Plasma Lipoprotein(a) Indicates Risk for 4 Distinct Forms of Vascular Disease

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Background: Increased lipoprotein(a) [Lp(a)] concentrations are predictive for coronary artery disease (CAD). The risk conferred by Lp(a) for other types of vascular disease compared with CAD has not been investigated within a single population. This study aimed to investigate Lp(a) risk association for 4 different types of vascular disease (including CAD) within a predominantly white population.

Methods: We used an Lp(a) ELISA that measures Lp(a) independently of apolipoprotein(a) size to measure plasma Lp(a) in patients [384 CAD, 262 peripheral vascular disease, 184 ischemic stroke (stroke), 425 abdominal aortic aneurysm] and 230 disease-free controls. We then conducted association studies with logistic regression, integrating the potential confounding effects of age, sex, diabetes, plasma lipids, and a history of previous hypertension, hypercholesterolemia, and smoking.

Results: Multivariate analyses with Lp(a) concentrations of >45 nmol/L (the 75th percentile value for controls) as the clinical cutoff showed increased Lp(a) concentrations to be a risk factor for all disease groups, with adjusted odds ratios ranging from 1.96 [95% confidence interval (CI) 1.24–3.08] for CAD to 2.33 (95% CI 1.39–3.89) for PVD. The risk conferred by Lp(a) appeared to be independent of other confounders, including exposure to statin/fibrate therapies. Similar odds ratios and CIs between disease groups indicated that increased Lp(a) conferred a similar risk for all groups studied.

Conclusions: Lp(a) constitutes a stable risk factor of similar magnitude for 4 major forms of vascular disease. This association was not altered by exposure to standard lipid-lowering therapy.

Atherosclerosis, a chronic condition characterized by the formation of lipid-rich plaques within the walls of medium and large arteries (1, 2), underlies many forms of vascular disease. The development of vascular disease is dependent on multiple genetic and environmental determinants (2), and there is heavy reliance on large multifactorial association studies to identify individual risk factors (3). Among the most prominent group of risk factors identified by this approach have been the plasma lipoproteins as measured by total serum cholesterol (TC), triglyceride (TG), LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C). These have proven to be reliable predictors of vascular disease risk in many large clinical cohorts (4, 5). Despite the advent of effective dietary (6) and drug treatments (7) to modify lipoprotein concentrations, however, studies show that vascular disease remains prevalent among individuals whose plasma lipoproteins have reached target concentrations (8).

Lipoprotein(a) [Lp(a)] is a plasma lipoprotein that consists of an LDL molecule covalently linked to the plasminogen “look-alike”, apolipoprotein(a) [apo(a)] (9). Unlike other plasma lipoproteins, Lp(a) is very resistant to change by diet or lipid-lowering drugs (10). The concentrations of Lp(a) in human plasma vary from 0 to >300 nmol/L, show ethnic differences (11), and appear to be strictly genetically controlled, largely by a well-characterized size polymorphism in the apo(a) gene (12). Although the exact physiological role of Lp(a) has not been definitively established, substantial evidence indicates that Lp(a) is both atherogenic and thrombogenic in

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nature (13). The high heritability of plasma Lp(a) concentrations and their lack of responsiveness to environmental influences suggest a potential value of Lp(a) as a stable risk factor for vascular disease.

Increased plasma Lp(a) has been shown to be an independent risk factor for many forms of vascular disease, including coronary artery disease (CAD), (14–16) peripheral vascular disease (PVD) (17–19), ischemic stroke (20–22), and abdominal aortic aneurysm (AAA) (23, 24). The status of Lp(a) as a risk factor has been controversial, however, with several large studies showing no apparent association (25–28). The general consensus, at least for CAD, is that Lp(a) is an independent risk factor as established by a recent metaanalysis of 27 prospective CAD cohorts involving 5436 cases (29).

Most studies evaluating Lp(a) as a risk factor have included just 1 form of vascular disease. Differences in the methods used to measure Lp(a) (10), the type of data analysis, and the population size and ethnicity preclude evaluation of the relative importance of Lp(a) as a risk factor for different forms of vascular disease across these studies. This study aimed to investigate the risk conferred by Lp(a) for 4 distinct forms of vascular disease (CAD, PVD, stroke, and AAA) within a predominantly white population by using the consensus reference method for Lp(a) (30) that is unaffected by bias from apo(a) isoform size.

**Materials and Methods**

**STUDY PARTICIPANTS**

Vascular disease patients, mainly of white origin (>97%), were recruited from the Otago region of New Zealand as previously described (31) and compared with a healthy elderly control group from the same geographical region. All participants provided written informed consent, and the study was undertaken with the approval of the Regional Ethics Committee. A total of 1255 patients were examined, in whom vascular disease consisted of coronary artery disease (CAD, n = 384), ischemic peripheral vascular disease (PVD, n = 262), ischemic stroke (stroke, n = 184), and abdominal aortic aneurysm (AAA, n = 425). Patients classified as having CAD all had angiographically proven coronary artery stenosis of ≥50% of the vessel internal diameter in at least 1 vessel. The percent-age diameter stenosis was visually estimated as the maximum percentage reduction in the vessel diameter expressed as a percentage of the angiographically normal adjacent vessel. Peripheral vascular disease was defined as significant stenosis in multiple segments, including clinical symptoms such as claudication, pain during rest, or tissue loss. The diagnosis of PVD was further confirmed with a resting ankle-brachial index <0.7, pulse volume recordings, arteriography, and/or duplex arterial scan. Stroke patients had clinical symptoms consisting of rapidly developing signs of a focal or global disturbance of cerebral function, with symptoms lasting more than 24 h. The diagnosis was confirmed by computerized tomography or magnetic resonance imaging of cerebral infarction. AAA patients examined in this study had infrarenal aneurysms >5 cm in maximum anteroposterior diameter, as determined by ultrasound scan. All patients with PVD, CAD, or stroke underwent abdominal ultrasound examination to identify concurrent AAA and were excluded if the maximum anteroposterior aortic diameter was >2.5 cm. All patients with disease of undetermined etiology were excluded. We recruited controls from local Otago community groups, with inclusion criteria of age >55 years, no history of ischemic heart disease, including angina pectoris, PVD, stroke (including transient ischemic attack), or AAA and being currently in good general health. All study participants completed a questionnaire to ascertain demographic risk factors, including age, sex, history of hypertension and hyperlipidemia, current medication, concurrent disease such as ischemic heart disease, PVD, stroke, and diabetes. An experienced clinical research technician assisted participants with questionnaire completion. Smoking habits (current and past) were assessed and the number of pack years (20 cigarettes per day for 1 year) was calculated.

**BLOOD COLLECTION AND LIPID MEASUREMENTS**

We obtained venous blood samples from all participants with vacuum tubes containing EDTA. Plasma was separated from cells and aliquots stored at −80 °C until Lp(a) and lipid concentrations were measured. Storage times before measurement ranged from 3 months for stroke samples to a maximum of 5 years for the AAA samples (mean 2.6 years). A subset of plasma samples from each group was subjected to apo(a) Western blot analysis (32) to check for sample degradation. We determined Lp(a) concentrations by a double-sandwich ELISA as previously described (30), using monoclonal antibody (MAb) a-6 as the capture antibody and MAb a-1 as the detection antibody. This assay detects all apo(a) isoforms on an equivalent molar basis, and is considered to be an accurate method for Lp(a) measurement (33). The limit of quantification of this assay was 2 nmol/L at a 1:200 sample dilution. We measured plasma total cholesterol and triglycerides using Roche Diagnostics enzymatic methods. HDL-C was measured with Roche HDL-C Plus reagents. LDL-Cholesterol was calculated using the Fried-wald formula (34).

**STATISTICAL ANALYSES**

We performed statistical analysis with StatView version 5.01 (SAS Institute). The χ² test was used to compare observed with expected frequencies. ANOVA tests were used to compare lipid variables of vascular disease patients with those of controls. Because the Lp(a) distribution was nonnormal, we used the Mann–Whitney U-test to compare median Lp(a) concentrations for each patient group with those of controls. We compared the distribution of plasma Lp(a) by plotting the concentrations against percentiles for each group. Relative risk was
estimated in terms of odds ratio and corresponding 95% confidence interval (CI). Risk assessment models used either Lp(a) concentrations <45 nmol/L (the 75th percentile value for controls) or <4.5 nmol/L (the 25th percentile value for controls) as cutoff values for the reference group. We conducted a secondary assessment using 75 nmol/L as the high cutoff so that comparison could be made with previously published results from the Framingham study control population (13). An assessment of the risk conferred by having an Lp(a) concentration <2 nmol/L was also performed using controls with Lp(a) concentrations >2 nmol/L as the reference group. We used multiple logistic regression to test interactive effects of variables, producing adjusted analyses assessing Lp(a) concentration as a risk factor for CAD, PVD, stroke, and AAA. Significant or suggestive (P < 0.15) univariate confounders of either patient group or Lp(a) concentration were identified and applied to a multivariate regression model. The resulting winnowed model included age, sex, history of hypertension, hypercholesterolemia, diabetes, total and HDL cholesterol, and smoking history. Because of interacting effects with other modeled variables, a separate analysis was conducted to determine the confounding influence of exposure to lipid-lowering therapies.

**Results**

Analyses of demographic profiles highlighted significantly higher frequencies of history of hypertension, hypercholesterolemia, and smoking in all vascular disease patients compared with controls without vascular disease (Table 1). The frequency of diabetes was significantly increased in patients with CAD, PVD, and stroke, but not patients with AAA, compared with controls (Table 1). The lipid profiles among the vascular disease groups were not hypercholesterolemic compared with the controls, although the AAA group did have a mean total cholesterol of 5.6 mmol/L, which could be considered hypercholesterolemic. This result was most likely due to the lower rate of lipid-lowering treatments in the AAA group. Indeed, total and LDL-C concentrations were significantly lower in the CAD, PVD, and stroke groups, likely a direct reflection of the higher incidence of lipid-lowering treatment in these groups compared with the AAA and control groups. HDL-C concentrations were significantly decreased in CAD and AAA patients (Table 1).

The integrity of samples for Lp(a) measurement, as checked by apo(a) Western blotting, showed little evidence of apo(a) degradation among subsets of samples from each disease group (see Fig. 1 in the Data Supplement in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol53/issue4). Within the AAA patient population (which had the largest range of sample storage times), there was no significant difference in Lp(a) concentrations between short- (<6 months) and long-term (>4 years) stored samples.

Plasma Lp(a) concentrations were significantly higher in patients within all 4 vascular disease groups compared with controls (Table 1). A plot of Lp(a) concentrations across percentiles demonstrated a nongaussian distribution, which was highly skewed toward lower concentrations. A divergence between the Lp(a) concentrations for the control group and that for all vascular disease groups was apparent from the 50th percentile (17 nmol/L in controls, Fig. 1). The 75th percentile of the control group corresponded to an Lp(a) concentration of 45 nmol/L. The commonly applied risk-associated concentration of 75 nmol/L (10, 33) corresponded to approximately the 80th percentile of controls in the current study. The proportion

| Table 1. Demographic profiles of the vascular disease populations. |
|-------------------------|----------------|----------------|----------------|----------------|
| Variable                | Controls n = 230 | CAD n = 384 | PVD n = 262 | Stroke n = 184 | AAA n = 425 |
| Sex, male, %            | 33.8            | 72.7<sup>a</sup> | 59.2<sup>a</sup> | 63.7<sup>a</sup> | 77.7<sup>a</sup> |
| Age, years              | 70.3 (6.9)      | 64.0 (9.7)  | 71.6 (9.1)  | 71.9 (10.0)  | 71.7 (7.6)  |
| Hypertension, %         | 31.0            | 51.3<sup>a</sup> | 64.9<sup>a</sup> | 68.5<sup>a</sup> | 55.3<sup>a</sup> |
| Hypercholesterolemia, % | 18.6            | 52.2<sup>a</sup> | 43.2<sup>a</sup> | 55.5<sup>a</sup> | 30.5<sup>c</sup> |
| Lipid-lowering treatment (statin/fibrate), % | 22.4 | 94.6<sup>a</sup> | 65.7<sup>a</sup> | 68.1<sup>a</sup> | 37.0<sup>a</sup> |
| Diabetes, %             | 8.7             | 20.3<sup>a</sup> | 22.9<sup>a</sup> | 23.9<sup>a</sup> | 5.9 |
| Smoking, pack years     | 9.8 (18.3)      | 19.6 (25.8)<sup>a</sup> | 30.6 (33.8)<sup>a</sup> | 21.2 (26.8)<sup>a</sup> | 29.2 (27.9)<sup>a</sup> |
| Ischaemic heart disease  | 0.100           | 100           | 26.7           | 34.7           | 42.8 |
| Total-C, mmol/L         | 5.5 (1.4)       | 4.3 (0.9)<sup>a</sup> | 5.0 (1.1)<sup>a</sup> | 4.9 (1.2)<sup>a</sup> | 5.6 (1.3) |
| LDL-C, mmol/L           | 3.3 (1.2)       | 2.2 (0.8)<sup>a</sup> | 2.6 (1.0)<sup>a</sup> | 2.8 (1.1)<sup>a</sup> | 3.4 (1.2) |
| HDL-C, mmol/L           | 1.3 (0.4)       | 1.1 (0.3)<sup>a</sup> | 1.3 (0.4)       | 1.2 (0.4)       | 1.1 (0.4)<sup>a</sup> |
| Triglycerides, mmol/L   | 2.0 (0.7—9.0)  | 1.8 (0.5—7.8) | 2.0 (0.7—8.0) | 1.7 (0.5—5.3) | 2.0 (0.5—11.2) |
| Lp(a), nmol/L; median, range | 17.0 (<8—285) | 25.5 (<8—471)<sup>a</sup> | 28.8 (<8—539)<sup>a</sup> | 30.6 (<8—386)<sup>a</sup> | 29.9 (<8—583)<sup>a</sup> |
| Lp(a), above 45 nmol/L, % | 24.7            | 40.6<sup>b</sup> | 41.5<sup>b</sup> | 39.1<sup>b</sup> | 39.8<sup>b</sup> |
| Lp(a), above 75 nmol/L, % | 19.5            | 34.6<sup>b</sup> | 31.5<sup>b</sup> | 30.4<sup>c</sup> | 29.3<sup>c</sup> |
| Lp(a), below 2 nmol/L, % | 17.3            | 17.5           | 12.7           | 10.9           | 11.7<sup>c</sup> |

Results are expressed as means (1SD), except for Lp(a) concentrations, which are expressed as medians and range. <sup>a</sup> P < 0.002; <sup>b</sup> P < 0.005; <sup>c</sup> P < 0.05.
of patients with Lp(a) > 45 nmol/L (or 75 nmol/L) was significantly greater in all vascular disease groups compared with controls (Table 1). Because ~5% more vascular disease patients were included in the “at risk” group with the 45 nmol/L cutoff, this cutoff was used for subsequent risk analyses.

The confounding effects of demographic variables on Lp(a) concentrations were assessed. Sex was not significantly associated with Lp(a) concentrations in controls or in PVD, stroke, or AAA patients. Female CAD patients, however, had significantly higher Lp(a) concentrations than their male counterparts (medians 28.8 vs 23.9 nmol/L, Mann–Whitney U-test P < 0.04). A previous history of hypercholesterolemia was significantly associated with increased Lp(a) concentrations within the CAD patient group (medians 18.4 vs 45.4 nmol/L, Mann–Whitney U-test P = 0.0002). Across all disease groups and controls, diabetic individuals had lower Lp(a) concentrations than persons without diabetes (medians 19.9 vs 27.6 nmol/L, Mann–Whitney U-test P < 0.01).

The adjusted odds ratios for increased Lp(a) concentrations (>45 nmol/L) as an indicator of vascular disease risk were determined using multivariate logistic regression. Adjusted odds ratios of 1.96, 2.33, 2.00, and 2.12 were obtained for the CAD, PVD, stroke, and AAA groups respectively, using the >45 nmol/L cutoff (Table 2). Similarly, adjusted odds ratios of 2.06, 2.86, 2.50, and 2.54 were obtained for the CAD, PVD, stroke, and AAA groups, respectively, using the 4th (>45 nmol/L) vs 1st (<4.5 nmol/L) control quartiles (Table 3). All analyses showed considerable overlap in odds ratios and confidence intervals between disease groups, and there was no significant difference in odds ratio between the 4 vascular disease groups. Adjustment for known confounders had very little effect on the odds ratio. The independence of the Lp(a) and vascular disease association, from exposure to lipid-lowering therapy (statin or fibrate medications) was specifically examined. Although Lp(a) odds ratios (>45nmol/L) were slightly reduced when modeled with lipid-lowering therapy, the association of Lp(a), and vascular disease remained significant, both in the combined vascular disease group (odds ratio 1.76, 95% CI 1.3–2.4, P < 0.0005) and the specific disease subgroups. Within subgroups, patients on lipid-lowering therapy did not have significantly different Lp(a) concentrations compared with untreated individuals.

A significant number study participants within the control (17.3%) and vascular disease groups (10.9%–17.5%) had Lp(a) concentrations below the sensitivity (<2 nmol/L) of the assay (Table 1). Only the AAA group had a significantly smaller proportion of individuals with Lp(a) <2 nmol/L than the control group. According to analysis of the adjusted odd ratios (Table 4), having an Lp(a) <2 nmol/L had no significant effect on the risk of vascular disease for any of the disease groups.

### Table 2. Logistic regression for Lp(a) >45 nmol/L and risk of various forms of vascular disease.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio for Lp(a) &gt;45 nmol/L</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>2.89</td>
<td>1.29–3.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVD</td>
<td>2.17</td>
<td>1.47–2.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.96</td>
<td>1.29–2.99</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>AAA</td>
<td>2.02</td>
<td>1.41–2.88</td>
<td>0.0001</td>
</tr>
<tr>
<td>All vascular disease patients</td>
<td>2.06</td>
<td>1.50–2.84</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>1.96</td>
<td>1.24–3.08</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>PVD</td>
<td>2.33</td>
<td>1.39–3.89</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.00</td>
<td>1.22–2.62</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AAA</td>
<td>2.12</td>
<td>1.37–2.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All vascular disease patients</td>
<td>2.03</td>
<td>1.37–2.98</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

The reference population were control individuals free of vascular disease, with Lp(a) <45 nmol/L. Odds ratios were expressed with 95% CI. A P value <0.05 was considered significant. The adjusted model accounted for age, sex, history of hypertension, hypercholesterolemia, diabetes, total and HDL cholesterol, and smoking history.
to evaluate Lp(a) as a risk factor for the development of multiple forms of vascular disease within the same population. The population studied was recruited from the same geographical area and was of uniform ethnicity. Lp(a) measurements were performed with an assay that recognizes apo(a) size isoforms on an equal basis and is considered to be the consensus reference method for Lp(a) measurement (33).

The demographics of Lp(a) within the population studied here were similar to those reported for other white populations, i.e., a nongaussian distribution that was highly skewed toward low concentrations. The median Lp(a) concentration of 17 nmol/L in our control group was similar to the 20 nmol/L value reported in a large study of American whites (35). The 75th percentile value for controls was 45 nmol/L (Fig. 1), which is lower than the commonly used cutoff concentration of 75 nmol/L derived as the 75th percentile value from the Framingham study control population (13). We used >45 nmol/L as the clinical cutoff for increased Lp(a) in this study, because the greatest divergence between the control and disease groups occurred at this concentration. Furthermore, at this concentration rather than 75 nmol/L, 5% more of the vascular disease patients were placed in the at risk group, a feature that may be of clinical benefit with respect to more aggressively treating patients for other risk factors. After adjustment for known risk factors, the risk conferred by Lp(a) >45 nmol/L ranged from 1.96 to 2.33 across all forms of vascular disease studied. Interestingly, similar adjusted odds ratios (all vascular disease patients, odds ratio 2.0; 95% CI 1.31–3.03, P < 0.002) were obtained if the commonly applied >75 nmol/L (33) cutoff was used. Slightly higher odds ratios, ranging from 2.06 to 2.86, were derived from comparison of the upper vs lower quartiles. Notably, there was no significant difference in risk ratios between disease groups for all 3 analyses, indicating a similar risk conferred by increased Lp(a) across all vascular disease groups.

A large proportion of individuals with Lp(a) >45 nmol/L had concentrations <2 nmol/L. We were originally concerned that a high number <2 nmol/L individuals in the <45 nmol/L reference group may have accentuated the risk ratio analysis. However, an analysis to establish the effect of having an Lp(a) <2 nmol/L on vascular disease risk showed no significant effect across all groups.

Lp(a) shows both atherogenic and thrombogenic properties. Atherogenic properties include a high affinity for extracellular matrix proteins (36) and an ability to accumulate oxidized phospholipids (37), which promote inflammation, and thrombogenic properties center around the ability of the apo(a) protein to inhibit plasminogen activation (38). The etiologies of the various forms of vascular disease studied here involve atherosclerotic and thrombotic processes, although the relative importance of these processes might be expected to vary between the

### Table 3. Logistic regression for Lp(a) 4th quartile and risk of various forms of vascular disease.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio for Lp(a) in 4th Quartile</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>1.98</td>
<td>1.26–3.13</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>PVD</td>
<td>2.29</td>
<td>1.39–3.77</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.36</td>
<td>1.35–4.13</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>AAA</td>
<td>2.25</td>
<td>1.43–3.54</td>
<td>0.0005</td>
</tr>
<tr>
<td>All vascular disease patients</td>
<td>2.18</td>
<td>1.47–3.25</td>
<td>0.0001</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>2.06</td>
<td>1.14–3.71</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>PVD</td>
<td>2.86</td>
<td>1.43–5.72</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.50</td>
<td>1.28–4.86</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AAA</td>
<td>2.54</td>
<td>1.41–4.56</td>
<td>0.002</td>
</tr>
<tr>
<td>All vascular disease patients</td>
<td>2.37</td>
<td>1.43–3.92</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The reference population was controls with Lp(a) in the first quartile (≤4.5 nmol/L). Odds ratios were expressed with 95% CI. A P value <0.05 was considered significant. The adjusted model accounted for age, sex, history of hypertension, hypercholesterolemia, diabetes, total and HDL cholesterol, triglycerides, and smoking history.

### Discussion

The majority of studies establishing Lp(a) as a vascular disease risk factor have done so in populations with CAD. The association with other forms of vascular disease is less clear, although some large cohorts have established Lp(a) as a risk factor for stroke (21, 22). There are fewer studies evaluating Lp(a) as a risk factor for PVD and AAA, and many are limited by small study populations (17, 19, 23). The many differences in population size, ethnicity, and method of Lp(a) measurement make it difficult to assess the value of Lp(a) as a risk factor across different vascular diseases. Indeed, many studies have used assays that are sensitive to apo(a) isoform size, therefore introducing some bias in the Lp(a) measurement. The present study is the first cross-sectional study

### Table 4. Logistic regression for Lp(a) <2 nmol/L and risk of various forms of vascular disease.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio for Lp(a) Null</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>1.01</td>
<td>0.66–1.55</td>
<td>0.97</td>
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<tr>
<td>PVD</td>
<td>0.69</td>
<td>0.42–1.14</td>
<td>0.15</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.58</td>
<td>0.33–1.04</td>
<td>0.07</td>
</tr>
<tr>
<td>AAA</td>
<td>0.63</td>
<td>0.40–0.99</td>
<td>&lt;0.05</td>
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<tr>
<td>Adjusted</td>
<td></td>
<td></td>
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<tr>
<td>CAD</td>
<td>1.03</td>
<td>0.56–1.83</td>
<td>0.91</td>
</tr>
<tr>
<td>PVD</td>
<td>0.65</td>
<td>0.32–1.34</td>
<td>0.25</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.57</td>
<td>0.29–1.15</td>
<td>0.12</td>
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<tr>
<td>AAA</td>
<td>0.68</td>
<td>0.37–1.24</td>
<td>0.21</td>
</tr>
</tbody>
</table>

The reference populations was controls with Lp(a) >2 nmol/L. Odds ratios are expressed with 95% CI. A P value <0.05 was considered significant. The adjusted model accounted for age, sex, history of hypertension, hypercholesterolemia, diabetes, total and HDL cholesterol, and smoking history.
different vascular diseases. For example, in the case of
AAA, there are pronounced proteolytic and inflammatory
components associated with the breakdown and remodel-
ing of the aortic wall compared with aortic atheroscle-
rotic occlusive disease (39, 40). Results from our study,
however, indicate that any possible difference in the
pathogenic role of Lp(a) is not associated with any signif-
icant changes in relative risk ratios between vascular
disease groups. This finding does not preclude possibility
that Lp(a) and other atherogenic or thrombogenic risk
factors may interact in some populations. For example,
some studies have documented large increases in risk
ratios for stroke when Lp(a) concentrations are combined
with certain thrombogenic risk factors such as factor V
Leiden and antithrombin III deficiency (41).

Although adjusting for known risk factors did not
significantly alter the risk relationship for Lp(a), there
were some interactions between Lp(a) and other vascular
disease risk factors worthy of mention. Of note, the
presence of diabetes was associated with a lower concen-
tration of Lp(a) in the controls and all vascular disease
groups, with the exception of stroke. Our study did not
have the power to dissect this relationship fully, because
some groups (AAA patients and controls) had low num-
bers of diabetics. This relationship, however, is consistent
with a recent study of 587 CAD patients, which showed
that type 2 diabetes patients within the cohort had signif-
ically lower concentrations of Lp(a) than those without
diabetes (42). The mechanism by which diabetes de-
creases Lp(a) is unknown, but merits further investiga-
tion. A highly significant relationship was also observed
in CAD patients between Lp(a) and a history of hyper-
cholesterolemia (typically increased LDL). This probably
reflects the higher risk for CAD when both Lp(a) and LDL
are increased, as has been reported in other studies
(14, 43), hence there is a selection bias for these individ-
uals. The relationship between Lp(a) and LDL cholesterol
was not significant in the current analysis because many
patients were already on lipid-lowering (predominantly
statin) treatment before recruitment. The rates of lipid-
lowering therapies varied considerably across the vascu-
lar disease groups examined in this study. This facilitated
analysis of a possible association between such treatment
and Lp(a) concentrations. Significantly, given the now
widespread use of such agents, this study confirms Lp(a)
as a predictive lipid marker of vascular disease risk,
regardless of exposure to standard lipid-lowering
therapy.

The strengths of this study include a relatively large
study population of uniform ethnicity and the use of an
apo(a) isoform-insensitive method for measuring Lp(a). A
weakness of this study was the likely presence of overlap
between disease groups. Although the presence of AAA
was excluded from other vascular disease groups, and
patients were recruited into disease groups based on the
clinical symptoms and diagnosis associated with their
initial event, we cannot discount the coexistence of other
forms of vascular disease in some patients. The main
finding of the study is that increased Lp(a) is a risk factor,
with similar magnitudes of effect, for CAD, PVD, stroke,
and AAA. The risk is not attenuated by other known risk
factors. We conclude that Lp(a) is a stable marker for
assessing the risk of all major forms of vascular disease.

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