Incident Stroke Is Associated With Common Carotid Artery Diameter and Not Common Carotid Artery Intima-Media Thickness

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Background and Purpose—The common carotid artery interadventitial diameter is measured on ultrasound images as the distance between the media-adventitia interfaces of the near and far walls. It is associated with common carotid intima-media thickness (IMT) and left ventricular mass and might therefore also have an association with incident stroke.

Methods—We studied 6255 individuals free of coronary heart disease and stroke at baseline with mean age of 62.2 years (47.3% men), members of a multiethnic community–based cohort of whites, blacks, Hispanics, and Chinese. Ischemic stroke events were centrally adjudicated. Common carotid artery interadventitial diameter and IMT were measured. Cases with incident atrial fibrillation (n=385) were excluded. Multivariable Cox proportional hazards models were generated with time to ischemic event as outcome, adjusting for risk factors.

Results—There were 115 first-time ischemic strokes at 7.8 years of follow-up. Common carotid artery interadventitial diameter was a significant predictor of ischemic stroke (hazard ratio, 1.86; 95% confidence interval, 1.59–2.17 per millimeter) and remained so after adjustment for risk factors and common carotid IMT with a hazard ratio of 1.52/mm (95% confidence interval, 1.22–1.88). Common carotid IMT was not an independent predictor after adjustment (hazard ratio, 0.14; 95% confidence interval, 0.14–1.19).

Conclusions—Although common carotid IMT is not associated with stroke, interadventitial diameter of the common carotid artery is independently associated with first-time incident ischemic stroke even after adjusting for IMT. Our hypothesis that this is in part attributable to the effects of exposure to blood pressure needs confirmation by other studies.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00063440.

Key Words: carotid arteries □ risk factors □ stroke □ ultrasonography

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Stroke 2014;45:00-00.

Stroke is available at http://stroke.ahajournals.org

Received January 16, 2014; final revision received February 20, 2014; accepted February 21, 2014.

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DOI: 10.1161/STROKEAHA.114.004850
Follow-up was ascertained at intervals of 9 to 12 months by telephone interview to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses and procedures, and deaths. Additional medical encounters through cohort clinic visits, participant calls, medical record abstractions, or obituaries were recorded when possible. Copies of death certificates and medical records for all hospitalizations and selected outpatient cardiovascular diagnoses and procedures were obtained and reviewed.

Risk Factors and Anthropomorphic Variables
Age, sex, race/ethnicity, and medical history were self-reported. Use of lipid-lowering and antihypertensive medications was recorded. Current smoking was defined as self-report of ≥1 cigarettes in the past 30 days. Resting BPs were measured in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL).

Glucose and lipids were measured after a 12-hour fast. Serum glucose was measured by rate reflectance spectrophotometry on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY). The presence of diabetes mellitus was based on self-reported physician diagnosis, use of insulin and oral hypoglycemic agent, or a fasting glucose value ≥126 mg/dL. Total cholesterol was measured using a cholesterol oxidase method (Roche Diagnostics), as was high-density lipoprotein based on a correlation coefficient of 0.93. The relative hazard rates for quartiles of IAD were estimated for descriptive purposes, and Kaplan–Meier failure curves were generated for quartiles of IAD. We also generated Kaplan–Meier failure curves for quartiles of IMT.

Carotid Artery Measures
For IAD measurements, participants were examined supine with the head rotated 45° toward the left side. Imaging was done with the ultrasound transducer parallel to the long axis of the neck with the jugular vein lying immediately above the common carotid artery (or at 45° from the vertical if the internal jugular vein is not visualized). Images of the right common carotid artery were centered 10 to 15 mm below (caudad to) the right common carotid artery bulb. End-diastolic images of the right common carotid artery bulb were captured. Measurements were made with an edge detector that identified the media-adventitia interfaces of the near and far walls. A diameter versus time curve was generated. An algorithm identified peak-systolic and end-diastolic fiduciary points. A reader reviewed these curves confirming valid end-diastolic values. The final IAD measurement was based on an average of 7 end-diastolic diameter measurements. The reproducibility of the IAD was assessed by blinded readings of a separate series of images acquired on the same 89 participants on the same day giving a correlation coefficient of 0.93.

IMT measurements were made of the common carotid artery near and far wall for a distance of ≈10 mm below the common carotid artery bulb. These tracings were then used to calculate maximum near and far wall IMT that was then averaged for the 4 locations.

Outcomes
All cardiovascular events were adjudicated and classified by 2 members of the mortality and morbidity review committee. Neurologists on the committee adjudicated the presence of strokes with all discordant cases requiring discussion to reach consensus.

Presence of incident atrial fibrillation during the follow-up period was determined by hospital review of hospital charts and the presence of International Classification of Diseases, Ninth Revision, diagnosis of atrial fibrillation or flutter (427.3, 427.31, 427.32) in 231 individuals and by self-report only in 154 for a total of 385 individuals. These individuals were excluded from the analysis. An additional 174 individuals did not have IAD measurements either because they did not have a carotid artery examination or because the measurements were not obtained. The final cohort included 6255 participants.

Incident stroke was defined as rapid onset of focal neurological deficit lasting 24 hours or until death, or if in <24 hours there was a clinically relevant lesion on brain imaging. Patients with focal neurological deficits secondary to brain trauma, tumor, infection, or other nonvascular cause were excluded. Strokes were classified on the basis of neuroimaging or other tests. We studied ischemic stroke (n=115) censoring participants at the time of a stroke if they had experienced a hemorrhagic stroke (n=22).

Statistical Analyses
The mean (and SD) values of continuous variables and the count (and percentage) of categorical variables are shown. Cox proportional hazards models were fit with time to stroke as the outcome variable, adjusted initially for age, sex, race/ethnicity, then additionally for high-density lipoprotein cholesterol, total cholesterol, lipid-lowering medications, systolic BP, antihypertensive medications use, diabetes mellitus status, current cigarette status, and common carotid IMT. Harrell C-statistics were obtained for the Cox proportional hazards models. The predictive value of common carotid artery IAD was compared with the baseline model using the differences in Harrell C-statistic.

The relative hazard rates for quartiles of IAD were estimated for descriptive purposes, and Kaplan–Meier failure curves were generated for quartiles of IAD. We also generated Kaplan–Meier failure curves for quartiles of IMT.

Results
Average age of our population of 6255 individuals was 62.2 years, with an average follow-up of 7.8 years. Key demographics and risk factors are shown in Table 1. Men constituted 47.3% of the population. The prevalence of diabetes mellitus was 12.7% and that of current smoking was 13.0%. Antihypertensive agents were being taken by 37.1% of the cohort, whereas lipid-lowering therapy was noted in 16.2%. Average IAD of the common carotid artery was 7.57 mm (±0.92 mm). There were 115 adjudicated ischemic strokes.

Table 1. Population Demographics and Risk Factors for the Population Studied (n=6255)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.2±10.2</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>47.3% (2958)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>38.4% (2405)</td>
</tr>
<tr>
<td>Chinese</td>
<td>12.1% (754)</td>
</tr>
<tr>
<td>Black</td>
<td>27.3% (1705)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>22.2% (1391)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>50.9±14.7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>194.1±35.8</td>
</tr>
<tr>
<td>Lipid-lowering medication use</td>
<td>16.2% (1016)</td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>126.5±21.5</td>
</tr>
<tr>
<td>Hypertension medication use</td>
<td>37.1% (2320)</td>
</tr>
<tr>
<td>Diabetes mellitus (yes)</td>
<td>12.7% (794)</td>
</tr>
<tr>
<td>Current smoker (yes)</td>
<td>13.0% (811)</td>
</tr>
<tr>
<td>Common carotid artery</td>
<td></td>
</tr>
<tr>
<td>Intima-media thickness, mm</td>
<td>0.87±0.19</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD for continuous variables and percentage values (numeric values) for categorical variables. HDL indicates high-density lipoprotein.
In Cox proportional hazards models, the hazard ratio for ischemic stroke was 1.86 (95% confidence interval [CI], 1.59–2.17) for each millimeter increase in IAD. This was attenuated to 1.67 (95% CI, 1.38–2.02) after adjustment for age, sex, and race/ethnicity. Further adjustment for risk factors (Table 2) gave a hazard ratio of 1.52 (95% CI, 1.22–1.88). Strong associations were seen between stroke and age, high-density lipoprotein cholesterol, total cholesterol, systolic BP, and diabetes mellitus. Participants with Chinese ethnicity had a lower stroke incidence rate than whites. Common carotid IMT was not a significant predictor of ischemic stroke.

The addition of carotid artery diameter did not significantly increase the C-statistic (0.0144; 95% CI, −0.0017 to 0.0305; $P=0.08$) when added to the multivariable Cox proportional hazards model that included IMT (0.783; 95% CI, 0.748–0.819).

Kaplan–Meier failure curves for quartiles of IAD are shown in Figure (A). The cumulative risks of ischemic stroke at 8 years by quartiles were 0.63% (3.97–6.92 mm), 1.80% (6.93–7.48 mm), 1.80% (7.49–8.12 mm) and 3.75% (8.13–13.2 mm) for the respective quartiles of IAD. For illustrative purposes, we also generated these curves for quartiles of IMT (Figure [B]). The association between IMT and stroke seems weaker than for IAD.

### Discussion

We have found that the IAD of the common carotid artery is a significant independent predictor of ischemic stroke after taking into consideration traditional (Framingham) cardiovascular risk factors. This association persisted after adjustment for common carotid artery IMT.

In this study, we have replicated the findings of a prior report from the Carotid Intima Media Thickness (IMT) and IMT-Progression as Predictors of Vascular Events in a High-Risk European Population (IMPROVE) study showing an association between stroke and common carotid IAD. We have done so in a North American multiethnic cohort selected without cardiovascular disease at baseline, whereas the prior report investigated the value of this measurement in a European population that was preselected to have a high burden of risk factors and subclinical cardiovascular disease. Our findings are slightly discordant with those of Baldassarre et al because we do not find a positive association between common carotid IMT and incident stroke. It is difficult to speculate on the reasons for this apparent discordance. One factor to take into consideration is the possibility that IMT is a better predictor of events in individuals with large burdens of subclinical cardiovascular disease. The other is that internal carotid artery IMT might be a better predictor of stroke than common carotid IMT. The IMPROVE trial preselected slightly >3000 individuals after screening 21 000 individuals. MESA participants were selected by a random sampling of the population with the exclusion of individuals with baseline cardiovascular disease. Enrollees in IMPROVE had an average Framingham risks score of 22%, whereas our cohort had an average of 11%. Another difference between our study and IMPROVE is the imaging protocol. IMPROVE
performed a comprehensive, multiancele sampling of the common carotid IMT and measured at 2 levels in the common carotid artery. The measurement more closely resembling our IMT measurement is the one showing weaker association with stroke. In MESA, the IMT was measured on one projection and just below the beginning of the carotid bulb. As such, MESA measurements might be weighted toward medial hypertrophy of the wall, whereas IMPROVE might be more representative of atherosclerotic changes. In addition, only 38% of our population were whites.

We did not find a significant association between IMT and incident stroke in our adjusted models, whereas the unadjusted Kaplan–Meier survival curves did show a positive trend for IMT quantiles (Figure B). Although the association between IMT and IAD explains part of the loss of statistical power through confounding when they are included in the same model, this also suggests that IAD is a stronger predictor of ischemic stroke than IMT. A similar lack of association between incident stroke has been suggested in the Tromso study, specifically in multivariable adjusted models. Our data confirm their observations although their event rates and observation period were greater than ours.

We used IAD for 2 principal reasons. The first was the semiautomatic method of measurement. An edge detector was used to track the displacement of the near wall and the far wall intima-media interfaces. Performance of the edge detector was robust because the final diameter measurement was based on an average of 7 cardiac cycles for the application of the edge detector to a 20-second-long sequence of images. We also selected the IAD based on observations linking increases in diameter to changes in IMT. The Glagov phenomenon holds that the arterial lumen diameter will tend to be maintained in the presence of plaque buildup. We have previously shown that this phenomenon also occurs in the common carotid artery. In summary, the outer diameter of the artery increases in response to increases in IMT but not the lumen diameter. As such, IAD or adventitia-to-adventitia diameter measurements might be more robust predictors of events than the lumen diameter.

Our previous work has shown a strong association between IAD, cardiovascular risk, IMT, and left ventricular mass. We therefore adjusted our multivariable model for all of these risk factors. We performed a sensitivity analysis to confirm that IAD was an independent predictor of ischemic stroke after adjusting for left ventricular mass (data not shown). IAD remained significant with a hazard ratio of 1.58 ($P=0.001$). We also performed additional analyses using all strokes as outcomes as well as R01 HL069003 and R01 HL081352.

We hypothesize that the association between stroke and IAD is in part a reflection of the effects of chronic BP elevations. We investigated this possibility by removing systolic BP from the model and noted a significant increase in the IAD hazard ratio to 1.7, suggesting that there is confounding or mediation between IAD and systolic pressure.

Limitations of our study include the difference in IMT imaging protocol reported in IMPROVE. However, our protocol resembles the protocol adopted for the Framingham Heart Study. We have a small number of exclusions that might have biased the analysis to a healthier subset of our cohort. However, we had complete data on 6255 of 6814 or 92% of our cohort. We also studied a population without prevalent cardiovascular disease at baseline, therefore limiting our ability to determine whether prevalent coronary heart disease or peripheral arterial disease might serve as risk factors for stroke. Our study might also be limited by the number of outcomes because the difference in C-statistic between the models without and with common carotid artery diameter was not statistically significant ($P=0.08$).

We conclude that the IAD of the common carotid artery is an independent predictor of ischemic stroke. The pathological source of this association is not clear but is likely in part mediated by the effects of BP elevation. Further research is needed to confirm this hypothesis.

Acknowledgments

We thank the investigators, the staff, and the participants of the Multi-Ethnic Study of Atherosclerosis (MESA) study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Sources of Funding

This research was supported by National Institutes of Health contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169 as well as R01 HL069003 and R01 HL081352.

Disclosures

Dr O’Leary owns stock in and is an employee of Medpace, Inc, a clinical research organization. The other authors report no conflicts.

References


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Stroke. published online March 18, 2014;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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http://stroke.ahajournals.org/content/early/2014/03/18/STROKEAHA.114.004850

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