and the risk of ischemic stroke in young women

Robert J. Wityk [a,*], Steven J. Kittner [b,c], Jennifer L. Jenner [d], J. Richard Hebel [c], Anne Epstein [b], Marcella A. Wozniak [b], Paul D. Stolley [c], Barney J. Stern [e], Michael A. Sloan [b,c], Thomas R. Price [b,c], Robert J. McCarter [c], Richard F. Macko [b], Constance J. Johnson [a], Christopher J. Earley [a], David W. Buchholz [a], Ernst J. Schaefer [d]

[a] *Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[b] *Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, USA*
[c] *Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD, USA*
[d] *Lipid Metabolism Laboratory, JM USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA*
[e] *Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA*

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Abstract

Background and purpose: lipoprotein (a) (lp (a)) is a lipid-containing particle similar to LDL which has been found in atherosclerotic plaque. The role of lp (a) in ischemic stroke remains controversial, but some studies suggest lp (a) is particularly important as a risk factor for stroke in young adults. We investigated the role of lp (a) as a risk factor for stroke in young women enrolled in the Stroke Prevention in Young Women Study. *Methods*: subjects were participants in a population-based, case-control study of risk factors for ischemic stroke in young women. Cases were derived from surveillance of 59 regional hospitals in the central Maryland, Washington DC, Pennsylvania and Delaware area. Lp (a) was measured in 110 cases and 216 age-matched controls. Demographics, risk factors, and stroke subtype were determined by interview and review of medical records. *Results*: lp (a) values were higher in blacks than whites, but within racial groups, the distribution of lp (a) values was similar between cases and controls. After adjustment for age, race, hypertension, diabetes, cigarette smoking, coronary artery disease, total cholesterol and HDL cholesterol, the odds ratio for an association of lp (a) and stroke was 1.36 (95% CI 0.80–2.29). There was no dose-response relationship between lp (a) quintile and stroke risk. Among stroke subtypes, only lacunar stroke patients had significantly elevated lp (a) values compared to controls. *Conclusions*: we found no association of lp (a) with stroke in a population of young women with ischemic stroke. Small numbers of patients limit conclusions regarding risk in ischemic stroke subtypes, but we could not confirm previous suggestions of an association of lp (a) with atherosclerotic stroke in young adults.

Keywords: Ischemic stroke; Lipoprotein (a); Stroke in the young

1. Introduction

The role of lipoprotein (a) (lp (a)) as a risk factor for ischemic stroke remains controversial [1]. Lp (a) is a particle structurally similar to low-density lipoprotein (LDL), but has the covalently-linked glycoprotein apo (a) as its distinguishing characteristic. Serum concentrations of lp (a) are primarily genetically determined and are minimally influenced by environmental factors, such as diet and most lipid-lowering agents [1,2]. Lp (a) has been observed in atherosclerotic plaques in the aorta [3], coronary arteries [4], and in the cerebral arteries of the circle of Willis [5]. In addition, homology of segments of apo (a) to the fibrin binding sites (kringles) of plasminogen suggest a possible interaction between this molecule and the fibrinolytic pathway [6]. In vitro studies show that lp (a) competes with plasminogen binding sites and may interfere with endogenous en-

* Corresponding author. Present address: Meyer 5-181b, 600 North Wolfe Street, Johns Hopkins Hospital, Baltimore, MD 21287, USA. Tel.: +1-410-9552228; fax: +1-410-6149807.
E-mail address: rwityk@jhmi.edu (R.J. Wityk)

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dothelial cell-mediated fibrinolysis [7–9]. The potential dual role of lp (a) in the development of atherosclerosis and thrombosis makes it a prime candidate as a risk factor for ischemic stroke.

Numerous case-control studies have shown an association between elevated lp (a) concentrations and either stroke or transient ischemic attack (TIA) [10–20] or carotid artery atherosclerosis [11,19,21–24]. In contrast, a few studies [20,25,26] have failed to show an association of lp (a) with stroke/TIA, except perhaps in certain stroke subtypes. The only prospective study of lp (a) and cerebrovascular disease, the Physicians Health Study, found no association between elevated lp (a) concentrations and the future risk of stroke [25]. Similarly, prospective studies of the role of lp (a) in the risk of coronary artery disease have shown mixed results [27–30].

Several authors have suggested that lp (a) is a particularly important risk factor for stroke in young adults, but the small numbers of young stroke patients in these studies have limited the strength of these conclusions [12,17]. We measured lp (a) concentrations in subjects and controls enrolled in the Stroke Prevention in Young Women Study to determine whether elevated lp (a) concentrations are a risk factor for stroke in this population. Most previous studies of lp (a) and stroke have been reported in white European [11,12, 14,15,19,20] and Asian populations [10,13,16,17]. Since a substantial portion of our participants were African-American, we obtained unique data on the risk of ischemic stroke associated with lp (a) in this racial group.

2. Methods

We studied subjects enrolled in the Stroke Prevention in Young Women Study, a population-based, case-control study of risk factors for ischemic stroke in young women. The study area included central Maryland, Washington DC and southern portions of Pennsylvania and Delaware. Cases were women aged 15–44 years with first cerebral infarction identified by surveillance of discharges at all 59 regional hospitals in the study area and by referral from regional neurologists. Details of study design, adjudication of data, and definitions of possible and probable causes of stroke have been previously described [31,32]. All subjects gave informed consent for participation. Recruitment and data collection followed guidelines provided by investigational review committees at the respective institutions.

Of 291 patients who were eligible and identified within 1 year of incident stroke, 227 agreed to participate, and a subgroup of 110 women had blood drawn for lp (a) measurement. Controls were women without a history of stroke who were frequency matched by age and geographic region of residence, and were recruited by random digit dialing. Of 450 eligible controls, 392 agreed to participate and 216 had blood drawn for lp (a) measurement.

Non-fasting blood was drawn for total cholesterol, HDL cholesterol and lipoprotein (a). Blood tests were drawn at a mean of 26 days after stroke (range 1–120 days) and were obtained greater than 2 months after stroke in 59% of patients. Lp (a) was measured in plasma using a commercially available ELISA (MACRA, Strategic Diagnostics, Newark). The ELISA uses a specific monoclonal anti-lp (a) antibody that recognizes all apo (a) isoforms and does not cross-react with plasminogen. Mean intra-assay and interassay coefficients of variation for this assay were 2.2 and 6.7%, respectively. Lp (a) plasma concentrations are reported as total lp (a) mass in mg/dl. Total cholesterol and HDL-cholesterol were measured according to standard practice [33]. *Hypercholesterolemia was defined as a total cholesterol measurement of greater than 240 mg/dl.*

Wilcoxan rank sum tests were used to compare means and Fisher exact tests were used to compare proportions. All *P*-values were two-sided. Adjusted odds ratios derived from logistic regression were used to determine if lp (a) concentration was associated with an increased risk for stroke after controlling for race and other potential confounding variables.

3. Results

There were 110 women with ischemic stroke and 216 controls. Mean age and the presence of traditional vascular risk factors of hypertension, diabetes, cigarette smoking, coronary artery disease *and hypercholesterolemia* are shown in Table 1. Risk factors were more prevalent among cases than controls, although not all reached statistical significance. The racial composition of cases and controls is also shown in Table 1. A larger proportion of controls were white as compared to cases. Among cases and controls, eight subjects were classified as 'other' races and included Hispanics, American Indians and Asians. For purposes of analysis, 'other' races were grouped with whites. Our results were unchanged when this small group of subjects was eliminated from analysis. Since lp (a) concentrations can be influenced by menopausal status or the use of estrogen-containing compounds, [34,35]. Table 1 also shows the distribution of subjects who were post- or perimenopausal, or who were on estrogen-containing medications at the time of incident stroke (cases) or time of interview (controls). The proportion of post- or perimenopausal subjects were similar between cases and controls, but a larger proportion of cases were using oral contraceptives (OCs) at the time of stroke.

Etiology of stroke for probable and possible causes is shown in Table 2. Among 110 stroke patients, 57 had at least one probable cause, 27 had at least one possible cause, and the remaining 26 were indeterminate. 'Other determined causes' of stroke include hematologic disorders, non-atherosclerotic vasculopathy (e.g. vasculitis, dissection), migraine, drug abuse and stroke associated with pregnancy or the postpartum state.

The distribution of lp (a) values differed markedly between blacks and whites/other, both for cases and controls (Figs. 1 and 2). Subsequent lp (a) and lipid analyses were done separately for these two groups. Mean and median lp (a) values were higher in blacks than whites/other, but within a racial group, lp (a) values were similar between cases and controls (Table 3). Lp (a) values for both racial groups were divided into quartiles, and the odds ratio for stroke was calculated for each quartile compared to the lowest quartile (Table 4). No significant association of lp (a) with stroke was seen for any quartile, and there did not appear to be a dose-response trend for higher lp (a) quartiles. We also analyzed our results using the median lp (a) concentration for all cases (14 mg/dl) as a cut-point to stratify into high and low lp (a) groups. The crude odds ratio was similar between blacks (1.33, 95% CI 0.57–3.10) and whites (1.54, 95% CI 0.84–2.80). After adjustment for age, race, hypertension, diabetes, cigarette smoking, coronary artery disease, total cholesterol and HDL cholesterol, the odds ratio was 1.36 (95% CI 0.80–2.29). *Power calculations were performed level to estimate a possible type II error due to insufficient sample size. The power of our study for detecting an lp (a) difference of 14 mg/dl between cases and controls was greater than 99%, and for detecting a difference of 6.1 mg/dl was 80%.*

Mean lp (a) values for patients grouped by stroke etiologies are shown in Table 5. Among stroke patients, 15 were classified as having either a possible or probable atherosclerotic cause for stroke. Atherosclerotic lesions involving cerebral vessels were demonstrated by cerebral angiography ($n=10$), carotid duplex ultrasound ($n=4$) and magnetic resonance angiography ($n=1$). Location of the atherosclerotic lesion was in the extracranial carotid artery ($n=9$), intracranial carotid artery ($n=2$) and middle cerebral artery ($n=4$). The mean lp (a) for this subgroup of patients was 29.7 mg/dl (mean for blacks, 37.6 mg/dl; mean for whites/other races, 14.0 mg/dl) and was not significantly different from controls (mean for blacks, 32.2 mg/dl; mean for whites/other races, 16.3 mg/dl).

Six patients had lacunar stroke in the absence of large artery atherosclerosis or cardiac source of embolism. Three black patients with lacunar stroke had markedly elevated lp (a) values (74, 76 and 120 mg/dl) resulting in a significantly elevated mean lp (a) value for that group. For other stroke etiologies, mean lp (a) values were not significantly different than controls.

Table 1
Demographics and risk factors

	Cases ($n=110$)	Controls ($n=216$)
Mean age (years)	35.6	35.1
White race (%)	57 (52)	145 (67)
Black race (%)	49 (44)	67 (31)
Other races (%)	4 (4)	4 (2)
Hypertension (%)	29 (26.6)[a]	24 (11.2)
Diabetes mellitus (%)	12 (10.9)[a]	4 (1.9)
Current cigarette smoking (%)	45 (41.3)	67 (31.0)
Coronary artery disease (%)	15 (13.6)[a]	7 (3.2)
Hypercholesterolemia (%)	32 (29.4)[a]	25 (11.9)
Post- or perimenopausal (%)	7 (6.4)	10 (4.6)
Replacement estrogen use (%)	7 (6.4)	9 (4.2)
Oral contraceptive use (%)	21 (18.9)[b]	21 (9.7)

[a] $P \leq 0.001$ for cases compared to controls.
[b] $P < 0.05$ for cases compared to controls.

Table 2
Stroke etiology

	Probable causes[a] ($n=57$)	Possible causes[b] ($n=27$)
Large artery atherosclerosis	9	6
Cardioembolism	11	15
Lacune (small vessel stroke)	5	1
Other determined cause	32	5

[a] Three patients had two probable, but only one cause is listed per patient using the following hierarchy: large artery atherosclerosis > cardioembolism > lacune > other determined cause.
[b] Most patients had multiple possible causes, but only one cause is listed per patient using the same hierarchy as for probable causes.

4. Discussion

Most, [10–14,16–19] but not all, [15,20,26] previous cross-sectional studies have found elevated lp (a) concentrations in patients with ischemic stroke or TIA as compared to controls. Several groups have found a particularly strong association of lp (a) with carotid artery atherosclerosis [19,23] or carotid intimal thickening [22]. In contrast, Ridker reported in the only prospective study that elevated lp (a) concentrations did not predict future stroke in patients [25], and a number of cross-sectional studies have found an effect of lp (a) on stroke risk only in certain stroke subtypes [10,15,20]. Association with a particular stroke subtype, however, has not been consistent among studies.

In our study of young women with stroke, we found no association of lp (a) concentrations with stroke risk, using either quartiles or median values for analysis. Calculated odds ratios were not significantly altered by adjustment for other risk factors. The distribution of lp (a) is different in blacks than whites, with blacks having higher mean and median values, and whites having a distribution skewed towards lower values. We found similar results in both cases and controls (Figs. 1 and 2), and within a racial group lp (a) concentrations were not significantly different between cases and controls. The risk of stroke is known to be higher in blacks than whites, even after adjusting for known risk factors [36]. A lipid component such as lp (a), which is genetically-influenced and is higher in blacks [18], would be an ideal risk factor to explain this difference. At least in young women, our data do not support this hypothesis.

Nagayama [17] reported significantly higher lp (a) concentrations in patients with atherothrombotic stroke as compared to controls and noted that this difference was more prominent in patients under the age of 45, suggesting lp (a) may be a more important risk factor in young stroke patients. The number of young stroke patients, however, was small ($n = 11$). In our study, 15 patients were classified as having possible/probable stroke due to large artery atherosclerosis. Although the mean lp (a) concentration was higher in this subgroup as compared to controls, the difference was not statistically significant. Mean lp (a) values were significantly elevated in the lacune group compared to controls, due

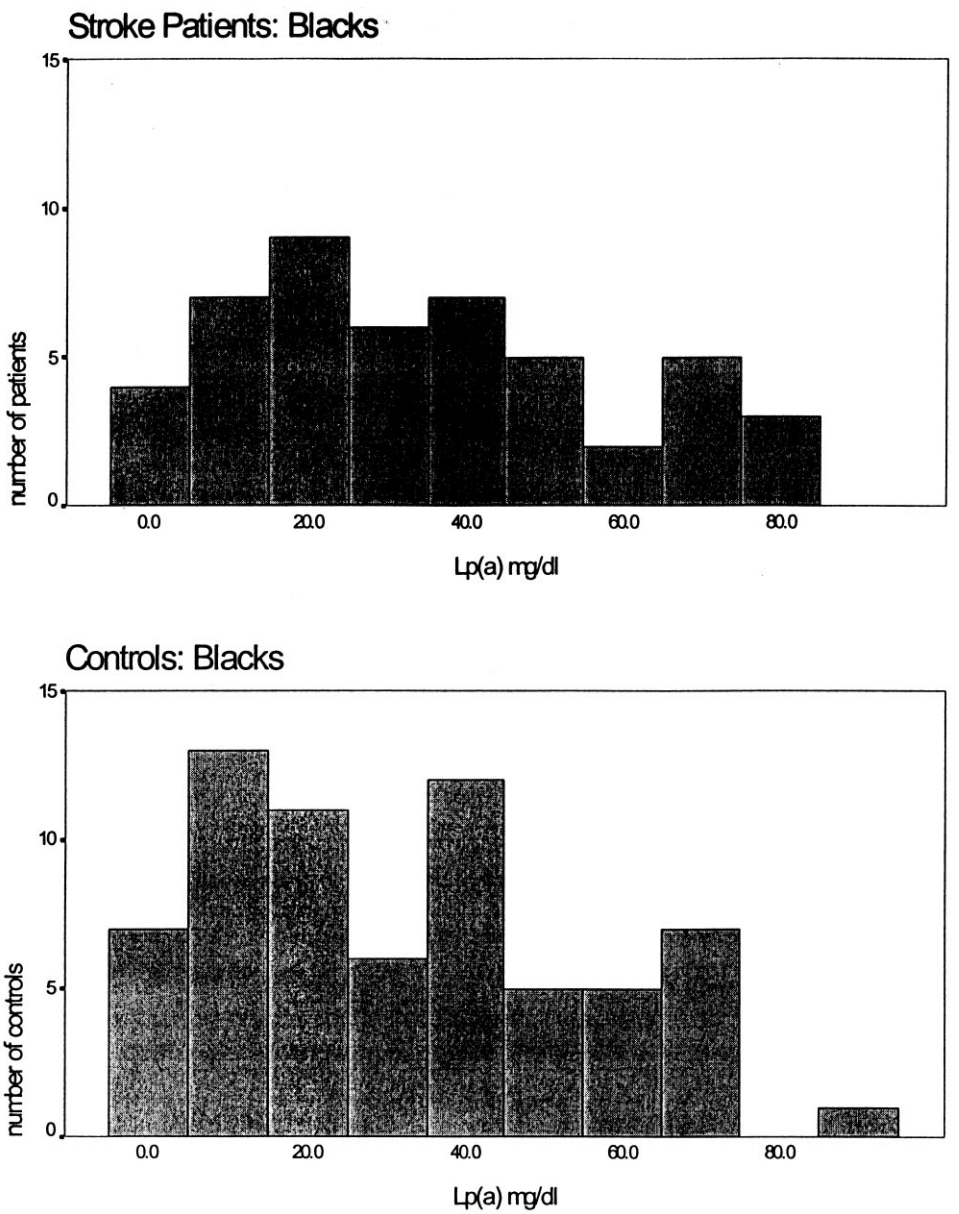

Fig. 1. The distribution of lp (a) values among black stroke patients and controls.

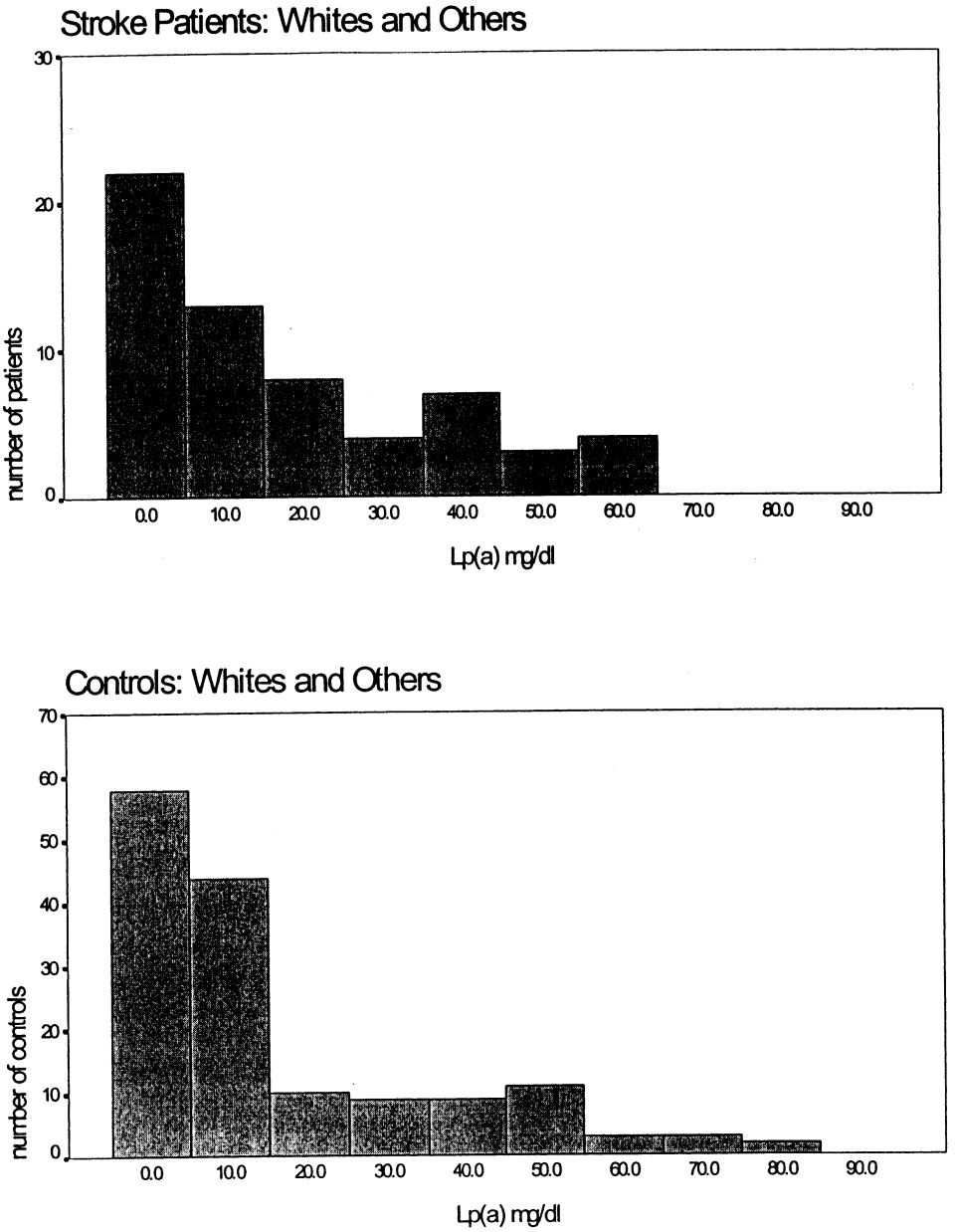

Fig. 2. The distribution of lp (a) values among white stroke patients and controls.

Table 3
Lipoprotein (a) and race

	Blacks		Whites/other	
	Cases ($n = 49$)	Controls ($n = 66$)	Cases ($n = 61$)	Controls ($n = 150$)
Mean lp (a) (SD) (mg/dl)	35.5 (25.8)	32.2 (28.3)	17.7 (18.7)	16.3 (19.7)
Median lp (a) (mg/dl)	31.3	28.3	8.9	6.9

to markedly elevated lp (a) values in three black patients. While this finding is of interest, the very small number of patients involved suggests a possible spurious result. No other stroke etiology was associated with lp (a) values that were significantly different from controls.

There are several reasons why our results may be at variance with other studies. Our patients are younger than those in previous studies and we evaluated only women. Lp (a) may be a greater risk factor for stroke in men than in women, although this has not been reported in other studies. A substantial proportion of our

Table 4
Odds ratio for stroke by lipoprotein (a) quartile

Quartile	Odds ratio for blacks (95% CI)	Odds ratio for whites/other (95% CI)
1st quartile	Reference group	Reference group
2nd quartile	1.23 (0.24–6.34)	0.75 (0.34–1.66)
3rd quartile	2.22 (0.48–10.2)	1.53 (0.70–3.36)
4th quartile	1.13 (0.25–5.12)	1.16 (0.48–2.77)

subjects were African-American, whereas most previous studies involved predominantly white or Asian populations. In the Atherosclerosis Risk in Communities (ARIC) Study, lp (a) was found to be an independent risk factor for self-reported stroke or TIA in both blacks and whites, with similar odds ratios for both races (blacks 1.17, whites 1.19). Blacks in the United States as well as in Africa have a different distribution of lp (a) concentrations [37,38] and lp (a) polymorphisms [38] compared to other races, and these differences may influence the risk of atherosclerosis. We did not assess lp (a) polymorphisms in our subjects, but there is some evidence that certain polymorphisms are more atherogenic [19,39] or are more potent inhibitors of fibrinolysis [9].

The variable time interval between stroke and blood draw in cases is a potential limitation of our data. Lp (a) may act as an acute phase reactant and has been reported to rise within the first week of myocardial infarction and surgical procedures [40]. Other studies, however, have not confirmed significant changes in lp (a) after acute myocardial infarction [41]. *Kargman et al.* [42] *recently reported serial lp(a) measurements over the first month after acute ischemic stroke and found no significant trend or fluctuation, suggesting the absence of an acute phase response*. The majority of patients in our study had blood drawn for lp (a) more than 2 months after stroke. On retrospective analysis, we found no significance difference in mean lp (a) values in cases who had blood draw before 2 months as compared to after 2 months, making timing of blood draw an unlikely source of bias.

The use of estrogen-containing compounds are known to lower lp (a) concentrations [34,35]. Although cases were more likely than controls to be on OCs at the time of stroke, the OCs were discontinued in all cases after the stroke, typically about a month prior to the time of blood draw for lp (a) and lipid measurements. The lp (a)-lowering effect of OCs would have been removed from these cases, therefore, resulting in relatively higher lp (a) concentrations for these patients. Despite this potential bias in favor of an association of high lp (a) with cases, our results still did not support such a finding. The proportion of women who were peri- or post menopausal or who were on replacement estrogen therapy was small and similar among cases and controls.

If the association of lp (a) with stroke were due to the promotion of premature atherosclerosis, we may have missed such an association because of a relatively small number ($n = 15$) of our cases having large-artery atherosclerotic stroke. Nevertheless, to our knowledge, this is the largest study to date to investigate this question in young stroke patients. Our results with lacunar stroke patients are of interest, but the small number of cases make this finding a preliminary one, needing further confirmation. If lp (a) acts primarily as a hypercoagulable agent, however, one would expect an association with all mechanisms of stroke, which we did not find. *Our study had 80% power to detect an lp (a) difference of 6.1 mg/dl between cases (using all stroke subtypes) and controls and greater than 99% power in detecting a difference of 14 mg/dl. These values are comparable to the range of between 4 and 28 mg/dl differences in lp (a) reported in other studies* [10–20]. Based upon our data, therefore, we cannot recommend routine measurement of lp (a) in young stroke patients at this time. Larger studies will be needed to determine

Table 5
Mean lipoprotein (a) by stroke etiology[a]

	All patients	Black		White/other	
	Mean lp (a) (mg/dl)	No. of cases	Mean lp (a) (mg/dl)	No. of cases	Mean lp (a) (mg/dl)
Large artery atherosclerosis	29.7	10	37.6	5	14.0
Cardioembolism	19.1	12	24.5	14	14.5
Lacune	58[b]	3	90.1[c]	3	26
Other determined cause	23.3	10	38	27	17.9
Indeterminate	23.3	14	29.4	12	20.7
Controls	21.3		32.2		16.3

[a] Patients with multiple etiologies are listed only once, using the following hierarchy: large artery atherosclerosis > cardioembolism > lacune > other determined cause > indeterminate.
[b] $P < 0.05$ cases compared to controls.
[c] $P < 0.01$ cases compared to controls.

if lp (a) is an important risk factor for certain mechanisms of stroke in young adults, such as those with atherosclerotic or lacunar stroke.

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