Lipoprotein-Associated Phospholipase A2 Activity Is Associated With Risk of Coronary Heart Disease and Ischemic Stroke

The Rotterdam Study

Hok-Hay S. Oei, MD; Irene M. van der Meer, MD, PhD; Albert Hofman, MD, PhD; Peter J. Koudstaal, MD, PhD; Theo Stijnen, PhD; Monique M.B. Breteler, MD, PhD; Jacqueline C.M. Witteman, PhD

Background—Lipoprotein-associated phospholipase A2 (Lp-PLA2) has been proposed as an inflammatory marker of cardiovascular disease. In the present study, we investigated whether Lp-PLA2 is an independent predictor of coronary heart disease and ischemic stroke.

Methods and Results—The Rotterdam Study is a population-based follow-up study in 7983 subjects ≥55 years of age. We performed a case-cohort study, including 308 coronary heart disease cases, 110 ischemic stroke cases, and a random sample of 1820 subjects. We used Cox proportional-hazard models with modification of the standard errors based on robust variance estimates to compute hazard ratios adjusted for age, sex, body mass index, systolic blood pressure, non-HDL cholesterol, HDL cholesterol, diabetes, smoking, alcohol consumption, cholesterol-lowering medication, white blood cell count, and C-reactive protein. Compared with the first quartile of Lp-PLA2 activity, multivariate-adjusted hazard ratios for coronary heart disease for the second, third, and fourth quartiles were 1.39 (95% CI, 0.92 to 2.10), 1.99 (95% CI, 1.32 to 3.00), and 1.97 (95% CI, 1.28 to 3.02), respectively (P for trend=0.01). Corresponding multivariate-adjusted hazard ratios for ischemic stroke were 1.08 (95% CI, 0.55 to 2.11), 1.58 (95% CI, 0.82 to 3.04), and 1.97 (95% CI, 1.03 to 3.79) (P for trend=0.03). The relation between Lp-PLA2 and coronary heart disease was present in both subjects with non-HDL cholesterol levels below the median and those with non-HDL cholesterol levels above the median.

Conclusions—This study shows that Lp-PLA2 activity is an independent predictor of coronary heart disease and ischemic stroke in the general population. (Circulation. 2005;111:570-575.)

Key Words: coronary disease ■ epidemiology ■ inflammation ■ stroke

Lipoprotein-associated phospholipase A2 (Lp-PLA2) has been proposed as an inflammatory marker of cardiovascular disease. The enzyme circulates in the blood bound to LDL cholesterol. The proinflammatory properties of the enzyme have been ascribed to its capacity to hydrolyze oxidized phospholipids, leading to the generation of lysophosphatidylcholine and oxidized free fatty acids. On the other hand, Lp-PLA2, sometimes called platelet-activating factor (PAF) acetylhydrolase, is also suggested to have antiinflammatory properties by hydrolyzing platelet-activating factor, which plays a role in the activation of platelets, monocytes, and macrophages.

The West of Scotland Coronary Prevention Study (WOSCOPS) suggested that Lp-PLA2 may be a risk factor for coronary heart disease, independent of traditional cardiovascular risk factors and C-reactive protein (CRP). The study was conducted among middle-aged men with elevated levels of LDL cholesterol who were enrolled in a primary prevention trial. In a nested case-control study within the Women’s Health Study, Lp-PLA2 was associated with coronary heart disease, but only in univariate analyses. No association was present after adjustment for cardiovascular risk factors. Lp-PLA2 was an independent predictor of coronary heart disease among middle-aged men and women of the Atherosclerosis Risk in Communities (ARIC) study and among middle-aged men of the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg survey, although the independent association in ARIC was confined to those with low LDL cholesterol. Currently, no data on the association between Lp-PLA2 and risk of future stroke are available.

Within the Rotterdam Study, a population-based cohort study among men and women ≥55 years of age, we investigated whether Lp-PLA2 activity is an independent predictor of coronary heart disease and ischemic stroke.
Methods

Study Population
The Rotterdam Study is a prospective population-based cohort study comprising 7938 men and women \(\geq 55\) years of age. Its overall aim is to investigate the incidence of and risk factors for chronic disabling diseases. From 1990 to 1993, all inhabitants of a suburb of the city of Rotterdam who were \(\geq 55\) years of age were invited to participate in an extensive home interview and 2 visits to the research center. The overall response was 78%. The Medical Ethics Committee of the Erasmus University Rotterdam approved the Rotterdam Study, and written informed consent was obtained from all participants. A more detailed description of the Rotterdam Study and the collection of data has been given elsewhere.8

Study Design
We used a case-cohort design9,10 in which a random sample, or “subcohort,” is drawn from the source population. Subjects who develop the disease but are not included in the subcohort are selected as additional cases.9,10 Baseline exposure is measured in the cases and controls included in the subcohort and in the additional cases.

Measurement of Lp-PLA2 Activity
Plasma aliquots prepared from nonfasting blood samples were collected at baseline and stored at \(-80^\circ\text{C}\). Lp-PLA2 activity was measured with a high-throughput radiometric activity assay. Briefly, plasma samples were divided into aliquots, placed in 96-well microtiter plates, and mixed with a substrate solution consisting of 0.4 \(\mu\text{mol/L [}^{3}\text{H}]\)-PAF (specific activity, 21.5 Ci/mmol, Perkin Elmer Life Sciences) and 99.6 \(\mu\text{mol/L C16-PAF (Avanti Polar Lipids Inc)}\) in assay buffer (100 \(\text{mmol/L HEPES, 150 \text{mmol/L NaCl, 5 \text{mmol/L EDTA, pH 7.4}}\). The reactions were allowed to proceed at room temperature for 5 minutes before sequestering of the phospholipid substrates by an ice-cold fatty acid–free BSA solution at a final concentration of 16.1 mg/mL. The BSA-lipid complexes were then precipitated with ice-cold trichloroacetic acid at a final concentration of 7.8% and pelleted by centrifugation at \(20000 \times g\) for 15 minutes at \(4^\circ\text{C}\). Aliquots of the supernatant containing the reaction products were transferred to another microplate (Perkin Elmer), and radioactivity was counted in a Topcount liquid scintillation counter (Perkin Elmer Life Sciences) on addition of Microscint-20 scintillation cocktail (Perkin Elmer Life Sciences). Lp-PLA2 activity was expressed as nanomoles of PAF hydrolyzed per minute per 1 mL plasma samples. On the basis of split samples, the coefficient of variation was 5.4%. Specimens of cases were assessed in the same cocktail (Perkin Elmer Life Sciences). Lp-PLA2 activity was ex-

Assessment of Covariates
At baseline, a trained investigator visited all participants at home and collected information using a computerized questionnaire. The obtained information included current health status, medical history, drug use, and smoking behavior. Alcohol consumption was assessed by a trained diettitian using a validated, semiquantitative food frequency questionnaire.12 Additionally, during 2 visits to the research center, clinical measures were obtained, and nonfasting blood samples were drawn. Height and weight were measured, and body mass index was calculated (kg/m\(^2\)). Blood pressure was measured at the right brachial artery with a random-zero sphygmomanometer with the participant seated. Total cholesterol, HDL cholesterol, and glucose were measured within 2 weeks, as described previously.13 Non-HDL cholesterol was computed by subtracting HDL cholesterol from total cholesterol. To assess the correlation of non-HDL cholesterol and total cholesterol with LDL cholesterol, LDL cholesterol was determined in fasting blood samples in 42 randomly selected subjects by use of an enzymatic method (Roche). Using a nephelometric method (Immage, Beckman Coulter), we measured CRP in blood samples kept frozen at \(-20^\circ\text{C}\). Immediately after blood sampling, white blood cell count was assessed in citrate plasma with a Coulter Counter T540 (Coulter Electronics), which has a coefficient of variation \(<2.0\%\). The quality of assessments was continu-

ous and monitored by Instruchemi. We defined diabetes mellitus as a random or postload glucose level \(\geq 11.1 \text{mmol/L}\) and/or the use of blood glucose–lowering medication. Baseline history of myocardial infarction and baseline history and incident cases of heart failure were determined as described previously.14,15

Follow-Up Procedures
Follow-up started after the baseline examination. For coronary heart disease, the study lasted until January 1, 2000; for stroke, until January 1, 1999. Collection of cardiovascular events was performed as described previously.14 Two research physicians independently coded all reported myocardial infarctions according to the Interna-tional Classification of Diseases, 10th edition (ICD-10).16 Codes on which the research physicians disagreed were discussed to reach consensus. Finally, a medical expert in cardiovascular disease, whose judgment was considered final, reviewed all events. Incident coronary heart disease was defined as the occurrence of a fatal or nonfatal myocardial infarction (ICD-10 code I21), other forms of acute (ICD-10 code I24) or chronic ischemic (ICD-10 code I25) heart disease, sudden (cardiac) death (ICD-10 codes I46 and R96), death caused by ventricular fibrillation (ICD-10 code I49), or death resulting from congestive heart failure (ICD-10 code I50) during follow-up. Information from reports on all possible strokes and transient ischemic attacks was reviewed by 2 research physicians. Codes on which the research physicians disagreed were discussed to reach consensus. Finally, an experienced neurologist (P.J.K.), whose judgment was considered final, reviewed all events. For the diagnosis of definite ischemic stroke, neuroimaging had to be performed to exclude other subtypes of stroke (performed in 61% of the stroke cases). For the diagnosis of probable ischemic stroke, at least 1 of the following 3 clinical symptoms had to be present: limited impairment of either isolated aphasia or isolated weakness of 1 limb, isolated facial weakness or isolated hemianopia, or complete improvement within 72 hours of documented atrial fibrillation at the time of diagnosis with no anticoagulants. In the present analysis, only strokes that met the criteria of definite or probable ischemic stroke were included as cases. During the follow-up for coronary heart disease, 47 subjects (2.2%) were lost to follow-up. During the follow-up for stroke, 49 subjects (2.5%) were lost to follow-up. For these subjects, the follow-up time was computed until the last date of contact.

Statistical Analysis
We used a test for continuous variable and a \(\chi^2\) test for dichotomous variables to test differences between the random cohort and the remainder of the Rotterdam Study. In the random cohort, age-adjusted (except for age) and sex-adjusted (except for sex) correlation coefficients were computed for the association of age, sex, cardiovascular risk factors, and inflammatory markers with Lp-PLA2.

The association of Lp-PLA2 activity with coronary heart disease and stroke was evaluated in a case-cohort design with standard Cox proportional-hazards models with modification of the standard errors based on robust variance estimates.9,10 We used the method according to Barlow in which the random cohort is weighted by the inverse of the sampling fraction from the source population. Members of the random cohort are included from baseline until failure or censoring, whereas cases outside the cohort are included at the time of their event.

We excluded subjects with a history of myocardial infarction for the analyses on coronary heart disease and subjects with a history of stroke for the analyses on ischemic stroke. We made quartiles of Lp-PLA2 activity and used the lowest quartile as the reference category. Cox proportional-hazard models for both coronary heart disease and stroke were performed by entering age, sex, and quartiles of Lp-PLA2 activity into the model (model 1). In model 2, we added non-HDL cholesterol and HDL cholesterol. In model 3, body mass index, systolic blood pressure, diabetes, smoking status, cholesterol-lowering medication, white blood cell count, CRP, and alcohol consumption were added. To examine whether the association between Lp-PLA2 and stroke is mediated by myocardial infarction
Results

Table 1 shows the baseline characteristics of the random cohort and the coronary heart disease, myocardial infarction, and stroke cases. The characteristics of the random cohort were similar to the baseline characteristics of the total population of the Rotterdam Study with few minor exceptions. Subjects in the random cohort were younger (69.6 versus 71.7 years) and had a lower systolic blood pressure (138 versus 140 mm Hg). Lp-PLA2 activity was higher in men than in women (46.8 versus 43.0 nmol · min⁻¹ · mL⁻¹) and was positively associated with body mass index, systolic blood pressure, total cholesterol, non-HDL cholesterol, and white blood cell count (Table 2). An inverse association was present with HDL cholesterol and alcohol consumption. Lp-PLA2 activity was not significantly associated with age, diastolic blood pressure, diabetes, smoking, and CRP. Associations with Lp-PLA2 were strongest for total cholesterol, non-HDL cholesterol, and HDL cholesterol, with correlation coefficients of 0.42, 0.48, and −0.28, respectively. Non-HDL cholesterol and total cholesterol were strongly associated with LDL cholesterol in a random sample of 42 subjects (r=0.97, P<0.001 for non-HDL cholesterol; r=0.91, P<0.001 for total cholesterol).

During a median follow-up of 7.2 years, incident coronary heart disease occurred in 308 subjects. Lp-PLA2 activity was associated with risk of coronary heart disease (Table 3).
Compared with the first quartile of Lp-PLA2 activity, age- and sex-adjusted hazard ratios for the second, third, and fourth quartiles were 1.53, 2.31, and 2.36, respectively ($P$ for trend $<0.0001$). After additional adjustment for cardiovascular risk factors, the strength of the association attenuated. Compared with the first quartile of Lp-PLA2 activity, hazard ratios for the second, third, and fourth quartiles were 1.39, 1.99, and 1.97, respectively ($P$ for trend $<0.01$). Attenuation of the association was caused mainly by adjustments for non-HDL and HDL cholesterol. The strength of the association was similar when we used myocardial infarction as an outcome ($n=153$) (Table 3). After additional adjustment for cardiovascular risk factors, the corresponding hazard ratios were

### Table 3. Hazard Ratios for Events According to Quartile of Lp-PLA2 Activity

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td><strong>Coronary heart disease ($n=308$)</strong></td>
<td></td>
</tr>
<tr>
<td>Quartile of Lp-PLA2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>2</td>
<td>1.53 (1.01–2.33)</td>
</tr>
<tr>
<td>3</td>
<td>2.31 (1.53–3.49)</td>
</tr>
<tr>
<td>4</td>
<td>2.36 (1.58–3.52)</td>
</tr>
<tr>
<td>Per SD</td>
<td>1.26 (1.12–1.42)</td>
</tr>
<tr>
<td>$P$ for trend</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td><strong>Myocardial infarction ($n=153$)</strong></td>
<td></td>
</tr>
<tr>
<td>Quartile of Lp-PLA2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>2</td>
<td>1.32 (0.70–2.49)</td>
</tr>
<tr>
<td>3</td>
<td>2.76 (1.55–4.92)</td>
</tr>
<tr>
<td>4</td>
<td>3.25 (1.85–5.70)</td>
</tr>
<tr>
<td>Per SD</td>
<td>1.41 (1.22–1.63)</td>
</tr>
<tr>
<td>$P$ for trend</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td><strong>Ischemic stroke ($n=110$)</strong></td>
<td></td>
</tr>
<tr>
<td>Quartile of Lp-PLA2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>2</td>
<td>1.06 (0.55–2.04)</td>
</tr>
<tr>
<td>3</td>
<td>1.56 (0.82–2.97)</td>
</tr>
<tr>
<td>4</td>
<td>1.97 (1.04–3.74)</td>
</tr>
<tr>
<td>Per SD</td>
<td>1.23 (1.03–1.46)</td>
</tr>
<tr>
<td>$P$ for trend</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, non-HDL cholesterol level, and HDL cholesterol level; model 3 was adjusted for age, sex, body mass index, systolic blood pressure, non-HDL cholesterol level, HDL cholesterol level, diabetes, smoking, cholesterol-lowering medication, CRP, white blood cell count, and alcohol consumption.

Lp-PLA2 was an independent and statistically significant predictor of coronary heart disease in subjects with a non-HDL cholesterol level below the median. Risk estimates were comparable in subjects with a non-HDL cholesterol level above the median ($P$ for interaction $=0.96$) (Table 4). No significant interaction was found between Lp-PLA2 activity and CRP ($P=0.36$) and Lp-PLA2 activity and gender ($P=0.13$) in relation to risk of coronary heart disease.

During a median follow-up of 6.4 years, incident ischemic stroke occurred in 110 subjects. Lp-PLA2 activity showed a graded association with the risk of ischemic stroke. Compared with the first quartile of Lp-PLA2 activity, age- and sex-adjusted hazard ratios for the second, third, and fourth quartiles were 1.06, 1.56, and 1.97, respectively ($P$ for trend $=0.02$) (Table 3). After additional adjustment for cardiovascular risk factors, the corresponding hazard ratios were

### Table 4. Multivariate-Adjusted Hazard Ratios For Coronary Heart Disease According to Lp-PLA2 Activity in Subjects With Non-HDL Cholesterol Levels Below and Above the Median

<table>
<thead>
<tr>
<th>Non-HDL Cholesterol</th>
<th>Below Median</th>
<th>Above Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile of Lp-PLA2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>2</td>
<td>1.32 (0.69–2.51)</td>
<td>1.26 (0.69–2.30)</td>
</tr>
<tr>
<td>3</td>
<td>1.41 (0.75–2.67)</td>
<td>1.85 (1.03–3.30)</td>
</tr>
<tr>
<td>4</td>
<td>1.80 (0.93–3.49)</td>
<td>1.76 (0.97–3.18)</td>
</tr>
<tr>
<td>Per SD</td>
<td>1.28 (1.01–1.63)</td>
<td>1.19 (0.98–1.44)</td>
</tr>
<tr>
<td>$P$ for trend</td>
<td>0.04</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, body mass index, systolic blood pressure, non-HDL cholesterol level, HDL cholesterol level, diabetes, smoking, cholesterol-lowering medication, CRP, white blood cell count, and alcohol consumption.
1.08, 1.58, and 1.97 (P for trend=0.03). The absence of a decrease in the hazard ratios for ischemic stroke after adjustment for cardiovascular risk factors is due to the much weaker associations of non-HDL cholesterol and HDL cholesterol with risk of ischemic stroke. The baseline prevalences of myocardial infarction and heart failure among stroke cases were 17% and 6%, respectively. Additional adjustment of the association between Lp-PLA2 activity and risk of stroke for baseline and incident myocardial infarction and heart failure did not materially change risk estimates.

**Discussion**

The present population-based study shows that Lp-PLA2 is an independent predictor of coronary heart disease and ischemic stroke. The associations are independent of classic cardiovascular risk factors and CRP. The association between Lp-PLA2 and coronary heart disease was present over the entire range of cholesterol levels.

Several methodological issues should be considered before we interpret the results. We have to be aware of potential confounding factors. Lp-PLA2 is bound to LDL cholesterol and therefore is highly correlated with LDL cholesterol levels. In the present study, because no LDL cholesterol levels were available, we adjusted for non-HDL cholesterol levels. Because of the high correlation between LDL cholesterol and total cholesterol in a random sample of our cohort, we believe that residual confounding by LDL cholesterol cannot explain our results. Furthermore, because cholesterol is not a strong predictor of stroke, the observed association between Lp-PLA2 and stroke supports the absence of confounding by LDL cholesterol in our study.

This is the first prospective population-based study that shows an association between Lp-PLA2 and risk of ischemic stroke. In a small cross-sectional study, Lp-PLA2 activity was found to be higher in ischemic stroke patients than in healthy control subjects. The importance of our result is 2-fold. First, the present study shows that Lp-PLA2 is a new and independent predictor of stroke in the general population. Subjects in highest quartile had an almost doubled risk of a future ischemic stroke compared with those in the lowest quartile. Second, because total cholesterol is not associated with risk of stroke, the association between Lp-PLA2 activity and stroke suggests that Lp-PLA2, although carried by LDL cholesterol, may convey a different risk. Evidence is accumulating that inflammation plays a role in the pathogenesis of ischemic stroke. A number of markers of inflammation are found to be associated with risk of ischemic stroke. Inflammatory processes are involved in atherosclerosis and plaque rupture, which in turn contribute to the development of ischemic stroke. Lp-PLA2 is an enzyme that hydrolyzes oxidized phospholipids, releasing lysophosphatidylcholine, which has proinflammatory properties. Our findings suggest that Lp-PLA2 may be added as an inflammatory marker that predicts risk of ischemic stroke. Adjustment for baseline and incident myocardial infarction and heart failure did not change the risk estimates, suggesting that these conditions are not intermediate pathways linking Lp-PLA2 to stroke.

Four studies reported on the association of Lp-PLA2 and coronary heart disease. In WOSCOPS, middle-aged men with elevated LDL cholesterol levels without a history of myocardial infarction were randomly assigned to pravastatin or placebo. In a nested case-control study with 560 cases and 1160 controls assigned to either pravastatin or placebo, a relative risk of 1.18 for coronary heart disease per 1-SD increase in Lp-PLA2 was found. This association was independent of cardiovascular risk factors. The Women’s Health Study is a trial of aspirin and vitamin E in women ≥45 years of age with no history of cardiovascular disease or cancer. In a nested case-control study with 123 cases and 123 controls, Lp-PLA2 levels were higher in the subjects with cardiovascular disease than in the controls; however, after adjustment for cardiovascular risk factors, this association virtually disappeared. In a case-cohort design with 608 coronary heart disease cases, the ARIC study found that subjects in the highest tertile of Lp-PLA2 had a relative risk of 1.78 for coronary heart disease compared with subjects in the lowest tertile. After adjustment for cardiovascular risk factors, an independent association was still present in subjects with low LDL cholesterol. In the MONICA Augsburg survey, Lp-PLA2 was an independent predictor of coronary heart disease among 934 middle-aged men. Results of this study were not presented in strata of LDL cholesterol. In the present study, Lp-PLA2 was an independent risk factor for coronary heart disease over the entire range of non-HDL cholesterol. The association was present in both subjects with non-HDL cholesterol levels below the median and, although of borderline significance, in those with non-HDL cholesterol levels above the median.

How can the difference between our findings and those of the Women’s Health Study and ARIC study be explained? The Women’s Health Study included middle-aged women who were health professionals who participated in a randomized trial and comprised a relatively low number of cardiovascular events. Both the ARIC study and the Rotterdam Study were conducted in population-based cohorts of men and women, with a comparable duration of follow-up, and with large numbers of events. The Rotterdam Study cohort included subjects ≥55 years (mean age, 70 years), whereas the cohort of the ARIC study included subjects 45 to 64 years of age (mean age, 58 years). We found no evidence for a modifying effect of gender on the association between Lp-PLA2 and risk of coronary heart disease, but the power for subgroup analyses in our study is relatively low, and the results do not exclude gender-specific associations. The Women’s Health Study and the ARIC study controlled for LDL cholesterol, whereas in the present study, we adjusted for total cholesterol level. Nevertheless, the correlation between Lp-PLA2 and non-HDL cholesterol in our study was comparable in size to the correlation between Lp-PLA2 and LDL cholesterol in WOSCOPS and ARIC. Therefore, we do not think that the absence of LDL cholesterol in our study can explain the different results. Although previous studies measured Lp-PLA2 mass, Lp-PLA2 activity was measured in our study with reasonable reproducibility. A correlation of 0.86 between Lp-PLA2 mass and activity has been reported, however; thus, a difference in assays is not likely to fully explain the difference in findings.

The high correlation between Lp-PLA2 and LDL cholesterol raises the question of whether Lp-PLA2 is a causal risk factor.
factor for coronary heart disease or whether the observed associations are due to differences in LDL cholesterol. An independent association was present among hypercholesterolemic men in the WOSCOPS study, among middle-aged men in the MONICA Augsburg survey, among older subjects in our study, and among middle-aged subjects with a low LDL in the ARIC study. Thus, the association has been found across all levels of cholesterol. More studies are needed to shed light on the characteristics of populations in which Lp-PLA2 is an independent predictor of coronary heart disease and those in which the predictive value is lost after adjustment for LDL cholesterol. Studies on the effects of genetic variation in the Lp-PLA2 gene may provide support for a causal role of Lp-PLA2. Recently, homozygosity for the V379 allele of the A379V polymorphism in the Lp-PLA2 gene, shown to result in lower Lp-PLA2 activity, was found to be associated with a reduced risk of coronary heart disease in a large European case-control study.

In conclusion, our results suggest that Lp-PLA2 activity is a new and independent predictor for ischemic stroke in the general population. This study provides further evidence for an independent role of Lp-PLA2 in the prediction of coronary heart disease. Our results suggest that the effect of Lp-PLA2 on cardiovascular disease is independent of a subject’s total cholesterol level and markers of inflammation.

Acknowledgments
This study is supported by an unrestricted grant from GlaxoSmithKline. The Rotterdam Study is supported by the Erasmus Medical Center and Erasmus University Rotterdam; the Netherlands Organization for Scientific Research; the Netherlands Organization for Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly; the Ministry of Education, Culture and Science; the Ministry of Health, Welfare and Sports; the European Commission; and the Municipality of Rotterdam. Dr Oei is supported by grant 21000022 from ZonMw. The authors thank Yun-Fu Oei et al Lp-PLA2 and Coronary Heart Disease and Stroke

References
11. Deleted in proof.
Lipoprotein-Associated Phospholipase A2 Activity Is Associated With Risk of Coronary Heart Disease and Ischemic Stroke: The Rotterdam Study
Hok-Hay S. Oei, Irene M. van der Meer, Albert Hofman, Peter J. Koudstaal, Theo Stijnen, Monique M.B. Breteler and Jacqueline C.M. Witteman

_Circulation_. 2005;111:570-575
doi: 10.1161/01.CIR.0000154553.12214.CD

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/111/5/570

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ 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_ is online at:
http://circ.ahajournals.org//subscriptions/