Asymptomatic Internal Carotid Artery Stenosis Defined by Ultrasound and the Risk of Subsequent Stroke in the Elderly

The Cardiovascular Health Study

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Background and Purpose—We sought in this study to relate carotid ultrasound findings in asymptomatic older adults to the 5-year risk of various cerebrovascular outcomes used in the Asymptomatic Carotid Atherosclerosis Study (ACAS).

Methods—The Cardiovascular Health Study (CHS) is a longitudinal study of people 65 years and older. Analyses of internal carotid artery stenosis defined by multiple different cutoffs of peak systolic velocity, rather than one particular cutoff, were performed in the 5441 participants who underwent carotid ultrasound and lacked a history of transient ischemic attack or stroke. The 5-year risks of 7 cerebrovascular disease outcomes used in ACAS were estimated for each cutoff.

Results—Associations with the 5-year risk of outcomes were substantially elevated only at cutoffs with high peak systolic velocities. In this population, the number of people with such high velocities was small. For example, with a cutoff of approximately 2.5 m/s, suggesting a stenosis of >70%, the 5-year risk of an ipsilateral fatal or nonfatal stroke was 5%, and only 0.5% of the group had velocities at least this high.

Conclusions—In a group of older adults likely to participate in a screening program, as evidenced by willingness to participate in CHS, high peak systolic velocities consistent with high-grade carotid stenosis were uncommon and risk of subsequent cerebrovascular disease outcomes was relatively low. These findings do not suggest that similar populations of older adults would benefit from a program using ultrasound to screen for asymptomatic carotid stenosis.

Key Words: aged ■ carotid artery diseases ■ ultrasonography, Doppler

The Asymptomatic Carotid Atherosclerosis Study (ACAS) concluded that carotid endarterectomy combined with medical therapy is more beneficial than medical therapy alone in patients with asymptomatic high-grade internal carotid artery (ICA) stenosis. In this randomized clinical trial, 1659 subjects (mean age, 67 years; 67% men) had asymptomatic carotid artery stenosis of ≥60% reduction in diameter. The aggregate 5-year risk for ipsilateral stroke was 5.1% for patients randomized to the surgical arm and 11.0% for those randomized to the medical arm. To help clinicians and policy makers decide how best to generalize the results of such clinical trials, information is needed from other populations on outcomes such as those reported in ACAS. The prognosis for patients enrolled in clinical trials may differ from the prognosis for people from the general population. If so, the results of such clinical trials should be generalized to other populations with caution, if at all.

The Cardiovascular Health Study (CHS) is a prospective, multicenter, epidemiological study of risk factors for coronary and cerebrovascular disease in older adults. As part of the study, >5000 participants underwent carotid ultrasound. CHS offers a unique opportunity to evaluate the frequency of high-grade ICA stenosis defined by ultrasound and the risk of subsequent cerebrovascular disease outcomes in an aged population likely to participate in screening programs, as evidenced by their willingness to participate in CHS. Thus, use of data from CHS can help us judge whether the findings of ACAS can be generalized to similar populations of elderly people. Use of data from CHS for this purpose is complicated because different studies have used different ultrasound definitions of high-grade carotid artery stenosis. In this article, rather than examining a single ultrasound velocity cutoff to define stenosis, we examine multiple cutoffs to document both their prevalence and their association with
Cerebrovascular Outcomes Examined in the Asymptomatic Carotid Atherosclerosis Study and the Cardiovascular Health Study

<table>
<thead>
<tr>
<th>Sets of Outcomes</th>
<th>Number of Events (% of CHS Participants)*</th>
<th>Peak Systolic Velocity Cutoff of ≥2.5 m/s†</th>
<th>Surgical Group in ACAS‡</th>
<th>Medical Group in ACAS‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral stroke</td>
<td>114 (2.1%)</td>
<td>5</td>
<td>5.1</td>
<td>11.0</td>
</tr>
<tr>
<td>Major ipsilateral stroke</td>
<td>28 (0.5%)</td>
<td>0</td>
<td>3.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Ipsilateral TIA or stroke</td>
<td>144 (2.7%)</td>
<td>9</td>
<td>8.2</td>
<td>19.2</td>
</tr>
<tr>
<td>Any stroke</td>
<td>309 (5.7%)</td>
<td>5</td>
<td>12.4</td>
<td>17.5</td>
</tr>
<tr>
<td>Any major stroke</td>
<td>105 (1.9%)</td>
<td>5</td>
<td>6.4</td>
<td>9.1</td>
</tr>
<tr>
<td>Any stroke or death</td>
<td>910 (16.7%)</td>
<td>36</td>
<td>25.6</td>
<td>31.9</td>
</tr>
<tr>
<td>Any major stroke or death</td>
<td>742 (13.6%)</td>
<td>21</td>
<td>20.7</td>
<td>25.5</td>
</tr>
</tbody>
</table>

*In the CHS, 5441 participants were followed for a median of 5 years.
†Kaplan-Meier estimate of 5-year risk (%) for CHS participants based on a point at which 0.5% of subjects had a peak systolic velocity on carotid ultrasound at the cutoff of approximately ≥2.5. Risks are from the 7 graphs in the Figure corresponding to the outcomes listed.
‡Kaplan-Meier estimate of 5-year risk (%) in the ACAS† groups treated surgically and medically.

Subjects and Methods

Members of the CHS cohort were recruited from a random sample of the Health Care Financing Administration Medicare eligibility lists in 4 US communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh (Allegheny County), Pennsylvania. Participants had to be aged ≥65 years, able to give informed consent, and able to respond to questions without the aid of a surrogate respondent. They could not be institutionalized, wheelchair-bound in the home, or under treatment for cancer. Details about the study design and characteristics of the 5888 participants are published elsewhere.5,6

Eligible and consenting participants underwent an extensive baseline evaluation that included standard questionnaires, physical examination, and laboratory testing, as detailed elsewhere.7,8 Testing included carotid ultrasound, which was performed in a standard fashion with all 4 centers using identically equipped imaging units capable of color Doppler imaging and pulsed Doppler analysis.4,5 All sonographers and readers underwent the same training. Ultrasound studies were recorded and sent weekly to the Ultrasound Reading Center for standardized readings. Pulsed-wave Doppler frequency spectra were obtained from the area of highest flow velocity in the internal carotid arteries.4 and peak systolic velocities were recorded. The peak systolic velocity of the ICA has been suggested as the single best Doppler measurement for identifying severe stenosis.4 In previous reports from CHS,4,5 peak systolic velocities of ≥1.5 m/s were assumed to indicate an ICA lumen stenosis of ≥50% diameter reduction and those of ≥2.5 m/s 70% or greater. Of the 5888 members of the CHS cohort, 5859 (99.5%) underwent carotid ultrasound. Thirty-six participants lacked results on the peak systolic velocity for technical reasons, and 2 participants had bilateral ICA occlusions. Thus, 5821 (98.8%) had results on the peak systolic velocity for at least 1 ICA.

For the analyses that follow, we tried to duplicate as closely as possible the methods used in ACAS. The study artery was defined as the ICA with the highest peak systolic velocity. If the velocities were identical on the right and left, the left was chosen, as in ACAS. If one ICA was occluded (n=23), the artery on the opposite side was the study artery. Participants with a confirmed history, prior to their carotid ultrasound examination, of carotid endarterectomy for asymptomatic carotid artery disease (n=49) or of transient ischemic attack (TIA) or stroke (n=331) were excluded because the side of the event was not always reliably known. After excluding these 380 participants, 5441 remained for the analyses.

Incident TIA or stroke was identified during annual follow-up examinations and at 6-month telephone contact.7,8 All potential TIA and stroke events were adjudicated by a committee of neurologists, neuroradiologists, and internists, who used information from interviews, medical records, and available brain imaging studies. Strokes were classified as ischemic or hemorrhagic, and both were included in these analyses because the two were not seemingly distinguished in ACAS. Strokes were further subdivided by vascular distribution.

Based on these adjudicated events, 7 sets of outcomes listed in the Table were defined as follows, using the same classification as in ACAS: (1) any ipsilateral stroke, fatal or nonfatal; (2) major ipsilateral stroke, where major stroke is defined as below; (3) any ipsilateral stroke or TIA; (4) any stroke, whether ipsilateral, contralateral, or in the posterior circulation; (5) any major stroke; (6) any stroke or death from any cause; and (7) any major stroke or death from any cause.

In ACAS, a major stroke was defined with use of the Glasgow Outcome Scale7 as resulting in moderate or severe disability, persistent vegetative state, or death. Because we did not have the Glasgow Outcome Scale available in CHS, we defined a major stroke as a fatal stroke or as a nonfatal stroke in which the score on the activities of daily living (ADL) measure2 deteriorated by 2 or more points between the most recent prestroke score and one performed at least 3 months but not more than 3 years after the incident stroke. After their stroke, some patients were no longer able to return for follow-up examinations, and no information was available on their ADL score after the stroke. If a CHS participant missed a visit, information was collected to establish the reason. If follow-up visits after a stroke were missed for health-related reasons, we assumed that such patients had experienced a major stroke.

In ACAS, the investigators included all strokes or deaths occurring within 42 days after randomization to the medical group as an outcome to make determinations comparable to the surgical group’s postoperative morbidity and mortality.1 No randomization occurred in CHS. To maintain comparability with ACAS as much as possible, we considered instead the 42 days following the day that the carotid ultrasound was performed. During this interval, 5 participants experienced strokes and 7 died. These events were included as outcomes in all the analyses described below.

For each of the 7 outcomes described above and listed in the Table, we constructed a separate graph to summarize the results. The horizontal axis included cutoffs for the peak systolic velocity, ranging from 0 to 4 m/s. Two vertical axes were used: one indicated the percentage of participants with a peak systolic velocity of that value or more, and the other indicated the 5-year risk of the particular cerebrovascular disease outcomes. These outcomes are contrasted with those reported in ACAS.
outcome in percentage for participants with a peak systolic velocity of that value or more. The 5-year risk was estimated in two ways, one with use of the Kaplan-Meier estimate and the other with more idealized estimates from Cox proportional hazards models. For the Cox models, we followed the approach taken by others. First, Cox models were used to compute the 5-year survival estimate when the degree of stenosis equals 0. The log of this baseline survival estimate was multiplied by the parameter estimated from the Cox model, with the peak systolic velocity as predictor, we computed the average hazard rate over 5 years for different cutoffs of peak systolic velocity.

For these survival analyses, participants were considered to have achieved 1 of the outcomes specified above at the time of the incident event that qualified for that particular outcome. A participant could have experienced >1 event and thus qualified for >1 of the 7 outcomes described above and in the Table, depending on which event occurred first. Death unrelated to stroke was a censoring event except for those outcomes that included death from any cause. Participants were also censored at the time of either their last follow-up or a carotid endarterectomy, regardless of side. Only 62 otherwise eligible participants underwent carotid endarterectomy during follow-up. The occurrence of a TIA or stroke prompted the endarterectomy in 24 participants. In the remaining 38, carotid endarterectomy was performed for asymptomatic disease. Two (5.3%) of the 38 experienced postoperative strokes on the day of surgery (95% confidence interval from the binomial distribution, 0.6 to 17.8).

All of these analyses were based on the updated CHS database, which incorporates minor corrections through March 1997. The analyses include all events adjudicated through June 30, 1995.

Results

The 5441 participants included in the analyses had a mean age of 72.7 years, with 41% being men and 84% white. They were followed up for a mean of 4.35 years (median, 5 years) after the ultrasound examination, with only 142 (2.6%) being lost to follow-up or dropping out of the study, at which time they were censored for these analyses. Among these 5441 participants, 90 were adjudicated as having an incident TIA and 309 as having an incident stroke, of which 32 (10.4%) were fatal and 105 (34%) were major. Only 27 of the 309 participants with stroke experienced a hemorrhagic stroke.

The table indicates the number of participants qualifying for each of the 7 outcomes. The 7 graphs comprising the Figure display the percent with a specified velocity or more and the two estimates of 5-year risk for each of the 7 outcomes considering multiple cutoffs for the peak systolic velocity. The percent with the specified velocity or more decreases as the cutoff of the peak systolic velocity increases. This curve is the same in all of the graphs. Only a small percentage of the participants are at or above cutoffs for high peak systolic velocities that would indicate high-grade ICA stenoses. For example, the percentage with peak systolic velocity of 1.5 m/s is 3.4%; 2.0, 1.1%; 2.5, 0.5%; and 3.0, 0.3%. The estimates of 5-year risk from the Kaplan-Meier analyses fall to 0 at the higher velocities for 5 of the 7 outcomes. The fall to 0 indicates that none of the participants with cutoffs for peak systolic velocity above these values experienced these outcomes. The estimates from the Cox models are more idealized and smoothly increase. In all of the figure panels, the 5-year risks of the outcomes tend to rise as the peak systolic velocity used for the cutoff increases, regardless of which method is used to estimate the risk.

The risk when the prevalence is at one half of 1% can be found on these graphs and is listed for each of the outcomes in the Table. This prevalence conveniently corresponds to a cutoff for peak systolic velocity of approximately 2.5 m/s. For comparison, the Kaplan-Meier estimate of 5-year risk of these outcomes based on subjects in ACAS who were randomized to the medical and surgical arms of the study are also listed.

Of the 5441 participants included in these analyses, 4743 (87.2%) had been examined in a standard fashion by study personnel for cervical bruits and 170 (3.6%) had a bruit on one or both sides. Of the 4743 participants who were examined for bruits, 28 (0.6%) had peak systolic velocity of 2.5 m/s or greater, and 12 of the 28 (42.9%) had a cervical bruit. Thus, considering all 170 participants with a cervical bruit, only 12 (7.1%) were found to have peak systolic velocities of 2.5 m/s or greater.

Discussion

In this group of elderly people, high-grade stenosis of the ICA suggested by ultrasound was encountered infrequently. To avoid having to select a single cutoff to define high-grade stenosis, we looked at multiple cutoffs as displayed in the Figure. Regardless of whether the Kaplan-Meier analyses or the Cox models were used to estimate the 5-year risks of various cardiovascular outcomes, the trend was for the risk to increase as the cutoff for the peak systolic velocity increased. A cutoff for peak systolic velocity of 2.5 m/s has been used previously in this study to suggest a stenosis of >70% and is consistent with cutoffs suggested in previous studies for similar degrees of stenosis. In this study, only one half of 1% of the 5441 participants studied had a high-grade stenosis by such a definition. In addition, the 5-year risk of ipsilateral fatal or nonfatal stroke using this cutoff was about 5%, more like the 5% 5-year risk reported for the surgically treated group in ACAS than the 11% 5-year risk reported for the medically treated group. In the current study, using a higher cutoff value in general resulted in greater risk, but fewer of the participants would have such high peak systolic velocities. Using a lower cutoff value resulted in more participants having such velocities, but then the risk in general was lower.

The only 5-year risks that approached those seen in the medically treated group in ACAS were for those outcomes that included death. This finding is not unexpected, given that the mean age of the ACAS subjects was 67 years compared with 73 years for the CHS participants. Also, the participants in CHS were not given optimal preventive care, as was attempted in ACAS. Although they were older, participants in CHS were less likely than those in ACAS to have coronary artery disease, hypertension, and diabetes, and they were less likely to be men and current cigarette smokers.

Cost-effectiveness analyses incorporating prevalence values for critical carotid stenosis from ACAS and other studies may provide exaggerated estimates of the benefits of screening for asymptomatic carotid artery disease in the elderly. In such studies, authors need to estimate the prevalence of key factors used in the decision analysis models. In one study, the authors estimated the prevalence of a critical stenosis in a “high-prevalence model” at 20% (range of
values, 10% to 30%) and in a “low-prevalence model” at 4% (range, 1% to 8%). In the other study, the authors estimated the prevalence of the critical stenosis at 5% (range, 2% to 13%). These authors showed that the cost of screening for asymptomatic carotid artery disease does not drop below $50 000 for a quality-adjusted life-year until the prevalence of a critical stenosis reaches 40%. In the current study, when we picked a definition of critical stenosis based on a peak systolic velocity cutoff of 2.5 m/s, prevalence was 0.5%, lower than the lowest estimates used in either study of cost-effectiveness. In addition, the risk associated with such stenoses in CHS is similar to the risk found in the patients treated surgically in ACAS (Table 1). Picking a lower cutoff would result in a higher prevalence but also in even lower risk. Using estimates from CHS on the prevalence of certain stenoses and the risk associated with such stenoses, benefit is unlikely to be derived from screening of aged people such as those in CHS, regardless of the cost.

Some investigators have suggested that the presence of a cervical bruit would identify a group of people in whom the yield from screening for high-grade carotid stenosis on ultrasound would be much higher. In CHS, such a strategy would increase the percent with peak systolic velocities of 2.5 m/s or greater on ultrasound from about 0.5% (see the Table and Figure) to 7%. Such a strategy would fail to identify over half of those with high-grade carotid stenosis on ultrasound. The major advantage to such a strategy would be that only 3.6% of the entire group being screened would need to undergo ultrasound.

CHS has many strengths, including having characterized a large group of elderly people with respect to cardiovascular and cerebrovascular risk factors and outcomes. Although carotid ultrasound has been performed in over 5000 participants, carotid angiography has not. Correlation of stenosis defined by ultrasound with stenosis defined by angiography is not practical in this study. To address questions about screening with ultrasound in a population like the CHS participants, such a correlation may not be necessary because the cutoffs associated with high risk are encountered in so few
participants. Of more concern, the participants studied may not be representative of all such elderly people. For example, 49 participants were excluded because of prior carotid endarterectomy. Such patients may have been eligible for inclusion in ACAS. In addition, 47 of 5441 participants in CHS (0.9%) underwent carotid endarterectomy for asymptomatic carotid artery disease during follow-up. According to the findings in ACAS, 11% (or 5) of them may have experienced an ipsilateral stroke if only treated medically. The influence of such considerations on the results presented is difficult to judge but unlikely to change the conclusions.

The findings of this study fail to support mass screening of aged populations with ultrasound to identify asymptomatic high-grade carotid stenosis for endarterectomy. CHS participants may be healthier than the general population over age 65, but they may be similar in health to the population of elderly people who would likely participate in a mass screening program, as reflected by their willingness to participate in CHS. To be effective, a screening program will need to identify a higher-risk population than the CHS participants and use more than just age and a single carotid ultrasound as a marker for increased risk of future stroke.

Appendix

Participating Institutions and Principal Staff

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References


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