Lipoprotein (a) and Stroke
A Meta-Analysis of Observational Studies

Barbara Smolders, MSc; Robin Lemmens, MD; Vincent Thijs, MD, PhD

Background and Purpose—The relationship between elevated lipoprotein (a) levels [Lp(a)] and stroke is controversial. We systematically reviewed the literature to determine whether Lp(a) is a risk factor for stroke.

Methods—We searched MEDLINE (1966 to 2006), EMBASE (1974 to 2006), and Google scholar for articles on Lp(a) and cerebrovascular disease. From potentially relevant references retrieved, we excluded uncontrolled studies, studies of children with stroke, studies investigating carotid atherosclerosis, and studies lacking adequate data.

Results—Thirty-one studies comprising 56 010 subjects with >4609 stroke events met all inclusion criteria and were included in the meta-analysis. In case-control studies (n=23 with 2600 strokes) unadjusted mean Lp(a) was higher in stroke patients (standardized mean difference, 0.39; 95% CI, 0.23 to 0.54) and was more frequently abnormally elevated (OR, 2.39; 95% CI, 1.57 to 3.63). Sensitivity analysis and meta-regression did not find any influence of study design, measurement period of Lp(a) in relationship to stroke episode, subtype, age, and sex to explain the substantial heterogeneity between studies (I²=83.7%; P<0.001). There was no evidence of publication bias. In nested case-control studies (n=3 with 364 strokes) Lp(a) was not a risk factor for incident stroke (OR, 1.04; 95% CI, 0.6 to 1.8). In prospective cohort studies (n=5 with >1645 strokes), incident stroke was more frequent in patients in the highest tertile of Lp(a) distribution compared with the lowest tertile of Lp(a) (RR, 1.22; 95% CI, 1.04 to 1.43). There was no publication bias or heterogeneity in the prospective studies (I²=0.00%; P=0.67).

Conclusion—This meta-analysis suggests that elevated Lp(a) is a risk factor for incident stroke. (Stroke. 2007;38:1959-1966.)

Key Words: lipids ▪ meta-analysis ▪ risk factors ▪ stroke

Lipoprotein (a) [Lp(a)] may be associated with coronary heart disease and stroke because of its potential proatherogenic, prothrombotic, and antifibrinolytic properties.¹,² Lp(a) concentrations vary widely between individuals as the result of genetic variation within the apolipoprotein(a) gene.³ A previous meta-analysis found an association between elevated Lp(a) concentration and incident coronary artery disease.⁴ Whether Lp(a) is a risk factor for stroke has not been well-established. We performed a meta-analysis of observational studies to investigate the relationship between elevated levels of Lp(a) and stroke.

Materials and Methods

Data Research and Inclusion Criteria
Three investigators (B.S., R.L., V.T.) selected possibly relevant articles in the electronic databases MEDLINE, EMBASE (January 1960 through May 2006) and Google Scholar with key words stroke, cerebrovascular accident, (transient) ischemic attack, cerebral hemorrhage, cerebrovascular disease, cerebrovascular disorders and lipoprotein(a), apolipoprotein(a), and Lp(a). We manually searched bibliographies of review articles, articles, and textbooks.

We limited our analysis to case-control studies, nested case-control studies, and cohort studies of fatal and nonfatal cerebrovascular disease. We excluded studies in languages other than English, French, German, or Dutch, case reports or series of patients without controls, studies of carotid artery stenosis or wall thickness measured by ultrasound, and studies of special populations such as young patients (<15 years), patients with stroke and diabetes who were compared with other diabetic patients, or patients with stroke and renal insufficiency, who were compared with other patients with renal insufficiency. Furthermore, we excluded studies which failed to report at least 1 of 4 types of data: mean (arithmetic or geometric) concentrations and SDs of Lp(a) for cases and control subjects, proportions of patients with abnormal Lp(a) levels, odds ratios, or measures of relative risk for elevated Lp(a) as reported in the original publication. We tried to contact the authors of the studies that mentioned the median Lp(a) levels to obtain (geometric) mean Lp(a) levels.

Statistical Analysis
Case-control and prospective studies were analyzed separately. Case-control studies were divided in studies reporting means or studies reporting proportions of patients with abnormal Lp(a) levels, defined as Lp(a) levels ≥30 mg/L. Because Lp(a) is positively skewed in most studies, transformation of the data provides less biased means. If a study did not report the transformed (geometric) mean, we used the arithmetic mean as reported in the original publication. The difference between cases and controls was expressed as the standardized mean difference and 95% CI for the
case-control studies reporting continuous outcomes and as an OR with 95% CI for studies reporting proportions of patients with abnormal Lp(a) levels. Crude values were used for these analyses.

The prospective studies were divided in nested case-control studies and prospective cohort studies. We avoided biases caused by methodological differences between studies by performing only within-study comparisons. Among the different studies, Lp(a) was measured by different assays, RRs were determined on the basis of various cut-off levels (comparisons of tertiles, quartiles, or quintiles or specific thresholds), or as increases in risk for a 1-SD increase in Lp(a) levels. Reported adjusted ORs or hazard ratios were transformed using the method proposed by Danesh et al to represent risk ratios that compared the adjusted risk of stroke in the highest tertile of the distribution compared with the adjusted risk of stroke in the lowest tertile of the Lp(a) distribution. One study, based on the interpretation of electrophoretic bands, reported only a few Lp(a) categories. The highest category was assumed to correspond with the top one-third of baseline values, the lowest, with the bottom one-third, as was performed in a previous meta-analysis. One author provided recalculated data.

To some degree, the effect sizes of individual studies included in a meta-analysis will always differ because of sampling error. If this difference is exclusively attributable to sampling error, the effect estimates are considered to be homogeneous and not attributable to systematic differences between studies. Often, however, the variability in effect size estimates exceeds the variability caused by sampling error. In that case, the variation between the effects reported in different studies is considered the result of real differences between studies beyond chance. In a fixed effect model, no variation beyond sampling error is assumed between the studies and the average effect reported in such a meta-analysis is an estimate of the true effect that is similar for each study. If heterogeneity is substantial, this assumption does not hold and the average effect size reported is not correct. One measure to estimate the heterogeneity is the I² value, which reports the amount of variation beyond what would be expected because of sampling error. Values of I² equal to represent low, moderate, and high heterogeneity. The random effects model, as opposed to the fixed effect model, assumes there are truly different effect sizes in each of the included studies, and the effect size reported in this model reflects the ranges of effect sizes that can be found in the different studies. We assumed a random effects model in all analyses.

The reason why the effect sizes in individual studies differ is essential in any meta-analysis with heterogeneous results. Heterogeneity between studies can be explored by comparing the effect sizes in studies with different characteristics. This can be performed using stratified analysis or with meta-regression. In stratified analysis the effect size of studies with different characteristics can be compared if the characteristics are dichotomous or ordinal. We stratified the studies based on the following prespecified characteristics that could explain heterogeneity: study design (population based versus other), measurement period of Lp(a) in relationship to stroke episode (>28 days after stroke versus other), and subtype (hemorrhagic versus ischemic stroke). Studies were classified as population-based if controls were randomly selected from the community. The 28-day period was chosen to divide studies that measured Lp(a) in the acute phase of stroke versus more chronic phases of stroke, because elevated Lp(a) has been reported to be a possible acute phase reactant. However, this is controversial. Meta-regression is used if the characteristics that vary between study characteristics are continuous. We performed meta-regression to estimate the influence of sex and age. These analyses cannot accommodate for within study variation. This can only be explored by collecting the individual patient data, which were not available to us.

When studies reported results separately in males or females, in ethnic groups, or with different timing after stroke or stroke subtype, these subgroups were considered as individual studies in the meta-analyses rather than using the overall combined result for these studies. The Egger test and a funnel plot were used to detect publication bias. Funnel plots depict the trial effect size estimates against sample size. Estimates from small studies will scatter at the bottom of the graph, with the dispersion narrowing among larger studies. In the absence of publication bias, the plot will resemble a symmetrical inverted funnel. Funnel plot asymmetry can be formally analyzed using Egger test. P<0.10 are considered indicative of publication bias. Statistical analysis was performed with Comprehensive Meta-analysis 2 (Biostat Inc).

We calculated the population-attributable risk from the prospective incidence studies, based on the relative risk from our meta-analysis and exclusively attributing excess risk in the highest tertile of the Lp(a) distribution. The population-attributable risk percentage is calculated according to the following formula: population-attributable risk %=population fraction (RR−1)/population fraction (RR−1)+1, where population fraction is the population fraction with the risk factor.

**Results**

**Search Results**

The study selection process is detailed in Figure 1.

**Case-Control Studies**

From the 40 articles with a case-control design, 17 studies could not be used because of the reporting of medians (n=7),23-25 or adjusted ORs (n=3).26-28 different cut-off levels to define abnormal Lp(a) (n=2),29-30 or partially overlapping study populations (n=2).31-34 One study reported twice on the same population.33,34 We used the most recent study after communication with the author.33 Another study was based on the same population but used different questionnaires, which caused some overlap in the populations.31,32 We used the most...
comprehensive study.32 The excluded case-control studies because of the reporting of medians examined 664 stroke cases and 824 controls. Except for 3 studies, these reported a positive association between elevated Lp(a) and stroke.21,22,30

Prospective Studies
From the 11 prospective studies,7,8,35–43 3 studies could not be included because of the reporting of medians examined 664 stroke cases and 824 controls. Except for 3 studies, these reported a positive association between elevated Lp(a) and stroke.21,22,30

Excluded Case-Control Studies
The excluded case-control studies because of the reporting of medians examined 664 stroke cases and 824 controls. For 3 of these studies, these reported a positive association between elevated Lp(a) and stroke.21,22,30

Prospective Studies
From the 11 prospective studies,7,8,35–43 3 studies could not be included because of incomplete data.35,39,42 One cohort study did not measure Lp(a) directly, but relied on a pattern on electrophoresis indicative of elevated Lp(a).35 Two of the 3 studies did not show an effect on incident stroke.39,42

Included Studies
We identified 23 case-control studies (n = 19 530) with 2600 strokes, 3 nested case-control studies (n = 1027) with 364 strokes and a median follow-up of 7.5 years, and 5 cohort studies (n = 35 453) with >1645 strokes and a median follow-up of 7.4 years. The characteristics and original results of
each study are listed in supplemental Tables I through IV, available online at http://stroke.ahajournals.org.

Analysis of Case-Control Studies
Figure 2 shows the results of analysis of the unadjusted case-control studies. Both the studies reporting means and SD (standardized mean difference, 0.39; 95% CI, 0.23 to 0.54) or proportions of abnormal Lp(a) (OR, 2.39; 95% CI, 1.57 to 3.63) show an increased risk with elevated Lp(a) (Figure 2). There is evidence for heterogeneity ($I^2 = 83.7\%; P<0.001$) but not for publication bias (intercept = 0.29; $P=0.86$; Figure 3). Sensitivity analysis (Figure 4) and meta-regression do not explain the important heterogeneity.

There were 6 studies that used hospital based controls and 17 studies with community controls. The delay between onset of symptoms and drawing of blood was detailed in 17 studies. Twelve studies reported the arithmetic mean and 3 studies reported the geometric mean. Five studies examined all strokes (hemorrhagic and ischemic) and 18 studies examined the risk in ischemic stroke alone. Three from the 5 studies reported separate risks for intracerebral hemorrhage versus ischemic stroke, and the risk of hemorrhage in these 3 studies is compared with the risk of ischemic stroke in all other studies. The heterogeneity is not explained by the proportion of male subjects in the individual studies ($P=0.15$) or the average age of the included subjects ($P=0.74$) in meta-regression analysis.

Analysis of Nested Case-Control Studies
Analysis was performed on 3 nested case-control studies. These studies were variably adjusted for age, sex, diabetes, weight, total cholesterol, and smoking status (supplemental Table III). All studies were performed in white patients. In 1 study, subjects were selected from a randomized trial; in 2 studies subjects were derived from population-based cohort studies. These studies report on ischemic cerebral infarction, ischemic stroke, or all strokes (ischemic or hemorrhagic). Only 1 study provides results for thromboembolic stroke separately. The RR for the risk of stroke in the highest tertile compared with the lowest tertile of the Lp(a) distribution is 1.04 (95% CI, 0.6 to 1.8; Figure 5). There is no evidence for heterogeneity ($I^2 = 0.00, P=0.87$) or publication bias (intercept = −1.00; $P=0.50$; Figure 3).
Analysis of Cohort Studies
There were 5 cohort studies with various control of other risk factors like age, gender, hypertension, systolic and diastolic blood pressure, diabetes mellitus, cigarette smoking (pack-years or ever smokers versus never smokers), total cholesterol, LDL and HDL levels, and body mass index (supplemental Table IV). All studies examined white patients, and 2 also examined black patients. These studies reported on TIA or cerebrovascular accident, TIA or ischemic strokes, ischemic stroke, or all strokes (ischemic or hemorrhagic) as outcome parameters. One study provided subtyping of strokes into lacunar, nonlacunar, and cardioembolic ischemic stroke. Three studies were derived from community-based cohorts, 1 study from general practices, and 1 study examined patients enrolled in a randomized controlled trial. Patients with Lp(a) values in the highest tertile had an increased risk for incident stroke developing (RR, 1.22; 95% CI, 1.04 to 1.43; Figure 5). There is no evidence of heterogeneity (I² = 2.85; P = 0.41) or publication bias (intercept = 0.61; P = 0.63; Figure 3). There is no influence of age (P = 0.72) or sex (P = 0.90) on the observed effect. The RR of 1.22 is associated with a population-attributable risk 6.8%, and the upper and lower confidence limits with a population-attributable risk of 1.3% or 12.4%.

Combined Analysis of Nested Case-Control Studies and Prospective Cohort Studies
Nested case-control studies and prospective cohort studies were combined in a single analysis. The ORs in the nested case-control studies were interpreted as RRs for this analysis. Patients with Lp(a) values in the highest tertile had an increased risk of incident stroke developing (RR, 1.22; 95% CI, 1.04 to 1.43; Figure 5). There is no evidence of heterogeneity (F = 2.85; P = 0.41) or publication bias (intercept = 0.61; P = 0.63; Figure 3). There is no influence of age (P = 0.72) or sex (P = 0.90) on the observed effect. The RR of 1.22 is associated with a population-attributable risk 6.8%, and the upper and lower confidence limits with a population-attributable risk of 1.3% or 12.4%.

Discussion
This meta analysis indicates that there is an association between Lp(a) and stroke, possibly because of low power, and the point estimate and upper confidence intervals fall within the range of the association found in the prospective studies. In the case-control studies, heterogeneous results were obtained, making interpretation of the combined effect size difficult.

The heterogeneity in the case-control studies remains unexplained with our a priori defined variables. Possible causes of heterogeneity are the choice of controls and the use of different measurement methods. Measurement of Lp(a) was performed with different methods: radial immunodiffusion, immunoradiometry, fluorescence immunoassay, immunonephelometry, turbidimetry, latex agglutination assay, and enzyme-linked immunosorbent assay. As a result, the mean concentration of Lp(a) found in controls varied between studies from 14 to 322 mg/L. Several case-control studies defined abnormal Lp(a) levels at the same cut-off of 30 mg/dL, even though the methods for measurement used were very diverse, and this cut-off has not been validated. Because of the variety of methods used, we were not able to include method as a covariate in our meta-analysis. The heterogeneity may also have been caused by the choice of included subjects. In most studies patients were admitted to the hospital, and different types of hospital controls were used. Also, some studies included patients with intracerebral hemorrhage or did not specify the subtypes of stroke patients that were included. Still, we were unable to show a difference when we compared the effect size in community controls versus hospital-based controls, nor was there a significant difference between the effect in studies of ischemic stroke versus hemorrhagic stroke. In the studies that reported unadjusted comparisons of Lp(a) levels in cases or controls, part of the heterogeneity may be explained by the use of arithmetic means instead of geometric means, but this also was not a significant factor in our sensitivity analysis. Lp(a) has a positively skewed distribution; hence, a geometric mean is preferred for use in meta-analysis because the arithmetic mean may be influenced by extreme values and give misleading results. Paradoxically, the studies reporting
on geometric means showed a larger difference between cases and controls.

Two prospective studies reported a significant association between Lp(a) and stroke. One of these studies compared the distribution of Lp(a) in intervals of 100 μg/mL and found a significant independent association with stroke once Lp(a) levels exceeded 300 μg/mL in women. However, when re-analyzed according to tertiles of the Lp(a) distribution and assuming a monotonous increase in risk with increasing Lp(a) levels, there was no association. The question whether there is a dose response or an increased risk above a certain threshold of Lp(a) remains unanswered at this moment. One other study found a 3-fold increased risk of stroke in men with Lp(a) in the highest quintile, but no increased risk in females.

Two meta-analyses link raised Lp(a) levels to an increased risk of coronary heart disease. The meta-analysis of prospective studies included 27 studies with an average follow-up of 10 years and >5400 cases. The global RR found was 1.7 (95% CI, 1.4 to 1.9). We found a smaller risk for stroke. Several reasons may explain this difference. The power to detect an effect on coronary artery disease was probably larger given the availability of more studies, the longer follow-up, and the presence of 4- to 5-times more cardiac end points in these studies. Another explanation for the reduced effect in stroke may be attributable to the more heterogenic etiology of stroke as opposed to coronary artery disease. The etiology of ischemic stroke involves large- and small-vessel atherosclerosis or embolization from cardiac or arterial sources, whereas coronary artery disease is almost exclusively caused by atherosclerosis.

The impact of a risk factor depends on its prevalence in the population. Risk factors with elevated risk ratios, but low prevalence, may not be as important on the population level as factors with more modest relative risk but high prevalence. We calculated that if Lp(a) was found to be a causal risk factor in randomized controlled trials, eliminating its excess risk may be associated with reduction of stroke incidence of up to 12.4%.

Limitations
The use of formal meta-analytic methods to observational studies is controversial, because weaknesses implicit in the

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**Figure 5.** Forest plot of nested case-control studies and prospective cohort studies. RR of upper third level of Lp(a) distribution with lower third of Lp(a) distribution. †Results reported for males (top) and females (bottom) separately. ‡Results reported from top to bottom for black men, black women, white men, and white women.
study design of case-control studies and cohort studies may bias the strength of associations within the data. Studies included in our analysis had different inclusion and exclusion criteria, and to combine results across studies may be inappropriate, especially when heterogeneity is high, as with the case-control studies. The results from the case control studies may artifactively report a stronger association than the true effect, because most studies reported arithmetic means that are more influenced by outliers than geometric means. Caution is therefore needed in interpreting the results from the case-control studies. We were unable to combine the results of different study designs because we were unable to convert the effect sizes from these studies to a common metric. The degree of control for different other covariates between studies varied; however, our method of analysis compares the within-study risk of stroke. One prospective study reported elevated Lp(a) in quartiles, instead of tertiles. Exclusion of this study from the meta-analysis did not modify the results substantially. Within-study heterogeneity could not be explored as we did not have access to individual patient data. We were not able to include all published case-control studies or cohort studies because data could not be analyzed or entered into the meta-analysis because of various ways of reporting data. The results of these studies are, however, in general agreement with the findings of our meta-analysis. Stroke subtypes were not reported uniformly in many studies precluding their analysis. Also, few studies examined patients with a stroke history. There was no evidence for publication bias in any of the study subtypes, but we acknowledge that Egger test for detection of publication bias has reduced power when the number of studies is limited.

Conclusion
Lp(a) is a risk factor for cerebrovascular disease. In future studies, uniform methods of Lp(a) measurement and reporting should be used. Whether Lp(a) is especially involved in the pathogenesis of certain subtypes of stroke remains unsettled.

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Disclosures
None.

References


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