



Published in final edited form as:

*Stroke*. 2009 February ; 40(2): 376–381. doi:10.1161/STROKEAHA.107.513259.

## Lipoprotein-Associated Phospholipase A<sub>2</sub> and High-Sensitivity C-Reactive Protein Improve the Stratification of Ischemic Stroke Risk in the Atherosclerosis Risk in Communities (ARIC) Study

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### Abstract

**Background and Purpose**—Inflammation plays a critical role in the development of vascular disease, and increased levels of the inflammatory biomarkers, lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>), and high-sensitivity C-reactive protein (hs-CRP) have been shown to be associated with an increased risk for ischemic stroke.

**Methods**—In a prospective case–cohort (n=949) study in 12 762 apparently healthy, middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study, we first examined whether Lp-PLA<sub>2</sub> and hs-CRP levels improved the area under the receiver operator characteristic curve (AUC) for 5-year ischemic stroke risk. We then examined how Lp-PLA<sub>2</sub> and hs-CRP levels altered classification of individuals into low-, intermediate-, or high-risk categories compared with traditional risk factors.

**Results**—In a model using traditional risk factors alone, the AUC adjusted for optimism was 0.732, whereas adding hs-CRP improved the AUC to 0.743, and adding Lp-PLA<sub>2</sub> significantly improved the AUC to 0.752. Addition of hs-CRP and Lp-PLA<sub>2</sub> together in the model improved the AUC to 0.761, and the addition of the interaction between Lp-PLA<sub>2</sub> and hs-CRP further significantly improved the AUC to 0.774. With the use of traditional risk factors to assess 5-year risk for ischemic stroke, 86% of participants were categorized as low risk (<2%); 11%, intermediate risk (2% to 5%); and 3%, high risk (>5%). The addition of hs-CRP, Lp-PLA<sub>2</sub>, and their interaction to the model reclassified 4%, 39%, and 34% of the low-, intermediate- and high-risk categories, respectively.

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Disclosures

C.M.B. has received honorarium from Merck and AstraZeneca. There are no other conflicts to report.

**Conclusion**—Lp-PLA<sub>2</sub> and hs-CRP may be useful in individuals classified as intermediate risk for ischemic stroke by traditional risk factors.

### Keywords

CRP; Lp-PLA<sub>2</sub>; risk; stroke

Inflammation plays a critical role in the development of atherosclerotic vascular disease.<sup>1,2</sup> Markers associated with inflammation have been evaluated for their association with atherosclerotic cardiovascular disease and their ability to improve cardiovascular risk stratification. C-reactive protein (CRP) is one marker of inflammation that has been associated with atherosclerosis, atherosclerosis-related outcomes in various vascular beds, and has been shown to improve risk stratification for coronary heart disease (CHD).<sup>3,4</sup> Lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>), a unique phospholipase that circulates primarily bound to low-density lipoprotein (approximately 80%), is another marker that has been associated with atherosclerosis and its adverse outcomes.<sup>5,6</sup> Increased levels of Lp-PLA<sub>2</sub> and CRP have been associated with increased risk for stroke in the Atherosclerosis Risk in Communities (ARIC) study.<sup>7</sup> However, it is not known whether the addition of these inflammatory markers improves risk assessment and risk classification for ischemic stroke in middle-aged adults when compared with traditional risk factors (TRF).<sup>8</sup> We examined if Lp-PLA<sub>2</sub>±high-sensitivity (hs)-CRP improved prediction of stroke risk beyond TRF in the ARIC study.

### Materials and Methods

The ARIC study is a prospective biracial study of atherosclerotic cardiovascular disease incidence. The study was approved by an Institutional Review Committee, and subjects gave informed consent. In all, 15 792 individuals, initially aged 45 to 64 years, were recruited between 1987 and 1989 from 4 communities in the United States (Forsyth County, NC, which includes the city of Winston-Salem; northwest suburbs of Minneapolis, Minn; Washington County, Md, which includes the city of Hagerstown; and Jackson, Miss [blacks only]). Three other triennial examinations were conducted. A complete description of the design, objectives, sampling strategies, and examination techniques of the ARIC study have been published previously.<sup>9</sup> Risk factors (cigarette smoking, blood pressure, antihypertensive medication use, total cholesterol and high-density lipoprotein cholesterol [HDL-C] levels, and diabetes) were measured in the ARIC study using standardized methods. Serum and plasma samples were collected and stored at  $-80^{\circ}\text{C}$ . High-sensitivity CRP and Lp-PLA<sub>2</sub> were measured in 2003 from blood samples collected during the second visit (1990 to 1992) in a sample of the ARIC study participants selected based on a case-cohort design.

From 12 762 apparently healthy, middle-aged men and women who participated in the second ARIC visit and were eligible for the current analysis, we excluded individuals with prevalent CHD, prevalent ischemic stroke, or a history of transient ischemic attack/stroke symptoms; individuals with missing prevalence data for CHD and stroke; individuals missing information on risk factors of interest (tobacco/smoking, diabetes, low-density lipoprotein cholesterol [LDL-C], HDL-C, total cholesterol, systolic blood pressure, diastolic blood pressure, body mass index, hypertension, and hypertension medication); and individuals who belonged to a race other than “white” or “black.” Although prior ischemic stroke was an exclusion criterion for this analysis, hemorrhagic strokes were not excluded. In all, there were 2 hemorrhagic strokes among the individuals included for this analysis (one in each group). A case-cohort design<sup>10,11</sup> was then used, and 183 individuals (cases) who developed incident ischemic stroke after Visit 2 (the baseline visit for this analysis) and before December 31, 1998 and 781 individuals from a cohort random sample (CRS) were followed for the same duration of time

were selected after stratifying the sampling by age (>55 versus <55 years), sex, and race. The comparison group members were randomly selected within these strata, and weighted data analysis was conducted to provide ARIC study population estimates. The total sample size was 949 (15 cases in the CRS were excluded).

Lp-PLA<sub>2</sub> was measured using the PLAC (diaDexus Inc, San Francisco, Calif) test, which uses a dual monoclonal antibody immunoassay standardized to recombinant Lp-PLA<sub>2</sub>.<sup>12</sup> hs-CRP was measured using the Denka Seiken assay, which has been validated to the Dade Behring method.<sup>13</sup>

### Ascertainment of Stroke

For the current analysis, we included definite or probable ischemic strokes (embolic or thrombotic). A stroke was classified as ischemic when a brain CT or MRI revealed acute infarction or showed no evidence of hemorrhage. All definite ischemic strokes were further classified as either lacunar or nonlacunar on the basis of the recorded neuroimaging results. Of the 183 ischemic strokes, there were 102 definite and 81 probable strokes. Of the definite ischemic strokes, 89 were classified as thrombotic and 13 as embolic. Only the definite, thrombotic strokes received further classification in terms of lacunar or nonlacunar infarction, and of the 89 definite, thrombotic strokes, 40 were classified as lacunar. Further descriptions of stroke classification into thrombotic or embolic, definite or probable, and lacunar or nonlacunar have been previously described.<sup>14</sup>

Incidence of stroke was found<sup>14</sup> by contacting participants (or next of kin in the case of death) annually to identify hospitalizations during the previous year and by surveying discharge lists from local hospitals and death certificates from state vital statistics offices for potential cerebrovascular events. A hospitalization was reviewed for evidence of acute stroke if the list of discharge diagnoses included a cerebrovascular disease code (code 430 to 438 of the International Classification of Diseases, 9th Revision),<sup>15</sup> if a cerebrovascular condition or procedure was mentioned in the discharge summary, or if a cerebrovascular finding was noted on a CT or MRI report. Relevant sections of the medical record, including the type, timing, and duration of neurological symptoms and signs, medical history, and results of relevant diagnostic procedures (including CT and MRI of the brain), were copied and abstracted by a single, trained nurse.

ARIC adopted the National Survey of Stroke criteria for the classification of clinical stroke.<sup>16</sup> The stroke criteria were translated into a computer algorithm. In addition, a physician reviewer, blinded to the computer classification of the event, used the hospital discharge summary and reports of neurology consultation and diagnostic procedures and classified each potential event. Disagreements between the computer and reviewer classification were adjudicated by a second physician reviewer.

### Statistical Analysis

All statistical analyses were performed using SAS software, Version 8 (SAS Institute Inc, Cary, NC). We examined if hs-CRP and Lp-PLA<sub>2</sub> improved the area under the receiver operator characteristic curve (AUC) when added to the TRF.<sup>17</sup> The AUC estimates the probability of the risk function assigning a higher risk probability to those who will develop an event than to those who will not develop an event. Essentially, this statistic quantifies the ability to discriminate events from nonevents. Receiver operator characteristic analysis is commonly used to determine whether addition of a new risk factor to risk prediction equations provides incremental, independent predictive power. Adding important new risk factors gives a new prediction equation and a corresponding increase in the AUC. The level of increase can be used to assess the value of new risk factors for discriminating events from nonevents.<sup>18</sup> Tertiles

were used for Lp-PLA<sub>2</sub>, whereas the cut points from the Centers for Disease Control and Prevention/American Heart Association guidelines<sup>19</sup> were used for hs-CRP. The AUC was first described for the TRF (age, sex, race, current smoking, systolic blood pressure [Joint National Committee VI blood pressure categories],<sup>20</sup> LDL-C, HDL-C, diabetes, antihypertensive medication, and body mass index) alone and then for TRF+hs-CRP and TRF+Lp-PLA<sub>2</sub>, respectively. We then described the AUC when hs-CRP and Lp-PLA<sub>2</sub> were added together to the TRF, and finally, we described the AUC when TRF was added to hs-CRP, Lp-PLA<sub>2</sub>, and their interaction term. The interaction term in the model is a term that allows us to estimate how the Lp-PLA<sub>2</sub> association with stroke varies depending on the level of hs-CRP or, equivalently, how the hs-CRP association with stroke varies depending on the level of Lp-PLA<sub>2</sub>. By testing the model coefficient of the term, we can test the statistical significance of that interaction (ie, whether the variation by hs-CRP level of the size of the Lp-PLA<sub>2</sub> association with stroke risk is statistically significant).

Bootstrapping was used to adjust for overoptimism, which occurs when the fit of a model is tested using the same data in which the model was initially described and to furnish confidence intervals for the differences in adjusted AUC between models with TRF and ones with the new risk factors added.<sup>21–23</sup>

To calculate risk, a Cox proportional hazards model was applied. Specifically, the log hazard was modeled by a linear function of traditional and novel (hs-CRP and Lp-PLA<sub>2</sub>) risk factors. The model was fit by a SAS macro available from the Barlow macro<sup>11</sup> that accounts for the case-cohort design and also allows differential weighting of the strata in the cohort random sample. This analysis and all others presented also account for the stratified random sample nature of the CRS. These aspects of the program, therefore, allow us to make inferences to the whole ARIC population that is at risk for incident ischemic stroke.

The risk for an individual was then taken as the predicted linear function evaluated at the given level of his or her risk factors. Therefore, using the Cox proportional hazard models, a 5-year risk for stroke was calculated using the TRF for each individual, and then the individual was reclassified (using cut points that we arbitrarily chose) into low (<2% 5-year risk for stroke), intermediate (2% to 5%), and high risk (>5%) for stroke. Then hs-CRP+Lp-PLA<sub>2</sub> were added to the TRF, and the 5-year stroke risk was recalculated; then individuals were classified into various risk groups as described previously and the numbers of individuals reclassified determined. This approach is similar to that used by Cook et al in the Women's Health Study.<sup>4</sup>

Subsequently, we compared the population-attributable risk (PAR) between the 2 models (ie, TRF-alone and TRF+hs-CRP+Lp-PLA<sub>2</sub>+their interaction). To calculate the PAR for each model, we used the estimated coefficients from the fitted Cox proportional hazards model to calculate the 5-year probability (p\*) of ischemic stroke for the group with the lowest decile of risk and then calculated the probability (p) for the rest of the population. The percentage of ischemic strokes that can be attributed to not being in the lowest risk group was then calculated as 100(p-p\*)/p.

## Results

Baseline characteristics of the 949 individuals (183 with incident ischemic stroke [cases] and 766 from the CRS) in the study are presented in Table 1. Individuals (102 men and 81 women) who developed incident stroke were more likely to be older; have diabetes; have higher body mass index, systolic, diastolic blood pressure, total cholesterol, LDL-C, triglycerides, hs-CRP, and Lp-PLA<sub>2</sub>; and have lower HDL-C than individuals in the comparison group from the CRS.

In the TRF-alone model, the AUC for incident ischemic stroke, after bootstrapping was carried out to adjust for the overoptimism, was 0.732. When hs-CRP was added to the model, the AUC improved to 0.743 (95% CI for the difference, -0.0005 to 0.0183). The addition of Lp-PLA<sub>2</sub> to the TRF-alone model, after adjustment for overoptimism, improved the AUC to 0.752 (95% CI for the difference, 0.0028 to 0.0310). When Lp-PLA<sub>2</sub> was added to the TRF+hs-CRP model, the adjusted AUC improved to 0.761 (95% CI for the difference, 0.0081 to 0.0448). The addition of the interaction term between hs-CRP and Lp-PLA<sub>2</sub> additionally improved the adjusted AUC to 0.774 (95% CI for the difference, 0.0182 to 0.0607; Table 2).

With the use of TRF and the ARIC stroke prediction algorithm, 86% of the participants had <2% (low) 5-year ischemic stroke risk, 11% had a 2% to 5% (intermediate) risk, and 3% had a >5% (high) risk, respectively. The addition of hs-CRP, Lp-PLA<sub>2</sub>, and their interaction to the model resulted in reclassification of approximately 14% of the study population (Table 3). In all 4.0% (approximately 32 of 815) of the individuals were reclassified from the low- to the intermediate-risk group; 10.7% (approximately 11 of 105 individuals) and 27.9% (approximately 29 of 105 individuals) of the individuals were reclassified from the intermediate-risk to the high- and low-risk groups, respectively; finally, 33.3% (approximately 10 of 29 individuals) of the individuals classified as high risk were reclassified to the intermediate-risk group. No individuals were reclassified from the low- to the high-risk group, although 0.6% of the individuals were reclassified from the high- to the low-risk group. Reclassification was most frequent in the intermediate-risk group. When we examined a similar strategy using alternate cut points of risk (low=<1%, intermediate=1% to 4%, and high=>4%), 69%, 27%, and 4% were in the low-, intermediate-, and high-risk groups, respectively using TRF alone. When hs-CRP, Lp-PLA<sub>2</sub>, and their interaction were added to this model, 6%, 35%, and 27% of the low-, intermediate-, and high-risk groups, respectively, were reclassified.

The hs-CRP+Lp-PLA<sub>2</sub>+interaction model did better than the TRF-alone model with respect to the PAR. For example, 90.7% of the ischemic strokes can be attributed to not being in the lowest risk group for the TRF-only model and 94.3%, for the model with Lp-PLA<sub>2</sub>+hs-CRP+interaction added to TRF, indicating that a greater percentage of strokes occur in the higher risk groups when Lp-PLA<sub>2</sub> and hs-CRP are added to the model. Similarly, the percentage PAR for not being in the lowest 2 deciles of risk was 87.9 for the TRF-only model compared with a percentage PAR of 90.8 for the model with Lp-PLA<sub>2</sub>+hs-CRP+interaction.

## Discussion

Risk stratification and preventive therapy based on calculated (ie, low, intermediate, or high) risk have formed the cornerstone of preventive strategies against CHD<sup>24</sup> over the last 2 decades with risk levels dictating the intensity of therapy (for example, target LDL-C levels). These risk stratification tools are not perfect, and efforts have been made to improve risk stratification by adding biomarkers and imaging to “traditional risk factors.” Although these efforts have resulted in statistically significant improvements in risk prediction, the magnitude has been modest and primarily in the intermediate-risk group for whom treatment decisions are often uncertain.<sup>4,25</sup>

Although risk stratification tools for prediction of strokes such as the Framingham stroke profile<sup>26–28</sup> and the ARIC stroke risk score<sup>29</sup> are available, and their use has received a Class IA recommendation in the 2006 American Heart Association/American Stroke Association primary prevention of stroke guidelines,<sup>30</sup> they are not routinely used in guiding the treatment intensity in primary prevention of stroke and do not classify individuals into risk groups. Given that stroke is the third leading cause of death in the United States, among the leading cause for functional impairment,<sup>31</sup> and, like CHD, clearly preventable, tailoring therapy based on estimated risk, like for CHD, may be useful. We examined whether such a strategy that

classifies patients into low-, intermediate-, and high-risk groups with TRF combined with hs-CRP and Lp-PLA<sub>2</sub> would improve the prediction of incident ischemic stroke in the ARIC study.

C-reactive protein and Lp-PLA<sub>2</sub> have been associated with stroke in several studies.<sup>7,32–34</sup> Our analysis now suggests that these biomarkers modestly improve ischemic stroke risk prediction and offer the most improvement when combined. As has been seen with the addition of biomarkers in coronary heart disease risk prediction,<sup>4</sup> and as is evident from Table 3, the intermediate-risk group had the greatest reclassification with approximately 39% of the individuals reclassified into lower or higher risk groups. Although approximately 33% of the high-risk individuals were reclassified to a lower risk, the overall number of individuals in the high-risk group was very small (only 3% of the total individuals in this study) and furthermore, the majority of reclassified high-risk individuals (approximately 98%) were reclassified to the intermediate-risk group. Given the known benefits of lifestyle modification and pharmacotherapy in high-risk individuals (based on TRF alone), we feel that these individuals should continue to be treated as high risk. Similarly, as expected from studies with other biomarkers and imaging tests, very few low-risk individuals (only 4% of this group) were reclassified, and none were reclassified into the high-risk group. We feel that from a clinical point of view, the measurement of these biomarkers for further stratification of clinical stroke risk should only be considered in individuals who have intermediate risk based on TRF alone (2% to 5% 5-year stroke risk). It is interesting to note that although several individuals were reclassified by the addition of the biomarkers, the overall number of individuals in the low-, intermediate-, and high-risk groups remained about the same after reclassification suggesting that biomarkers did not change the proportion of the different risk categories. We chose somewhat arbitrary ranges (ie, <2%, 2% to 5%, and >5%, 5-year predicted risk of stroke) to classify individuals into “low-,” “intermediate-,” and “high-risk” groups, respectively, but a classification of <1%, 1% to 4% and >4% yielded similar results.

When examining the usefulness of a marker in improving the overall risk prediction, important parameters to consider include improvement in the AUC of a receiver operator characteristic and the calibration (how well the expected/predicted events correlate with the observed events). The addition of the biomarkers increased the AUC by 0.011 for hs-CRP alone, 0.020 for Lp-PLA<sub>2</sub> alone, and 0.042 when hs-CRP, Lp-PLA<sub>2</sub>, and its interaction term were added even after correcting for the overoptimism that could result from risk prediction score use and testing in the same population. Recent papers have discussed the advantages and problems with using the receiver operator characteristic analysis.<sup>35–38</sup> The receiver operator characteristic analysis is dependent on the sensitivity, specificity, and relative risk associated with the new factor and covariation between risk factors and the new factor. Although improving the AUC should not be a requirement for a marker to be a risk factor, it is important in risk prediction schema for population screening. The addition of hs-CRP and Lp-PLA<sub>2</sub> to the TRF not only improved the AUC, but also modestly improved PAR.

Based on our analysis, the addition of both hs-CRP and Lp-PLA<sub>2</sub> seems to satisfy the statistical requirements for a test to improve risk prediction. However, the more important question is whether the improvement conferred by the addition of the marker is clinically important and cost-effective. The addition of hs-CRP and Lp-PLA<sub>2</sub> did change risk categories in approximately 13% of our study population. It would be ideal to validate our findings in other cohorts, conduct studies to examine if changes in therapy secondary to such a risk stratification scheme will improve ischemic stroke prevention, and examine cost-effectiveness of such a strategy.

Currently, the stroke prevention guidelines recommend following the National Cholesterol Education Program/Adult Treatment Panel III guidelines for dyslipidemia management. Although, in most observational studies, LDL-C does not seem to be associated with the risk

of stroke, therapy with statins has significantly reduced stroke rates.<sup>39–43</sup> Furthermore, statins were also recently shown to decrease the 90-day National Institutes of Health Stroke Survey score when initiated between 3 to 9 hours postacute stroke.<sup>44</sup> Identifying and classifying individuals as low, intermediate, and high risk for stroke may be important in identifying individuals who may benefit from preventive strategies such as statins and aspirin. Using the Framingham CHD risk scores alone to determine therapy targets for dyslipidemia may miss individuals at high risk for stroke due to the different degrees that various risk factors contribute to stroke risk and CHD. For example, a 60-year-old nonsmoking, nondiabetic man with an untreated systolic blood pressure of 118 mm Hg, total cholesterol of 320 mg/dL, HDL-C of 28 mg/dL, triglyceride of 250 mg/dL, and LDL-C of 242 mg/dL has a 10-year CHD risk of 22%, whereas the 10-year stroke risk is 4%. On the other hand, a 55-year-old nonsmoking, nondiabetic man with treated systolic blood pressure of 177 mm Hg, left ventricular hypertrophy on his electrocardiogram, total cholesterol of 170 mg/dL, HDL-C of 60 mg/dL, triglyceride of 200 mg/dL, and LDL-C of 70 mg/dL has a 10-year predicted CHD risk of 8% but a stroke risk of 20%. These examples make evident how one may be at high risk for CHD while at lower risk for stroke, and vice versa. To improve cardiovascular risk prevention, a strategy of using both CHD and stroke risk assessment tools to calculate and classify patients into risk groups, assessing their global vascular risk,<sup>45</sup> and then treating individuals to the target determined by the higher estimated risk may be required but would need careful validation before being routinely used.

### Limitations

The analysis was carried out in a case-cohort random sample of 949 individuals. The entire ARIC cohort was not analyzed because the biomarkers were measured only in a sample of the ARIC participants. We have not validated the new risk prediction score (ie, with the addition of hs-CRP and Lp-PLA<sub>2</sub>) in a separate cohort. However, we did correct for the “overly optimistic assessment,” which can occur when one fits and tests a model using the same set of data. The blood samples were stored at –80°C for many years, which could potentially lead to some protein degradation, but this limitation would have been the same in both the cases and comparison group. Furthermore, the majority of studies that have examined the association of these biomarkers with atherosclerosis have also used samples frozen for long time periods.

### Summary

hs-CRP and Lp-PLA<sub>2</sub> improved ischemic stroke risk prediction in the ARIC study. The improvement was most enhanced when the markers were combined with the greatest benefit in reclassification present in individuals who were intermediate risk for ischemic stroke by traditional risk factors.

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

### Acknowledgments

We thank the staff and participants of the ARIC study for their important contributions and Joanna Brooks, BA, for editorial assistance.

#### Sources of Funding

The National Heart, Lung, and Blood Institute (NHLBI) participated in the design and conduct of the study, and the NHLBI Project Office participated in the preparation and review of the manuscript. The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by NHLBI contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022 from the (NHLBI,

Bethesda, Md. This research was also supported by an unrestricted research grant from GlaxoSmithKline, Research Triangle Park, NC.

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**Table 1**

Baseline (Visit 2 ARIC study if not otherwise mentioned) Characteristics in Cases of Incident Ischemic Stroke and Noncases: ARIC Study Sample

	No Incident Stroke (n=766)	Incident Stroke (n=183)	P Value
Age, * years	56.8	59.7	<0.0001
Men, * %	42.6	55.7	0.0001
Women, * %	57.4	44.3	0.0001
Whites, * %	75.7	56.8	<0.0001
Blacks, * %	24.3	43.2	<0.0001
Body mass index, kg/m <sup>2</sup>	28.1	28.4	0.46
Hypertension, %	32.3	58.7	<0.0001
Systolic blood pressure, mm Hg	121.4	129	<0.0001
Diastolic blood pressure, mm Hg	72.5	74.8	0.02
Diabetes, %	15.9	30.7	<0.0001
PAD, n, % <sup>†</sup>	26 (3.5%)	9 (5.0%)	0.36
Total cholesterol, mg/dL	208	212.9	0.19
LDL-C, mg/dL	131.9	136.5	0.2
HDL-C, mg/dL	50.9	47	0.001
Triglycerides, mg/dL	126	147.1	<0.001
Current tobacco use, %	19.7	33.5	<0.0001
hs-CRP, mg/L	3.08	3.8	0.01
Lp-PLA <sub>2</sub> , mg/L	0.37	0.45	<0.0001
Aspirin, % <sup>‡</sup>	41.5	44.9	0.41
Antihypertensive medication, %	22.9	51.9	<0.001
Antilipidemic drugs, %	5.1	5.8	0.70
Statins, %	1.9	2.2	0.76
Anticoagulants	0.37	0.63	0.57
Atrial fibrillation, %	0.45	0.98	0.33
Atrial flutter, % <sup>§</sup>	0.14	0	<0.001

\* Weighted but unadjusted, all other variables are adjusted for age, race, and gender.

<sup>†</sup> PAD was defined as an ABI <0.9 and is based on ABI obtained in the first ARIC visit (1987 to 1989).

<sup>‡</sup> Aspirin use was defined as taking any aspirin, Alka-Seltzer, cold medicine, or headache power in the last 2 weeks before the visit.

<sup>§</sup> Unable to weight and adjusted for atrial flutter because there was no atrial flutter observed in the control subjects.

PAD indicates peripheral artery disease; ABI, ankle/brachial index.

**Table 2**  
AUC for Prediction of Ischemic Stroke With Traditional Risk Factors, CRP, and Lp-PLA<sub>2</sub>

	AUC Adjusted for Optimism	95% CI for the Difference <sup>†</sup>
TRF* alone	0.732	
TRF+hs-CRP	0.743	-0.0005 to 0.0183
TRF+LpPLA2	0.752	0.0028 to 0.0310
TRF+hs-CRP+LpPLA2	0.761	0.0081 to 0.0448
TRF+hs-CRP+LpPLA2+interaction	0.774	0.0182 to 0.0607

\* Age, sex, race, current smoking status, systolic blood pressure, LDL-C, HDL-C, diabetes, antihypertensive medication use, body mass index.

<sup>†</sup>The AUC for each model was compared with the “TRF-alone” model.

Table 3

Percent of ARIC Sample Who Have Low, Medium, or High Predicted 5-Year Risk of Ischemic Stroke Using TRF and TRF+hs-CRP+Lp-PLA<sub>2</sub> and Observed 5-Year Risk (in parentheses)

Ischemic Stroke Risk by TRF	Ischemic Stroke Risk by TRF+hs-CRP/Lp-PLA <sub>2</sub> (interaction)							
	Low (<2%)		Intermediate (2% to 5%)		High (>5%)		Overall	
	Percent of TRF	Observed 5-Year Risk	Percent of TRF	Observed 5-Year Risk	Percent of TRF	Observed 5-Year Risk	Percent of Sample	Observed 5-Year Risk
Low (<2%)	96.03	0.0049	3.97	0.0255	0.00	...	85.86	0.0057
Intermediate (2% to 5%)	27.92	0.0128	61.42	0.0339	10.66	0.0593	11.03	0.0307
High (>5%)	0.59	0.0122	33.29	0.0316	66.12	0.1093	3.10	0.0829
Overall	85.56	0.0051	11.22	0.0312	3.23	0.0911	...	0.0108