Carotid Atherosclerosis and Stroke in Atrial Fibrillation

The Atherosclerosis Risk in Communities Study

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Background and Purpose—Whether consideration of carotid intima-media thickness (cIMT) and carotid plaque would improve risk prediction of ischemic stroke in persons with atrial fibrillation (AF) is unknown. The purpose of this study was to assess the improvement in risk prediction of stroke by adding cIMT and carotid plaque to the CHA₂DS₂-VASc (variables age, heart failure, hypertension, diabetes mellitus, myocardial infarction, and peripheral arterial disease) score.

Methods—We included participants from the Atherosclerosis Risk in Communities (ARIC) study (mean age, 63 years) who developed AF within 5 years after carotid measurement, were not on warfarin, and had no prior stroke at AF diagnosis. AF was ascertained from study ECGs and diagnosis codes, and stroke was physician adjudicated. Multivariable Cox models were used to assess association between carotid indices and ischemic stroke. Improvement in 10-year risk prediction of stroke was assessed by the C-statistic, net reclassification improvement, and relative integrated discrimination improvement.

Results—There were 81 (11.2%) stroke events that occurred among 724 participants with AF during a mean follow-up of 8.5 years. Increased cIMT and presence of carotid plaque were significantly associated with increased stroke risk. The addition of cIMT+plaque to the CHA₂DS₂-VASc score marginally increased the C-statistic (95% confidence interval) from 0.685 (0.623–0.747) to 0.698 (0.638–0.759). The net reclassification improvement and integrated discrimination improvement for cIMT+plaque were 0.091 (95% confidence interval, 0.012–0.170) and 0.101 (95% confidence interval, 0.002–0.226), respectively.

Conclusions—Increased cIMT and presence of carotid plaque are associated with increased risk of ischemic stroke in individuals with AF. Furthermore, they may improve risk prediction of stroke, over and above the CHA₂DS₂-VASc score.

Key Words: atherosclerosis • atrial fibrillation • carotid artery plaque • risk factors • stroke

The association of carotid atherosclerosis (carotid intima-media thickness [cIMT] and the presence of carotid plaque) with the risk of stroke in a large cohort of community-dwelling adults with atrial fibrillation (AF) has not been examined. It is unknown whether addition of cIMT and carotid plaque would improve risk prediction of stroke over the CHA₂DS₂-VASc (variables age, heart failure, hypertension, diabetes mellitus, myocardial infarction, and peripheral arterial disease) risk score among individuals with AF.

We evaluated the association of carotid atherosclerosis with ischemic stroke among participants with AF in the Atherosclerosis Risk in Communities (ARIC) study.

Methods

Study Population

The ARIC study is a population-based prospective study of cardiovascular disease in a biracial cohort of 15792 participants aged 45 to 64 years at enrollment (1987–1989) sampled from 4 US communities.

Measurements

AF was ascertained using standardized methods. cIMT and carotid plaque were measured by ultrasound. Carotid indices and covariates were taken from the most recent visit before AF ascertainment. Covariates included age at time of AF ascertainment, sex, race, ARIC field center, heart failure, hypertension, diabetes mellitus, coronary heart disease, peripheral arterial disease, and warfarin use.

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Statistical Analyses

cIMT was evaluated in quintiles and as a continuous variable. To estimate the association of cIMT and carotid plaque with time to incident ischemic stroke, we calculated hazard ratios and 95% confidence intervals (CIs) using multivariable Cox models. Person-years at risk were calculated from AF ascertainment until date of development of stroke, death, loss to follow-up, or end of follow-up (December 2011), whichever occurred first. The first multivariate model was adjusted for age, sex, race, and field center. The second model additionally adjusted for CHA2DS2-VASc variables (heart failure, hypertension, diabetes mellitus, coronary heart disease, and peripheral arterial disease). Race was included in the models because AF risk factors, incidence, and outcomes differ by race.6

We utilized the CHA2DS2-VASc score just before AF diagnosis as the benchmark to assess the role of arterial indices in enhancing risk prediction for stroke in AF. We considered 4 models: the benchmark alone, addition of cIMT or carotid plaque alone, and addition of both cIMT and carotid plaque. To assess model discrimination, we computed the C-statistic. We also calculated net reclassification improvement, Grønnesby–Borgan statistic, and the integrated discrimination improvement. Statistical analyses were performed with SAS version 9.3 (SAS Inc, Cary, NC).

Results

Participants who had strokes during follow-up were more likely to be women, black, had traditional atherosclerotic risk factors, higher cIMT, and presence of carotid plaque (Table 1).

Association of cIMT and Carotid Plaque With Ischemic Stroke Risk in AF

There were 81 (11.2%) stroke events occurring among 724 participants with AF during a mean follow-up of 8.5 years (Figure I in the online-only Data Supplement). Compared with participants in the lowest quintile, the hazard ratio (95% CI) of stroke for those in the highest quintile of cIMT was 2.30 (1.12–4.74), P value for trend=0.005, after adjustment for age, sex, race, and field center (Figure II in the online-only Data Supplement). This association was attenuated after additional adjustment for CHA2DS2-VASc variables. Each 1 SD increase in cIMT was associated with a 23% increased risk of stroke. The relationship between cIMT and stroke did not differ by sex (interaction P=0.25) or race (P=0.53; Table 2).

Compared with participants without plaque, the presence of plaque was associated with a 56% increased risk of stroke.

Table 1. Participant Characteristics at the Time of Atrial Fibrillation Diagnosis, Atherosclerosis Risk in Communities (ARIC) Study, 1987 to 2011

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Sample (n=724)</th>
<th>No (n=643)</th>
<th>Yes (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>63.3 (5.8)</td>
<td>63.3 (5.9)</td>
<td>63.3 (5.6)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>40.1</td>
<td>39.5</td>
<td>44.4</td>
</tr>
<tr>
<td>Black race, %</td>
<td>16.4</td>
<td>15.4</td>
<td>24.7</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>23.1</td>
<td>21.8</td>
<td>33.3</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>51.8</td>
<td>49.8</td>
<td>67.9</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>4.83</td>
<td>4.20</td>
<td>9.88</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>3.18</td>
<td>2.80</td>
<td>6.17</td>
</tr>
<tr>
<td>Peripheral artery disease, %</td>
<td>6.77</td>
<td>6.53</td>
<td>8.64</td>
</tr>
<tr>
<td>cIMT, mean (SD), mm</td>
<td>0.922 (0.31)</td>
<td>0.916 (0.31)</td>
<td>0.969 (0.28)</td>
</tr>
<tr>
<td>Plaque, %</td>
<td>38.1</td>
<td>37.1</td>
<td>46.9</td>
</tr>
</tbody>
</table>

cIMT indicates carotid intimal medial thickness; and MI, myocardial infarction.

Table 2. Association of Carotid Intima-Media Thickness and Carotid Plaque With Ischemic Stroke in Participants With Atrial Fibrillation, Atherosclerosis Risk in Communities (ARIC) Study, 1987 to 2011

<table>
<thead>
<tr>
<th>cIMT Quintiles, mm (n=713)</th>
<th>&lt;0.705</th>
<th>0.705–0.789</th>
<th>0.790–0.899</th>
<th>0.900–1.079</th>
<th>≥1.080</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke cases/AF (N)</td>
<td>13/147</td>
<td>10/139</td>
<td>18/136</td>
<td>18/140</td>
<td>22/151</td>
</tr>
<tr>
<td>Person-years</td>
<td>1472.8</td>
<td>1313.1</td>
<td>1110.4</td>
<td>1157.3</td>
<td>977.1</td>
</tr>
<tr>
<td>Incidence rate (95% CI)*</td>
<td>8.8 (4.7–15.1)</td>
<td>7.6 (3.7–14.0)</td>
<td>16.2 (9.6–25.6)</td>
<td>15.6 (9.2–24.6)</td>
<td>22.5 (14.1–34.1)</td>
</tr>
<tr>
<td>HR (95% CI), unadjusted</td>
<td>1 (ref.)</td>
<td>0.88 (0.38–2.00)</td>
<td>1.78 (0.87–3.65)</td>
<td>1.74 (0.85–3.57)</td>
<td>2.42 (1.21–4.82)</td>
</tr>
<tr>
<td>HR (95% CI), M1</td>
<td>1 (ref.)</td>
<td>0.82 (0.36–1.88)</td>
<td>1.63 (0.79–3.39)</td>
<td>1.68 (0.80–3.52)</td>
<td>2.30 (1.12–4.74)</td>
</tr>
<tr>
<td>HR (95% CI), M2</td>
<td>1 (ref.)</td>
<td>0.73 (0.32–1.68)</td>
<td>1.42 (0.68–2.97)</td>
<td>1.25 (0.58–2.67)</td>
<td>1.56 (0.74–3.32)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>cIMT continuous per 1 SD†</th>
<th>HR (95% CI), unadjusted</th>
<th>1.26 (1.08–1.46); P=0.003</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI), M1</td>
<td>1.26 (1.08–1.48); P=0.003</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI), M2</td>
<td>1.23 (1.04–1.46); P=0.02</td>
<td></td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, race, and field center; model 2: adjusted for M1+CHA2DS2-VASc variables (age, heart failure, hypertension, diabetes mellitus, myocardial infarction, and peripheral arterial disease). AF indicates atrial fibrillation; CI, confidence interval; cIMT, carotid intima-media thickness; and HR, hazard ratio.

*Incidence rates are crude stroke incidence rates, per 1000 person-years.
†1-SD=0.281.
‡P values for trend were calculated across quintile categories using the quintile term.
after adjustment for age, sex, race, and field center. These results remained unchanged after additional adjustment for CHA2DS2-VASc variables, hazard ratio (95% CI), 1.56 (1.00–2.45). There was no interaction of the relationship between carotid plaque and stroke by sex (P=0.31) or race (P=0.43).

**Model Discrimination, Calibration, and Reclassification**

C-statistic increased from 0.685 (95% CI, 0.623–0.747) for the model including race and CHA2DS2-VASc variables to 0.698 (95% CI, 0.638–0.759) after addition of both cIMT and plaque information. Addition of both plaque and cIMT to this model resulted in a significant net reclassification improvement, 0.091 (95% CI, 0.012–0.170). Overall, the risk levels for participants reclassified because of cIMT and carotid plaque data were more accurate (Table I in the online-only Data Supplement; Table 3).

The integrated discrimination improvement showed improved risk classification after the addition of cIMT and plaque information. The Grønnesby–Borgan statistic also showed good model fit, after the addition of cIMT and plaque information. Overall, the best model for prediction of stroke in AF was one comprising race and CHA2DS2-VASc variables, with addition of cIMT and plaque information.

### Discussion

In this population-based prospective study of participants with incident AF, cIMT and carotid plaque were found to be independent predictors of 10-year ischemic stroke risk in middle-aged adults. The addition of cIMT and carotid plaque information provided incremental predictive value for risk of stroke in adults with AF over the CHA2DS2-VASc risk score. Direct evaluation of carotid plaque and cIMT using noninvasive and readily available imaging modalities like carotid ultrasonography may contribute to improvement in risk prediction of stroke in AF over the CHA2DS2-VASc risk score that uses clinical variables alone.

For patients with intermediate risk of stroke (CHA2DS2-VASc score of 1), the 2012 ESC guidelines recommend oral anticoagulation; whereas the 2014 American Heart Association/ACC/HRS guidelines recommend no antithrombotic therapy, oral anticoagulant, or aspirin. Hence, there is equipoise in management of these patients. Our findings provide preliminary evidence that carotid ultrasonography may be useful in reclassifying these patients. These results also reinforce the concept that atherosclerosis plays an important role in the cause of stroke in AF.

Strengths of this study include the extensive measurement of covariates, large number of AF cases, >40% women, and inclusion of nonwhite participants. There are however, a few limitations. First, it is possible that nonhospitalized stroke events that were not validated in the study could influence the results. However, the magnitude of any potential underestimation of the rate of stroke is likely to be small (<5%). Second, there may be misclassification of AF. However, prior analysis within the ARIC cohort to determine the validity of hospital discharge diagnoses for AF reported 84% sensitivity and 98% specificity in AF ascertainment. Third, our study population has a mean age of 63 years followed by an 8.5-year mean follow-up. This may limit generalizability to the elderly.

### Conclusions

Additional studies are needed to validate these findings in other populations and develop a scoring system that would enhance stroke risk prediction by incorporating cIMT and carotid plaque into the CHA2DS2-VASc score.

### Acknowledgments

We thank the staff and participants of the Atherosclerosis Risk in Communities (ARIC) study.

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### Disclosures

Dr Lip is a consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. The other authors report no conflicts.

### References

1. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial


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SUPPLEMENTAL MATERIAL

Carotid Atherosclerosis and Stroke in Atrial Fibrillation:
The Atherosclerosis Risk in Communities (ARIC) Study

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Supplemental Appendix

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- Supplemental methods
- Supplemental statistical analysis
- Supplemental references
- Supplemental table
- Supplemental figures
Methods

Study Population

The ARIC study is a population-based prospective study of cardiovascular disease (CVD) in a bi-racial cohort of 15,792 participants aged 45 to 64 years at enrollment (1987-1989) sampled from four US communities: suburban Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi. Only blacks were recruited in Jackson. The baseline visit (visit 1) and three triennial visits - 1990–1992 (visit 2), 1993–1995 (visit 3), and 1996–1998 (visit 4), included interviews, laboratory measurements, and clinic examinations, including an electrocardiogram that was centrally read for AF. Participants were also contacted annually by phone to obtain medical updates. We included participants who developed incident AF within 5 years after measurement of carotid indices (1987-89, 1990-92, 1993-95 and 1996-98) and had no prior stroke at the time of AF diagnosis. Of the 771 participants who met these criteria, we excluded individuals who were of a racial/ethnic group other than white or black and nonwhites in the Minneapolis and Washington County field centers (n=2), and those taking warfarin within 1 year of AF diagnosis (n=45). Participants with missing cIMT measurements were excluded for the analysis involving cIMT (n=11), leaving a total of 713 participants with AF and cIMT data, and 724 participants with AF and carotid plaque data. The ARIC study protocol was approved by the institutional review boards of each participating center, and informed consent was obtained from each study participant.

cIMT and carotid plaque measurements
A Biosound 2000 (Biosound, Indianapolis, Indiana) IISA system was used and images recorded on a VHS tape. The cIMT was measured centrally by trained readers and was assessed in three segments: the distal common carotid (1 cm proximal to dilation of the carotid bulb), the carotid artery bifurcation (1 cm proximal to the flow divider), and the proximal internal carotid arteries (1 cm section of the internal carotid artery immediately distal to the flow divider). At each segment, 11 measurements of the far wall (in 1-mm increments) were attempted. The mean of the mean IMT measurements across these segments of both the right and the left sides was calculated. Trained readers adjudicated plaque presence or absence if two of the following three criteria were met: abnormal wall thickness (defined as cIMT >1.5mm), abnormal shape (protrusion into the lumen, loss of alignment with adjacent arterial wall boundary), and abnormal wall texture (brighter echoes than adjacent boundaries).

Ascertaining of Incident AF and Ischemic Stroke

AF was identified through hospital discharge diagnosis codes, or electrocardiograms (ECG) performed at study visits, when International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) code 427.31 or 427.32 or ICD-10 code I48, was listed in any position. All study visit ECGs coded by ECG software as AF were visually re-checked by a cardiologist or trained coder to confirm the diagnosis.
Incident stroke events were identified from annual telephone interviews, study visits, surveillance of the ARIC community hospitals for all participants' hospitalizations through December 31, 2011. Hospital reports were abstracted and reviewed if the discharge diagnosis included a cerebrovascular disease code (ICD-9 codes 430 to 438), if a cerebrovascular procedure was mentioned in the discharge summary, or if a CT or MR report showed evidence of cerebrovascular disease. ARIC adapted the National Survey of Stroke criteria for its stroke definition (1). A computerized algorithm and physician reviewer independently classified the diagnosis of definite or probable stroke and the stroke subtype, with differences adjudicated by another physician.

Ascertainment of Covariates

Race was based on self-report. Hypertension was defined as use of medication to treat high blood pressure, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. Diabetes mellitus was defined as a self-reported physician's diagnosis of diabetes, use of diabetic medications, nonfasting serum glucose levels ≥200 mg/dL, or fasting serum glucose level ≥126 mg/dL. Heart failure at baseline was defined as the reported use of medications to treat heart failure in the previous 2 weeks or the presence of heart failure according to Gothenburg criteria (2); incident heart failure at follow-up visits was defined as the presence of ICD-9-CM code 428 in any hospitalization during follow-up. Prevalent coronary heart disease (CHD) was defined as self-reported, physician-diagnosed CHD or the presence of a previous myocardial infarction (MI) by ECG.
Questionnaires during study visits assessed self-reported smoking status (current, former, never) and smoking amount. PAD was defined as ankle-brachial index <0.9. During an ultrasound exam, trained and certified sonographers measured ankle and brachial systolic blood pressures with a Dinamap™ 1846 SX automated oscillometric device (Critikon, Inc, Tampa, Florida) using standard protocols. Only one ankle was measured in each participant. Decision as to right or left was made based on a random number displayed on the computer screen. The ABI was then calculated as the average of the two ankle systolic measurements divided by the average of the first two brachial readings (3). PAD was defined as ankle-brachial index of <0.9.

**Statistical analysis**

We calculated the net reclassification improvement (NRI) which examines the net effect of adding a marker to the risk prediction scheme (4); values greater than zero indicate improved reclassification. Using Cox-proportional hazards, the 10-year ischemic stroke risk for each of the models was calculated, and participants were classified into <10%, 10%-20%, and >20% (approximately 1%, 1%-2%, and >2% per year). The number of individuals who changed risk groups (i.e., reclassified after adding arterial indices) was described. We also described the clinical NRI, or the NRI in intermediate risk individuals (CHA2DS2-VASc of 1), i.e., individuals in which the addition of carotid indices may be of most use. To test the model calibration, we compared the “goodness-of-fit” of the observed and expected number of events within estimated risk decile groups using the Grønnesby-Borgan statistic (5). Large values of the test statistic (and therefore, small, significant ‘p’ values) suggest poor
model fit. Finally, we estimated the integrated discrimination improvement (IDI) (6) which is the difference in an $R^2$-like statistic between the benchmark and augmented models.

References

**Table I.** Number and Percent Reclassified When cIMT and Carotid Plaque were added to the CHA2DS-VASc Score, Atherosclerosis Risk In Communities (ARIC) Study, 1987-2011

<table>
<thead>
<tr>
<th></th>
<th>Non-Cases</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benchmark + cIMT</td>
<td>Total</td>
</tr>
<tr>
<td>Benchmark &lt;0.05</td>
<td>133 (88.7)</td>
<td>15 (10.0)</td>
</tr>
<tr>
<td>Benchmark 0.05-</td>
<td>24 (8.5)</td>
<td>236 (83.1)</td>
</tr>
<tr>
<td>Benchmark &gt;0.10</td>
<td>0 (0)</td>
<td>53 (25.0)</td>
</tr>
<tr>
<td>Total</td>
<td>157</td>
<td>304</td>
</tr>
</tbody>
</table>

|                  | Benchmark + cIMT | Total | Benchmark + cIMT | Total | Benchmark + plaque | Total | Benchmark + cIMT + plaque | Total |
| Benchmark <0.05  | 137 (91.3)      | 13 (8.7)  | 0 (0) | 150 | Benchmark <0.05    | 27 (90.0) | 3 (10.0) | 0       | 30   |
| Benchmark 0.05-  | 16 (5.6)        | 246 (86.6) | 22 (7.8) | 284 | Benchmark 0.05-0.10| 2 (14.3)  | 15 (71.4) | 3 (14.3) | 21   |
| Benchmark >0.10  | 0 (0)           | 65 (30.7)  | 147 (69.3) | 212 | Benchmark >0.10    | 0 (0)    | 2 (12.5)  | 14 (87.5) | 16   |
| Total            | 153             | 324      | 169       | 646 | Total              | 30       | 20        | 17       | 67   |

|                  | Benchmark + cIMT + plaque | Total | Benchmark + cIMT + plaque | Total |
| Benchmark <0.05  | 131 (88.3)      | 18 (12.0) | 1 (0.7) | 150 | Benchmark <0.05    | 27 (90.0) | 3 (10.0) | 0       | 30   |
| Benchmark 0.05-  | 41 (14.4)       | 213 (75.0) | 30 (10.6) | 284 | Benchmark 0.05-0.10| 3 (14.3)  | 14 (66.7) | 4 (19.1) | 21   |
| Benchmark >0.10  | 0 (0)           | 58 (27.4)  | 154 (72.6) | 212 | Benchmark >0.10    | 0 (0)    | 2 (12.5)  | 14 (87.5) | 16   |
| Total            | 172             | 289      | 185       | 646 | Total              | 30       | 19        | 18       | 67   |
Values are n (%) 

Benchmark: race and CHA2DS-vasc variables (age, heart failure, hypertension, diabetes, PAD, MI) 
¶ represents incident stroke risk per year, with 0.05-0.10 representing the intermediate risk category
Figure I. Study Flow chart: Inclusion and Exclusion Criteria. Atherosclerosis Risk In Communities (ARIC) Study, 1987-2011.
Figure II. Incidence rate of stroke in AF (per 1000 person years) by cIMT cohort quintiles. Atherosclerosis Risk In Communities (ARIC) Study, 1987-2011.