Lipoprotein(a) Genetic Variants Associated With Coronary and Peripheral Vascular Disease but Not With Stroke Risk in the Heart Protection Study

Jemma C. Hopewell, PhD; Robert Clarke, FRCP; Sarah Parish, DPhil; Jane Armitage, FRCP; Mark Lathrop, PhD; Jorg Hager, PhD; Rory Collins, FRCP; on behalf of the Heart Protection Study Collaborative Group

Background—Genetic studies have identified 2 single-nucleotide polymorphisms (SNPs) at the LPA locus (rs3798220 and rs10455872) that are strongly and independently related to lipoprotein(a) levels and to coronary disease risk, but their relevance for other atherothrombotic disease is uncertain.1–4 The Precocious Coronary Artery Disease (PROCARDIS) study identified 2 SNPs explained about half of the genetic variation in Lp(a) levels at the LPA locus (rs3798220 and rs10455872) that are strongly and independently related to lipoprotein(a) levels and to coronary disease risk, but their relevance for other atherothrombotic disease is uncertain.

Methods and Results—These 2 LPA SNPs were examined together as an LPA genotype score for associations with vascular outcomes among participants in the Heart Protection Study. The LPA score was examined first in 12,236 participants with prevalent vascular disease (9277 coronary disease cases, and 1326 ischemic stroke and 2011 peripheral vascular disease cases with no history of coronary disease) and 3687 vascular disease-free controls and, subsequently, in 3251 participants who had incident major vascular events during follow-up (2106 coronary disease, 507 ischemic stroke, and 707 peripheral vascular disease events). For prevalent disease, the LPA score was strongly associated with coronary disease (odds ratio [OR] per variant allele, 1.19; 95% CI, 1.08 to 1.30) and peripheral vascular disease (OR, 1.18; 95% CI, 1.04 to 1.34) but not with ischemic stroke (OR, 1.03; 95% CI, 0.89 to 1.20). Similarly, for incident disease, the LPA score was strongly associated with coronary disease (hazard ratio [HR], 1.20; 95% CI, 1.09 to 1.30) and peripheral vascular disease (HR, 1.20; 95% CI, 1.02 to 1.40) but not with ischemic stroke (HR, 0.83; 95% CI, 0.67 to 1.03).

Conclusions—The comparable strength of associations of the LPA score with coronary disease and peripheral vascular disease but not with stroke suggest that lipoprotein(a) may have effects on atherothrombotic vascular disease that are only relevant at specific sites.


Key Words: lipoproteins ■ genetics ■ stroke ■ coronary disease ■ peripheral vascular disease

Lipoprotein(a) [Lp(a)] is a particle composed of both apolipoprotein [apo](a) and apoB linked by a disulfide bond. Recent studies have demonstrated the importance of genetic variants associated with Lp(a) for risk of coronary artery disease, but the relevance of such variants for stroke and other vascular diseases is uncertain.1–4 The Precocious Coronary Artery Disease (PROCARDIS) study identified 2 single-nucleotide polymorphisms (SNPs) at the Lp(a) locus (LPA) on chromosome 6q26–27 (rs3798220 and rs10455872) that each was strongly and independently related to Lp(a) levels and risk of coronary disease. These 2 SNPs explained about half of the genetic variation in Lp(a) levels at the LPA locus. After adjustment for Lp(a) levels, the effect of the LPA genotype score on risk of coronary disease was completely attenuated, thereby providing strong support for a causal role of Lp(a) levels for coronary disease.1

Received July 20, 2010; accepted December 13, 2010.


The online-only Data Supplement is available at http://circgenetics.ahajournals.org/cgi/content/full/CIRCGENETICS.110.958371/DC1.

Correspondence to Jemma C. Hopewell, PhD, Clinical Trial Service Unit and Epidemiological Studies Unit, Richard Doll Building, Old Road Campus, Roosevelt Dr, Oxford, OX3 7LF, England. E-mail Jemma.Hopewell@ctsu.ox.ac.uk

© 2011 American Heart Association, Inc.

Circ Cardiovasc Genet is available at http://circgenetics.ahajournals.org

DOI: 10.1161/CIRCGENETICS.110.958371

68
Methods

Study Population
Details of the HPS have been reported previously. Between 1994 and 1997, 20,536 men and women aged 40 to 80 years were recruited from 69 collaborating hospitals in the United Kingdom (with ethics committee approval). Participants were eligible for inclusion provided that they had nonfasting total cholesterol concentrations of at least 135 mg/dL (3.5 mmol/L) and had been given either a previous diagnosis of coronary disease, ischemic stroke, other occlusive disease of noncoronary arteries, diabetes mellitus, or (if men aged ≥65 years) treated hypertension. None of the participants were on statin therapy. At the initial screening visit, all participants provided written consent and began a run-in phase involving 4 weeks of placebo followed by 4 to 6 weeks of 40 mg simvastatin daily, after which compliant and eligible individuals were randomly allocated to 40 mg simvastatin daily or matching placebo for approximately 5 years. A nonfasting blood sample was taken at screening (ie, before starting any statin therapy) and at the end of the run-in (ie, while on 40 mg simvastatin daily).

Participants were to be seen in the study clinics for routine follow-up checks at 4, 8, and 12 months and then every 6 months until the final follow-up visits at a mean of 5 years. Information was recorded at each follow-up of any suspected myocardial infarction, stroke, or peripheral vascular disease event. Coronary heart disease events included nonfatal myocardial infarction, coronary revascularization, or coronary death. Deaths attributed to myocardial infarction, other coronary disease (including heart failure due to coronary disease), and sudden or unexpected deaths (without postmortem evidence of another cause) were classified as coronary death. Confirmation of myocardial infarction required evidence of either (1) 2 or more of (a) typical symptoms, (b) diagnostic electrocardiographic changes, and (c) diagnostic elevations of cardiac enzyme concentrations or (2) necrospy findings of myocardial infarction that corresponded to symptom onset. (“Silent” myocardial infarctions were not to be included.) Strokes included nonfatal or fatal ischemic, hemorrhagic, or unclassified stroke and were defined as rapid (or uncertain) onset of focal or global neurological deficit lasting >24 hours or leading to death, with clinical evidence supplemented by neurological imaging or necropsy required to classify strokes as probably ischemic or probably hemorrhagic. (Subarachnoid hemorrhage was to be included, but subdural hematoma or transient cerebral ischemia was not.) Peripheral vascular disease included aortic, carotid, or peripheral revascularization.

Laboratory Assays
The coordinating center laboratory at the Clinical Trial Service Unit in Oxford, England, used standard spectrophotometric enzymatic methods to measure total cholesterol and lipid fractions (including low-density lipoprotein cholesterol [LDL-C] directly) on Beckman autoanalyzers and immunoturbidometric methods to measure apoA1 and apoB. Extraction of DNA from stored WBCs and genotyping were carried out at the Centre Nationale de Génotypage in Evry, France. Genotyping of 14,481 HPS participants of white ethnic origin was performed with a custom IPLEX panel. Genotyping of the rs10455872 (A/G) and rs3798220 (T/C) LPA polymorphisms each showed >99% success rates, with both genotypes available for 14,465 of these HPS participants. ISIS participants were genotyped for the 2 SNPs with the use of a Taqman platform as previously described1 and showed >98% success rates. The minor allele frequencies in successfully genotyped HPS participants were 8.9% for rs10455872 (G) and 2.0% for rs3798220 (C), and both SNPs were in Hardy-Weinberg equilibrium (P=0.09 and P=0.22, respectively). The information from the 2 SNPs was combined into a single LPA genotype score, with values corresponding to the sum of the variant alleles (C for rs3798220 and G for rs10455872) in either of the 2 SNPs.

Statistical Analysis
Differences between among characteristics were assessed by ANOVA (for continuous variables) and by χ² test (for categorical variables) and reported as 2-sided P values. ORs per variant allele were estimated using logistic regression for prevalent disease associations, and hazard ratios (HRs) per variant allele were estimated using Cox proportional hazard models for incident disease associations. The HR estimates for incident events were adjusted for history of coronary disease (as a 3-way variable coding myocardial infarction, other coronary disease, and no coronary disease); history of ischemic stroke, peripheral vascular disease, and diabetes (as a 5-way variable coding each alone, multiple, and none); and randomized treatment allocation. Sensitivity analyses assuming a dominant effect of the LPA genotype score (1 or more LPA variants versus none) also were performed for both prevalent and incident disease associations. SAS version 9.1 was used for all analyses, and the figures were generated using R version 2.10.1.

Results
Baseline Characteristics and Lipid Associations
Table 1 shows selected characteristics at baseline by LPA genotype score. More than 20% of individuals had 1 or more variant alleles, including 1.3% of genotyped individuals who carried 2 variants (and no individuals with >2 variants were observed). The LPA genotype score was positively associated

1.03, for rs1800769). Furthermore, previous studies examining the associations of Lp(a) concentrations with carotid artery intima-media thickness and flow-mediated arterial dilation failed to demonstrate significant associations. Understanding the effects of Lp(a) at different arterial sites may be informative about the mechanisms by which Lp(a) causes vascular disease and have relevance for potential therapies to lower Lp(a) levels for the prevention of atherothrombotic disease.

The 2 LPA SNPs most strongly related to coronary disease were combined as an LPA genotype score and examined for associations with different vascular outcomes in the Heart Protection Study (HPS), a trial of 40 mg of simvastatin versus placebo in persons at high risk of vascular disease. The aim was to examine the associations of LPA variants with coronary heart disease, stroke, and peripheral vascular disease by first using prevalent cases at enrollment and, secondly, using incident vascular events during an average of 5 years of follow-up.
with age and aspirin use and inversely associated with preexisting diabetes mellitus, although the trend with aspirin use was not consistent. Table 2 shows mean plasma levels of cholesterol fractions and apolipoproteins by LPA genotype score in the statin-free prevalent disease controls. Directly measured LDL-C and the related measure of apoB were weakly positively associated with the LPA score, but again, there was no consistent trend across the score for apoB. The distributions of the LPA genotype score by prevalent and incident disease status are given in online-only Data Supplement Table 1.

### Associations of LPA With Prevalent Vascular Disease

Figure 1 shows the associations of the LPA genotype score with prevalent coronary disease, ischemic stroke, and peripheral vascular disease. Individuals with prior coronary disease were excluded when considering LPA associations with ischemic stroke and peripheral vascular disease to control for potential bias. The LPA genotype score was strongly associated with coronary disease (P=0.0002) and, among individuals without known coronary disease, with peripheral vascular disease (P=0.0086), with an ∼20% higher risk per additional LPA variant allele for each disease. By contrast, there was no significant association of the LPA score with ischemic stroke (OR, 1.03; 95% CI, 0.89 to 1.20; P=0.67). The effect of the LPA genotype score differed significantly when coronary disease and stroke cases were compared (P=0.04), but not when coronary disease and peripheral vascular disease cases were compared (P=0.93). Sensitivity analyses assuming a dominant model resulted in slightly stronger, but comparable effect sizes, as would be anticipated based on the allele frequencies (online-only Data Supplement Table 2). Estimates of the effects of the LPA genotype score in men and women considered separately are given in online-only Data Supplement Table 3 and show no significant interaction of the LPA score with sex in any of the disease groups. Associations of prevalent disease with rs10455872 and rs3798220 genotypes considered separately are provided in online-only Data Supplement Table 4. The estimated effects of the 2 SNPs had considerably overlapping CIs in each of the disease groups. Furthermore, the individual SNPs provided no statistically significant information over and above the LPA genotype score, suggesting that the LPA score represented all the relevant information (online-only Data Supplement Table 4). Overall, among the 2381 participants who had previously had a stroke and the 4896 participants with peripheral vascular disease, 44% and 59%, respectively, also had coronary disease. Online-only Data Supplement Figure 1 shows the associations for stroke and peripheral vascular disease when those with coronary disease were not excluded. The association of the LPA score with ischemic stroke was somewhat increased (OR, 1.09; 95% CI, 0.97 to 1.23; P=0.14), and the association with peripheral vascular disease was slightly strengthened (OR, 1.21; 95% CI, 1.09 to 1.33; P=0.0002).

### Association of LPA With Incident Vascular Events

Figure 2 shows the associations of the LPA genotype score with incident coronary events, strokes, and peripheral vascu-
lar disease after adjustment for prior vascular disease and randomized treatment. The LPA genotype score was associated with a \( \approx 20\% \) higher relative risk of coronary events per variant allele (HR, 1.19; 95% CI, 1.09 to 1.30; \( P = 0.0002 \)). LPA genotype score also was associated with a 20% higher relative risk of peripheral vascular disease (HR, 1.20; 95% CI, 1.02 to 1.40, \( P = 0.03 \)). By contrast, there was no significant association of LPA score with the incidence of ischemic stroke (HR, 0.83; 95% CI, 0.67 to 1.03; \( P = 0.09 \)) or stroke overall (HR, 0.84; 95% CI, 0.71 to 1.00; \( P = 0.06 \)). Additional adjustment for risk factors for vascular disease, including age, sex, LDL-C, high-density lipoprotein cholesterol, blood pressure, and smoking had no material impact on these results (data not shown). Furthermore, there was no significant interaction between the LPA genotype score and sex (online-only Data Supplement Table 3), randomized treatment allocation, age, or aspirin use for any of the disease outcomes. The association results for the individual SNPs showed comparable effect sizes for rs3798220 and rs10455872 in all disease groups (online-only Data Supplement Table 4).

Discussion

The present study demonstrated that LPA variants were significantly associated with some, but not all atherothrombotic vascular disease outcomes. The LPA genotype score, which had previously been shown to explain more than half of the genetic variation in plasma levels of Lp(a), \(^1\) was associated with a 20% higher risk per additional variant allele for both prevalent and incident coronary disease and peripheral vascular disease. In contrast, there was no significant association of the LPA genotype score with prevalent or incident ischemic stroke.

The present study (1326 prevalent and 507 incident ischemic stroke cases) and a meta-analysis carried out by Wang et al\(^6\) involving 3550 stroke cases have reported no significant association of stroke with LPA variants. In contrast, the Women’s Health Study\(^1\) (123 ischemic stroke cases) suggested a positive association of rs3798220 with stroke; albeit, it failed to detect a significant association with myocardial infarction (fully adjusted \( P = 0.11 \)). In addition, a meta-analysis of observational studies involving 1684 ischemic stroke cases reported that Lp(a) levels were similarly associated with coronary disease and stroke.\(^6\) The apparent discrepancy between evidence in the HPS (and other genetic studies\(^6\)) and results linking LPA and plasma levels of Lp(a) with risk of ischemic stroke may be partly due to confounding by incomplete control for prior coronary disease or by concomitant nonfatal coronary events. Consequently, the association between Lp(a) level and stroke in the meta-analysis of obser-
vational studies may have been inflated by the association of Lp(a) with coronary disease. To minimize such biases when analyzing the HPS, individuals with prior coronary disease were excluded from analyses of prevalent stroke, and the associations with incident stroke were adjusted for prior coronary disease. The magnitude of the effect of this confounding is indicated by sensitivity analysis of the HPS, which showed that inclusion of individuals with prior coronary disease increased the association of LPA score with prevalent stroke from 1.03 ($P=0.67$) to 1.09 ($P=0.14$). Thus, differences in ascertainment of cases, population differences (eg, prior disease), the effect of chance, and competing risks of coronary disease and stroke may explain the discrepant results of Lp(a) levels, LPA variants, and stroke in different studies. Differing effects of LPA variants on individual stroke subtypes also may contribute to inconsistencies between the results of the HPS and some previous studies. However, because the HPS is unable to assess the effects of LPA on different stroke subtypes, further studies are required to examine potentially variable effects of LPA on strokes of differing etiology.

The HPS is a secondary prevention population of older individuals (mean age, 64 years) and, hence, has higher incident event rates than the general population. The impact of the survivor bias in such populations with prevalent disease is not known. Although the observed effect sizes for LPA and coronary disease in the HPS are weaker than those reported in the PROCARDIS study, PROCARDIS was a genetically enriched study of early-onset coronary disease. The higher event rates observed in the HPS compared with the general population provides additional statistical power and when examining the associations with incident disease, allows us to explore the impact of the LPA variants on secondary events (ie, events in those with a history of vascular disease). Indeed, the comparability of the effects of the LPA variants for prevalent and incident vascular disease is of considerable interest.

The lack of availability of Lp(a) levels in the HPS is a potential limitation of the study because it does not allow us to assess the variability of measured values within this secondary prevention population. Although Lp(a) levels were not measured, the 2 SNPs contributing to the LPA genotype score have been strongly and consistently associated with Lp(a) levels in 4 independent studies involving 3422 individuals, and a further study has shown rs3798220 to be strongly associated with Lp(a) levels in >25 000 individuals. Although the LPA variants studied encode higher plasma levels of Lp(a), the mechanism by which elevated levels of Lp(a) cause atherothrombotic vascular disease, are not fully understood, it may involve LDL-C, the inhibition of the expression of tissue factor, the inhibition of conversion of plasminogen to plasmin, or the carriage of proinflammatory oxidized phospholipids. Lp(a) is believed to exert both proatherogenic and prothrombotic effects, some of which depend on apo(a) and others that depend on apoB. It is unclear whether this dependency of Lp(a) on apoB is relevant to the lack of association with ischemic stroke. In a meta-analysis of prospective studies involving 12 000 stroke deaths, there was only a weak positive association between cholesterol and ischemic stroke mortality in middle-age and little or no association at older ages. In contrast, randomized trials have shown that reducing LDL-C with statin therapy produces comparable reductions in the risk of coronary disease and of ischemic stroke. Consequently, the lack of evidence of an association of LPA and stroke in the present study does not exclude the possibility that lowering Lp(a) would have beneficial effects on the risk of ischemic stroke. A large-scale randomized trial of niacin, which reduces Lp(a) levels, is in progress and may help to address the uncertainty of the effects of lowering Lp(a) levels on vascular outcomes, including stroke. Further studies are required to assess the relevance of LPA variants with other vascular disease outcomes, including venous thromboembolism. Specificity of the effects of LPA variants for different atherosclerotic and thrombotic diseases also may be informative for our understanding of the pathophysiology of Lp(a).

In conclusion, we have demonstrated that the associations of LPA variants with coronary disease and peripheral vascular disease are of comparable strength, but there appears to be little or no association of LPA with ischemic stroke in the HPS. These findings suggest that Lp(a) may have effects on atherothrombotic vascular disease that are only relevant at specific sites.

Acknowledgments

The HPS was designed and conducted by Clinical Trial Service Unit (CTSU) at the University of Oxford. This study of LPA was designed, analyzed, and interpreted by the CTSU (Drs Hopewell, Clarke, Parish, Armitage, and Collins), and genotyping was done by the Centre National de Génotypage, Evry, France (Drs Lathrop and Hager). The most important acknowledgments are to the participants in the study, to the steering committee, and to the HPS Collaborative Group collaborators.

Sources of Funding

The HPS was funded by the UK Medical Research Council, British Heart Foundation, Merck & Co (manufacturers of simvastatin), and Roche Vitamins Ltd (manufacturers of vitamins). Genotyping was supported by a grant to Oxford University and Centre National de Génotypage from Merck & Co.

Disclosures

Drs Hopewell, Clarke, Parish, Armitage, and Collins have received research grants from the British Heart Foundation (BHF), BHF Centre for Research Excellence, Oxford, England, EC Sixth Framework Programme, AstraZeneca AB, and Merck (for genotyping in the Heart Protection Study). The CTSU received a grant from Merck for a trial of niacin, which reduces Lp(a). The funders had no role in the design of the study, in the data collection or analysis, or in the decision to submit the results for publication. The CTSU has a policy of not accepting honoraria or other payments from the pharmaceutical industry, except for reimbursement of costs to participate in scientific meetings. Dr Lathrop has no disclosures. Dr Hager has received research grant (EU-FP6) support.

References


**CLINICAL PERSPECTIVE**

Recent genetic studies have demonstrated strong support for a causal role of plasma levels of lipoprotein(a) (Lp(a)) in coronary disease. The current findings from the Heart Protection Study, which are based on >12,000 prevalent disease cases and >3000 incident events, increase our understanding of the relevance of Lp(a) for vascular disease risk. The Heart Protection Study demonstrates comparable strength of associations of an LPA genotype score, previously shown to explain more than half of the genetic variation in Lp(a) levels with coronary disease and peripheral vascular disease but not with stroke. These results indicate that Lp(a) may have effects on atherosclerotic and thrombotic diseases that are only relevant at specific sites. Furthermore, as indicated by the paradoxical results from prospective and randomized evidence for cholesterol and ischemic stroke risk, the lack of evidence of an association of LPA and stroke in the present study does not exclude the possibility that lowering Lp(a) could have beneficial effects on the risk of stroke or stroke subtypes. The results of large-scale randomized trials of plasma levels of Lp(a), such as niacin and cholesterol ester transfer protein inhibitors, will help to assess the safety and efficacy of lowering Lp(a) levels on a broad range of vascular outcomes.
Lipoprotein(a) Genetic Variants Associated With Coronary and Peripheral Vascular Disease but Not With Stroke Risk in the Heart Protection Study
Jemma C. Hopewell, Robert Clarke, Sarah Parish, Jane Armitage, Mark Lathrop, Jorg Hager and Rory Collins

Circ Cardiovasc Genet. 2011;4:68-73; originally published online January 20, 2011; doi: 10.1161/CIRCGENETICS.110.958371
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1942-325X. Online ISSN: 1942-3268

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circgenetics.ahajournals.org/content/4/1/68

Data Supplement (unedited) at:
http://circgenetics.ahajournals.org/content/suppl/2011/02/15/CIRCGENETICS.110.958371.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Genetics can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Genetics is online at:
http://circgenetics.ahajournals.org/subscriptions/
### SUPPLEMENTARY MATERIAL

Supplementary table 1: Distribution of the *LPA* genotype score in (i) prevalent and (ii) incident disease groups

<table>
<thead>
<tr>
<th></th>
<th>LPA genotype score</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

#### (i) Prevalent vascular disease

**Coronary heart disease**
- Cases: 7307 | 1846 | 124
- Controls: 3014 | 633 | 40

**Ischemic stroke**
- Cases: 1077 | 234 | 15
- Controls: 3014 | 633 | 40

**Peripheral vascular disease**
- Cases: 1583 | 404 | 24
- Controls: 3014 | 633 | 40

#### (ii) Incident vascular disease

**Coronary heart disease**
- Events: 1614 | 454 | 38
- All: 11486 | 2794 | 185

**Any stroke**
- Events: 617 | 133 | 3
- All: 11486 | 2794 | 185

**Peripheral vascular disease**
- Events: 536 | 159 | 12
- All: 11486 | 2794 | 185
Supplementary table 2: Dominant model (1 or more LPA variants versus none) associations of the LPA genotype score with (i) prevalent and (ii) incident vascular disease

### (i) Prevalent vascular disease

<table>
<thead>
<tr>
<th>Prior disease</th>
<th>Cases / controls</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>9277 / 3687</td>
<td>1.21 (1.10-1.33)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1326 / 3687</td>
<td>1.04 (0.88-1.22)</td>
<td>0.1791</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2011 / 3687</td>
<td>1.21 (1.06-1.39)</td>
<td>0.0057</td>
</tr>
</tbody>
</table>

### (ii) Incident vascular disease

<table>
<thead>
<tr>
<th>Disease event</th>
<th>Events / total</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>2106 / 14465</td>
<td>1.19 (1.08-1.32)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Any stroke</td>
<td>753 / 14465</td>
<td>0.87 (0.72-1.04)</td>
<td>0.1309</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>707 / 14465</td>
<td>1.21 (1.02-1.44)</td>
<td>0.0296</td>
</tr>
</tbody>
</table>
Supplementary table 3: Associations of the \textit{LPA} genotype score in women and men with (i) prevalent and (ii) incident vascular disease

(i) Prevalent vascular disease

<table>
<thead>
<tr>
<th>Prior disease</th>
<th>Women</th>
<th>Men</th>
<th>Interaction p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases / controls</td>
<td>Odds ratio (95% CI)</td>
<td>Cases / controls</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2258 / 1332</td>
<td>1.23 (1.04-1.44)</td>
<td>7019 / 2355</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>335 / 1332</td>
<td>1.18 (0.90-1.55)</td>
<td>991 / 2355</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>494 / 1332</td>
<td>1.26 (1.00-1.59)</td>
<td>1517 / 2355</td>
</tr>
</tbody>
</table>

(ii) Incident vascular disease

<table>
<thead>
<tr>
<th>Disease event</th>
<th>Women</th>
<th>Men</th>
<th>Interaction p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events / total</td>
<td>Hazard ratio (95% CI)</td>
<td>Events / total</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>367 / 3696</td>
<td>1.36 (1.10-1.69)</td>
<td>1739 / 10769</td>
</tr>
<tr>
<td>Any stroke</td>
<td>191 / 3696</td>
<td>0.84 (0.59-1.19)</td>
<td>562 / 10769</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>127 / 3696</td>
<td>1.29 (0.90-1.85)</td>
<td>580 / 10769</td>
</tr>
</tbody>
</table>

* P-value for interaction between the \textit{LPA} genotype score and sex
Supplementary table 4: Association of rs10455872 and rs3798220 with (i) prevalent and (ii) incident vascular disease

(i) Prevalent vascular disease

<table>
<thead>
<tr>
<th>Prior disease</th>
<th>Cases / controls</th>
<th>Odds ratio (95% CI)</th>
<th>P-value for test of additional information of SNPs separately over the LPA score*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>rs10455872</td>
<td>rs3798220</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>9277 / 3687</td>
<td>1.17 (1.06-1.29)</td>
<td>1.21 (0.99-1.48)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1326 / 3687</td>
<td>1.00 (0.85-1.17)</td>
<td>1.18 (0.86-1.63)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2011 / 3687</td>
<td>1.14 (0.99-1.30)</td>
<td>1.33 (1.02-1.74)</td>
</tr>
</tbody>
</table>

(ii) Incident vascular disease

<table>
<thead>
<tr>
<th>Disease event</th>
<th>Events / total</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value for test of additional information of SNPs separately over the LPA score*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>rs10455872</td>
<td>rs3798220</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2106 / 14465</td>
<td>1.18 (1.07-1.30)</td>
<td>1.17 (0.96-1.43)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>753 / 14465</td>
<td>0.86 (0.71-1.03)</td>
<td>0.83 (0.56-1.22)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>707 / 14465</td>
<td>1.18 (0.99-1.40)</td>
<td>1.19 (0.86-1.66)</td>
</tr>
</tbody>
</table>

*P-value from the likelihood ratio test of inclusion of individual SNP information over and above the LPA genotype score (based on nested models).
Supplementary figure 1: Association of LPA genotype score with prevalent coronary disease, ischemic stroke and peripheral vascular disease (irrespective of history of coronary disease).