Carotid Artery Intimal-Medial Thickness Distribution in General Populations As Evaluated by B-Mode Ultrasound

George Howard, DrPH; A. Richey Sharrett, MD, DrPH; Gerardo Heiss, MD, PhD; Gregory W. Evans, MS; Lloyd E. Chambless, PhD; Ward A. Riley, PhD; Gregory L. Burke, MD for the ARIC Investigators

Background and Purpose: B-mode ultrasound is a widely used technique for the clinical and epidemiological assessment of carotid atherosclerosis. This article provides a description of the distribution of carotid atherosclerosis in the general population.

Methods: Intimal-medial arterial wall thickness was measured by B-mode real-time ultrasound as an index of atherosclerotic involvement in the extracranial carotid arteries as part of the population-based Atherosclerosis Risk in Communities (ARIC) study. The distribution was described by race-sex strata, in which 759 to 4952 individuals were imaged depending on strata and location in the carotid system.

Results: Median wall thickness ranged between 0.5 and 1 mm at all ages; fewer than 5% of ARIC participants had values exceeding 2 mm. Individuals tended to have a larger wall thickness in the carotid bifurcation than in the common carotid artery. Internal carotid artery values were more variable, with higher proportions of both large and small wall thicknesses than in the common carotid artery. The proportion of individuals with a large wall thickness was greatest at the bifurcation and smallest at the common carotid artery. Men had uniformly larger wall thickness than women. Cross-sectional analysis suggests that age-related increases in wall thickness average approximately 0.015 mm/y in women and 0.018 mm/y in men in the carotid bifurcation, 0.010 mm/y for women and 0.014 mm/y for men in the internal carotid artery, and 0.010 mm/y in both sexes in the common carotid artery.

Conclusions: Estimates provided for wall thickness percentiles can serve as “nomograms” by age, race, and sex. (Stroke. 1993;24:1297-1304.)

Key Words • atherosclerosis • carotid arteries • ultrasonics

Before the introduction of noninvasive high-resolution imaging, assessment of arterial wall atherosclerosis was restricted to pathology and angiography studies. More recently, reports have appeared using ultrasonography of the extracranial carotid arteries to establish the extent of atherosclerosis in clinical populations.1 Although some investigators have described the extent of carotid disease in neurologically asymptomatic patients with carotid bruits,2-5 these patients are not representative of general populations.6 Most studies of carotid arteries in nonclinical populations have used stenosis as the measure of atherosclerosis,7-11 which is a relatively late manifestation of the disease. Early phases of atherosclerotic plaque formation may result in thickened arterial walls with simultaneous dilatation, thereby preserving the lumen.12,13

Thus, there is growing interest in measuring intimal-medial thickness (IMT) to study the natural history of earlier changes.

The Atherosclerosis Risk in Communities (ARIC) study uses B-mode ultrasonography to estimate arterial wall IMT in general populations of middle-aged black and white men and women.14 This report describes far wall (relative to the skin surface) IMT distributions in extracranial carotid arteries.

Subjects and Methods

The ARIC cohort is a population-based probability sample of 15 800 participants aged 45 to 64 years from four US communities.14 From May 15, 1987, through December 1989, 13 870 carotid B-mode real-time ultrasound examinations were performed as part of the baseline examination. The reduced sample size (15 800 versus 13 870) was because the results from “early” ultrasound exams in ARIC were considered unreliable and were excluded from this analysis. Of the 13 870 ultrasound scans, 46 were performed on participants who were neither black nor white, and these subjects are omitted from this report. As shown in Fig 1, the IMT was measured in the far (deeper) wall of three segments of the right and left extracranial carotid arteries: (1) the...
right carotid arteries (Table 1), only estimates for the left carotid system are shown in the figures.

Race- and sex-specific distributions of IMT have also been described as a function of the participant’s age. The cross-sectional relation of the mean IMT as a function of age was estimated by ordinary least-squares (OLS) regression. The cross-sectional description of the percentiles of IMT as a function of age relies on percentile regression, using the asymmetric residual weighting approach described by Efron.\textsuperscript{17} To estimate points on the distribution other than the mean (ordinary least squares), the asymmetric regression approach “shifts” the regression line by assigning a differential weight to residuals above and below the regression line. To allow for curvature of percentile lines, a quadratic model (IMT = β₀ + β₁AGE + β₂AGE\(^2\)) was fit relating age to IMT. Percentile regression lines were estimated for the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles. Results are presented graphically and as a table of estimated IMT at 5-year age intervals.

**Results**

There were 2219 black women studied, and of these the CCA was imaged in 1974 (89%), the BIF in 1512 (68%), and the ICA in 919 (41%). There were 1391 black men studied, and of these the CCA was imaged in 1284 (92%), the BIF in 998 (72%), and the ICA in 759 (55%). There were 5377 white women studied, and the CCA was imaged in 4952 (92%), the BIF in 4396 (82%), and the ICA in 2007 (37%). Lastly, there were 4837 white male participants, and the CCA was imaged in 4419 (91%), the BIF in 3780 (78%), and the ICA in 3036 (63%).

Fig 2 shows distributions of IMT at the CCA, carotid BIF, and ICA for the four race-sex groups. For all race-sex groups and all carotid segments, IMT distributions were right skewed, with many participants having small to moderate IMT and fewer participants having very large IMT. Right-skewness was most pronounced for the BIF and least pronounced for the CCA. CCA values were more tightly clustered than BIF or ICA values. For example, 2.2% of participants had left CCA IMT values less than 0.4 mm and 2.5% had IMT values greater than 1.1 mm, compared with 1.8% and 15.3% for the BIF and 8.8% and 8.8% for the ICA.

For all four race-sex groups, the BIF had generally larger IMT than the CCA. The frequency polygons of IMT for the BIF peak approximately 0.1 mm greater than for the CCA, and the corresponding medians also differ by approximately 0.1 mm (Table 1). The frequency polygons show greater variation in IMT at the BIF than at the CCA, and the BIF also had a greater difference between the 25th and 75th percentiles (interquartile range). For example, in Table 1 it can be seen that at age 55 the interquartile range for black women at the CCA is 0.19 mm compared with 0.31 mm at the BIF, for black men 0.22 mm compared with 0.34 mm, for white women 0.17 mm compared with 0.27 mm, and for white men 0.21 mm compared with 0.39 mm. The proportion of participants with IMTs greater than 1.0 mm is considerably greater for the BIF than for either the CCA or the ICA.

The ICA had IMT values similar to those observed for the CCA with respect to both peak values and medians. However, there are larger proportions of

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**Fig 1. Schematic showing sites of intimal-medial arterial wall thickness evaluation in the carotid system.**

1-cm segment proximal to the dilation of the carotid bulb, which will be referred to as the common carotid artery (CCA); (2) the 1-cm segment proximal to the flow divider, referred to as the bifurcation (BIF); and (3) the 1-cm segment in the internal branch distal to the flow divider, referred to as the internal carotid artery (ICA). In each of these segments, 11 measurements of the IMT of the far wall were attempted at 1-mm increments, and for purposes of this analysis, the IMT at each segment was estimated as the mean of these 11 measurements. Details of the scanning and reading procedures have been previously published.

Ultrasound examinations were performed using the Biosound 2000IISA, with a nominal center transducer frequency of 8 MHz. This system provides an axial resolution of approximately 0.10 mm. This implies that adjacent boundaries that are not spaced by at least 0.10 mm cannot be distinctly observed and thus cannot be resolved on the image. The pixel size of the B-mode image after being digitized at the reading station is 0.067 mm. This implies that measurements of any IMT that can be resolved (ie, that has a value greater than 0.10 mm) are quantized during the measurement process in multiples of 0.067 mm.

At any carotid segment, it was sometimes not possible to visualize the far wall intima-media boundary sufficiently to make any measurements. Because images are more difficult to obtain in deeper segments, the proportion of participants with visualized walls was greatest at the CCA, followed by the BIF, with the least at the ICA. Hence, the realized sample size is smaller at the more distal segments. Moreover, it may not be reasonable to assume that missing data is a random phenomenon. Strictly speaking, our results describing the distribution of IMT apply only to the subgroup with visualized far walls, and inference to the general population must be made with caution. However, analyses undertaken to evaluate the impact of missing data have shown little effect, and we do feel that these results are representative of the general population.

Two approaches were used to describe the IMT distributions. Frequency polygons are presented, with formats chosen to facilitate comparisons of the IMT at the three arterial segments. The midpoints of the IMT were plotted at intervals of 0.067 mm, the approximate resolution of the ultrasound equipment used in the ARIC study. Separate polygons are presented for black women, black men, white women, and white men. Because similar results were obtained for the left and right carotid arteries (Table 1), only estimates for the left carotid system are shown in the figures.

Race- and sex-specific distributions of IMT have also been described as a function of the participant’s age. The cross-sectional relation of the mean IMT as a function of age was estimated by ordinary least-squares (OLS) regression. The cross-sectional description of the percentiles of IMT as a function of age relies on percentile regression, using the asymmetric residual weighting approach described by Efron.\textsuperscript{17} To estimate points on the distribution other than the mean (ordinary least squares), the asymmetric regression approach “shifts” the regression line by assigning a differential weight to residuals above and below the regression line. To allow for curvature of percentile lines, a quadratic model (IMT = β₀ + β₁AGE + β₂AGE\(^2\)) was fit relating age to IMT. Percentile regression lines were estimated for the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles. Results are presented graphically and as a table of estimated IMT at 5-year age intervals.

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<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Black women</th>
<th>Black men</th>
<th>White women</th>
<th>White men</th>
</tr>
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<tr>
<td>45</td>
<td>55</td>
<td>65</td>
<td>45</td>
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<tr>
<td>LCCA</td>
<td>OLS</td>
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<td>P05</td>
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<tr>
<td>LCCA</td>
<td>OLS</td>
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<td>P10</td>
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<tr>
<td>LBIF</td>
<td>OLS</td>
<td></td>
<td>P05</td>
<td>P10</td>
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<tr>
<td>LICA</td>
<td>OLS</td>
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<td>P05</td>
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<td>RCCA</td>
<td>OLS</td>
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<tr>
<td>RICA</td>
<td>OLS</td>
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<td>P10</td>
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LCCA, left common carotid artery; LBIF, left carotid bifurcation; LICA, left internal carotid artery; RCCA, right common carotid artery; RBIF, right carotid bifurcation; RICA, right internal carotid artery. Estimates of mean wall thickness (in millimeters) were estimated by ordinary least-squares (OLS) regression, and percentiles (P) were estimated by the percentile regression techniques of Efron. 

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participants with both large and small IMT, and interquartile range for IMT was greater for the ICA compared with the CCA.

Fig 3 shows scattergrams of participant age and IMT for the CCA, BIF, and ICA for each of the four race-sex groups, the estimated mean IMT as a function of age (OLS), and estimated percentile regression lines. For all carotid segments and all race-sex groups, median IMTs are greater for older participants. Cross-sectional estimates of mean (or other percentile) progression rates with age can be calculated by the ratio of the increase in IMT between age 45 and age 65 to the increase in age. These estimates show that mean IMT increased more rapidly with age at the BIF than either the CCA or ICA (Table 2). With the exception of the 5th and 10th percentile lines for the left ICA for black women, all estimated percentile regression lines increased with age.

There was greater variation in IMT among older participants for all race-sex groups in all carotid segments. For example, the difference between the estimated 5th and 95th percentile was greater at age 65 than at age 45 in all 24 of race-sex and carotid segments combinations (Table 1). White's test showed there to be a significant (P ≤ .05) degree of heteroskedasticity for each race-sex-site combination except the left ICA of black men (P = .10), the right ICA of black men (P = .17), and the right ICA of black women (P = .40). For each of these exceptions, there was a trend for greater variance with older age; however, the relatively small sample at the ICA in blacks reduced the power of the statistical evaluation. The heteroskedasticity is evidenced in the divergence of the percentile regression lines, which is more pronounced at both the BIF and ICA than at the CCA, although some subgroups demonstrate a plateau at the highest percentiles of the BIF. The appendix provides estimates of percentile cut-points at the CCA, BIF, and ICA for both the right and left carotid system at 10-year intervals for each race-sex group.

**Discussion**

All four race-sex groups of middle-aged adults demonstrated similar age-related, arterial segment-specific distribution patterns for carotid IMT. Individuals tended to have greater IMT in the BIF than in the CCA. ICA values were more variable, with higher proportions of both smaller and larger IMT than in the CCA. The proportion of individuals with large IMT was greatest at the BIF and smallest at the CCA. Among both blacks and whites, men had larger IMT than did women at all segments and all percentiles.

Intimal-medial arterial wall thickness, as reported in this article, may be the most sensitive and reliable indicator of the presence and extent of early atherosclerosis obtainable by noninvasive procedures. Several kinds of evidence support the validity of this measure-
ment as an index of atherosclerosis. One kind of evidence is the correspondence between the population distributions of the measurements presented here and the known distributions for atherosclerosis. The International Atherosclerosis Project\(^{19}\) used standardized measurement of arteries collected in medicoegal departments of general hospitals and examined carotid arteries from both Guatemala, which had a low prevalence of atherosclerosis, and Oslo (Norway) with a high prevalence. Among persons aged 45 to 64 years, raised atherosclerotic lesions were found in the common or the extracranial portion of the ICAs from all 265 persons examined in Oslo and more than 90% of the 100 persons examined in Guatemala. Raised lesions covered approximately 8% of the intimal surface of these arteries in Guatemala and 20% in Oslo, with marked predilection for the area within 1 to 2 cm of the bifurcation, which is the same area as is studied here. Pignoli et al\(^{20}\) dissected atheromatous and disease-free aortic and carotid arteries to show strong correlations between histological and ultrasound measurements. Further, early ultrasound-measured IMT has been shown to be closely associated with plasma lipids and other classic atherosclerosis risk factors in ARIC participants\(^{21}\) and in other populations.\(^{22}\) Finally, Salonen and Salonen\(^{23}\) have found IMT in the CCA, as well as extracranial carotid plaque and stenoses, to be predictive of incident acute myocardial infarction.

Median IMT ranged between 0.5 and 1 mm in all arterial segments at all ages, and fewer than 5% of ARIC participants had values exceeding 2 mm, except in the BIF in the oldest age group studied (Table 1). Because early atherosclerosis involves only the intima, which is much thinner than the media in the absence of disease, small changes of 0.1 to 0.2 mm in total IMT may represent a substantial increase in atherosclerotic involvement. Results from the International Atherosclerosis Project\(^{19}\) suggest that some degree of atherosclerotic involvement of the carotid arteries may be nearly universal among participants in the ARIC age range. However, thickenings of this magnitude do not interfere significantly with blood flow. Mean lumen diameters in ARIC were approximately 6.1 mm in women and 6.8 mm in men in the CCA, 7.2 mm in women and 8.1 mm in men in the BIF, and 6.3 mm in women and 7.0 mm in men in the ICA. Fewer than 1% of ARIC participants had evidence of potentially clinically significant carotid disease, as defined by a minimal residual lumen of 2 mm or less. This finding is consistent with reports in the literature for general populations. Zhu and Norris\(^{24}\) found only 6% of 500 patients with an average age of 64 years with nonvascular diagnoses (such as epilepsy and headache) had a “mild” or greater stenosis, and only 1.2% had a “severe” stenosis. In the Augsburg MONICA population, greater than 75% stenosis was observed in only 0.6% of the participants aged 25 to 65 years, although plaques were identified in 24% of participants.\(^{8}\) Colgan et al\(^{8}\) also reported that among 31% of 348 participants screened at a health fair (average age, 61 years) had some evidence of plaque, only 4% had greater than 50% stenoses and only 1% had stenosis above 80%. Langsfeld and Lusby,\(^{9}\) reporting on 250 participants aged older than 40 years scanned at a health fair, found that 4% of participants had stenosis of greater than 20%, while only 1% of participants had stenosis exceeding 50%.

Although the relations between age and IMT seen in ARIC were observed cross-sectionally, an analysis that does not permit tracking individuals as they age, they suggest that IMT increases with advancing age in all carotid segments. The mean far wall increases approximated 0.015 mm/y in women and 0.018 mm/y in men at the BIF and 0.010 mm/y in both sexes at the ICA. The upper percentiles of IMT distributions indicated much greater progression rates and greater differences between the BIF and the CCA in those men and women aged 45 to 65 years. Autopsy studies have reported that the extent of atherosclerotic involvement is greatest near the carotid BIF and in the proximal portion of the ICA.\(^{25,26}\) Thus, the steeper relations between IMT and age at the BIF and ICA suggest more rapid atherosclerotic progression at these segments.

Data from the ARIC study suggest that IMT increases with age in most of the population. Even the 5th percentile of IMT, at the thinnest end of the distribution, is somewhat greater in older than in younger participants (Fig 3). The upper percentiles suggest much more rapid change. If atherosclerosis is the pathology underlying most of these changes, as we believe, its progression in the extracranial carotid arteries appears to be nearly universal in the study communities.

These cross-sectional data suggest that longitudinal estimates of progression rate among ARIC participants will be substantially less than the mean rate of 0.06 mm/y reported for the CCA in Finnish men.\(^{22}\) The conclusion that would follow from the Finnish data seems improbable, because progression at a rate of 0.06 mm/y in both far and near walls in the absence of compensatory dilation would completely occlude a 6-mm lumen in 50 years, unlikely in all but a small proportion of 50-year-old individuals.

The higher percentiles at the left BIF of both white men and black women appears to reach a plateau at older ages. There are several possible explanations for this apparent flattening. First, the variance of this relation increases at the upper percentiles, so that this finding may reflect chance variation in our estimation of the true percentile line. Secondly, the flattening could be a “healthy participant” effect, by which older individuals with large IMT are not represented in the cohort because of early mortality, perhaps from cardiovascular diseases. Unfortunately, in this cross-sectional examination there are not data that are part of the ARIC study to assist in documenting the source of this plateauing.

There is a possibility that the thicknesses of the nonvisualized segments differ from those that were visualized, resulting in a bias in the description of the distribution of thickness. This, however, is unlikely to dramatically affect the estimation of the distributions because visualization is primarily related to arterial depth and ponderosity, factors that in the ARIC data are not strongly related to wall thickness. For example, statistical adjustment for arterial depth and body mass index in white men aged 65 years (chosen to be likely to have large effects from missing data) resulted in a mean absolute difference of less than 0.0064 mm at all sites from those reported herein. The reported distributions are likely to be representative of the general population.
There is an decrease in the ability to visualize and evaluate IMT from the CCA to the BIF and from the BIF to the ICA. This is unfortunate because the ICA tends to be the site of prime clinical interest. However, because of the large sample size of the ARIC study, even with this reduced ability to visualize the ICA there is a sufficient sample size to reliably estimate the percentiles of the distribution.

Efron's percentile regression technique provides an excellent description of the relation between age and the distribution of IMT. Unfortunately, Efron's technique does not yet provide estimates of the standard errors for the parameters specifying the percentile regression lines (βs) and so does not allow for statistical tests between groups (race or sex groups) or within groups (tests for differences in slopes between the
percentile regression lines). This clearly is an area where the technique requires development. In addition, the technique does not allow for adjustments for missing data, which are developing for ordinary linear models. Finally, estimation of regression lines for extreme percentiles (5th or 95th) may be especially sensitive to outliers and hence should not be considered a robust technique. Despite these limitations, we believe that the technique provides an excellent framework for the descriptive tasks required for this article and will likely prove useful in a variety of other applications.

These data are presented to provide a description of the distribution of carotid artery IMT in a general population. The descriptive nature of this report can also establish a "nomogram" for carotid artery wall thickness, providing a useful contrast and reference value for more thoroughly studied patient populations.

### Table 2. Expected Differences in Mean Wall Thickness Between Participants Differing in Age by 1 Year

<table>
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<tr>
<th>Difference in mean IMT (mm)</th>
<th>Black women</th>
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<th>White women</th>
<th>White men</th>
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<td>CCA</td>
<td>0.0085</td>
<td>0.0115</td>
<td>0.0088</td>
<td>0.0095</td>
</tr>
<tr>
<td>BIF</td>
<td>0.0138</td>
<td>0.0168</td>
<td>0.0150</td>
<td>0.0195</td>
</tr>
<tr>
<td>ICA</td>
<td>0.0088</td>
<td>0.0133</td>
<td>0.0100</td>
<td>0.0148</td>
</tr>
</tbody>
</table>

Estimates are based on the average of left and right carotid arteries and calculated as difference in estimated mean intimal-medial thickness (IMT) divided by 20 (number of years' difference). Because quadratic regression techniques were used to estimate the mean IMT as a function of age, the estimates will differ slightly between specific ages. This table is provided for summary comparisons. CCA, common carotid artery; BIF, bifurcation; ICA, internal carotid artery.
Acknowledgments

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Correction

In the article by Howard et al, “Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators,” which appeared in the September 1993 issue of the journal (Stroke. 1993;24:1297-1304) an error occurred.

On page 1300, an appendix is mentioned: "The appendix provides estimates of percentile cut-points at the CCA, BIF, and ICA for both the right and left carotid system at 10-year intervals for each race-sex group." However, there is no appendix for this article. The authors regret the error.