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Carotid Wall Thickness is Predictive of Incident Clinical Stroke

The Atherosclerosis Risk in Communities (ARIC) Study

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Few studies have determined whether carotid artery intima-media thickness (IMT) is associated prospectively with risk of first ischemic stroke. In the Atherosclerosis Risk in Communities Study, carotid IMT, an index of generalized atherosclerosis, was defined as the mean of IMT measured by B-mode ultrasonography at six sites of the carotid arteries. The authors assessed the relation of mean IMT to stroke incidence over 6–9 years' follow-up (1987–1995) among 7,865 women and 6,349 men aged 45–64 years without prior stroke at baseline in four US communities. There were 90 incident ischemic stroke events for women and 109 for men. In sex-specific Cox proportional hazards models adjusting only for age, race, and community, the hazard rate ratios comparing extreme mean IMT values (≥1 mm) to values less than 0.6 mm were 8.5 for women (95% confidence interval: 3.5, 20.7) and 3.6 for men (95% confidence interval: 1.5, 9.2). The relation was graded, and models with cubic splines indicated significant nonlinearity, with hazards increasing more rapidly at lower IMTs than at higher IMTs. Thus, models using linear IMT values substantially underestimate the strength of the association at lower IMTs. The strength of the association was reduced by the inclusion of putative stroke risk factors, but it remained elevated at higher IMTs. Hence, mean carotid IMT is a noninvasive predictor of future ischemic stroke incidence. *Am J Epidemiol* 2000;151:478–87.

carotid arteries; cerebrovascular disorders; incidence; risk factors; ultrasonography

The intima-media thickness (IMT) of the carotid arteries, as determined by B-mode ultrasonography, is a measure of preclinical atherosclerosis. IMT also serves as a marker of generalized atherosclerosis, and as such it has been shown to be positively associated with coronary heart disease, both prevalent (1) and, recently, incident (2–5). One study (5) found a positive association between carotid IMT and incident stroke of all types. We examined this relation for ischemic stroke over 6–9 years' follow-up (1987–1995) in a population study of middle-aged adults, the Atherosclerosis Risk in Communities (ARIC) Study. We hypothesized a positive association between mean IMT and ischemic stroke incidence which would be attenuated but still positive after controlling for putative ischemic stroke risk factors. Furthermore, we hypothesized that the relative risk for a given difference in IMT would be greater at lower levels of baseline mean IMT. Finally, we were interested in comparing the IMT association with stroke to that with coronary heart disease, previously described (2) in the same population.

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Abbreviations: ARIC, Atherosclersis Risk in Communities; CI, confidence interval; IMT, intima-media thickness.

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MATERIALS AND METHODS

Cohort examination

The ARIC study population consists of 45- to 64-year-old members of households sampled in four US communities: selected Minneapolis suburbs, Minnesota; Forsyth County, North Carolina; Washington County, Maryland; and Jackson, Mississippi (the latter sample comprising Black residents only). The sampling procedures have been described in detail previously (6, 7). The 15,792 participants had baseline clinical examinations in 1987–1989 as described below.

The ARIC Study's ultrasound measurements are based on the technique validated by Pignoli et al. (8), using a scanning protocol common to the four field

centers (9, 10) and standardized central reading of scans (11, 12). Analyses are based on the mean IMT of the far wall for 1-cm lengths of the carotid bifurcation and the internal and common carotid arteries, right and left. Maximum likelihood techniques for linear models were used to adjust for site-specific reader differences and downward measurement drifts in mean IMT over the baseline visit. Since only 13 percent of the sample had IMTs observed at all six carotid artery sites, the mean IMTs at the missing sites were imputed from sex- and race-specific multivariate linear models of mean IMT as a function of age, body mass index, and arterial depth, fitted by maximum likelihood methods using BMDP 5V (13). On average, values were imputed for 2.3 sites per person. The mean values at the six sites were combined in an unweighted average to produce an overall mean IMT, or an IMT averaged over the left and right sides of the carotid bifurcation and the internal and common carotid arteries. Estimated correlations between scans made by different sonographers and read by different readers at different visits 7–10 days apart were 0.77, 0.73, and 0.70 for mean far-wall IMT at the bifurcation, internal carotid artery, and common carotid artery, respectively (14). For categorical analysis of IMT, both sex-specific percentiles and overall absolute cutpoints were used. The cutpoints 0.6, 0.7, 0.8, and 1.0 mm were chosen for simplicity, starting with 0.6 mm because there were few incident strokes below that level and stopping with 1.0 mm because there were few persons in the sample (6 percent) above that level.

Participants were asked to fast for 12 hours before the clinical examination. Details on the methods used have been given elsewhere for blood collection (15, 16) and for centralized measurement of plasma total cholesterol (17, 18), triglycerides (17, 19), high density lipoprotein cholesterol (17), calculated low density lipoprotein cholesterol (20), fibrinogen (21–24), and glucose (25). Estimates of intraindividual variability in blood measurements have been reported elsewhere (26–28). White blood cell counts were made with Coulter counters (Coulter Electronics, Hialeah, Florida) in hospital laboratories in the four communities. Prevalent diabetes mellitus was defined as a fasting glucose level of ≥140 mg/dl, a nonfasting glucose level of ≥200 mg/dl, a self-reported physician diagnosis of diabetes, or pharmacologic treatment for diabetes.

Methods have been described previously for the measurement of body mass index (weight (kg)/height $(m)^2$) and waist:hip ratio (29), systolic and diastolic blood pressure (30), and sporting activity (using a sport activity index) (31). Prevalent hypertension was defined as systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, or self-reported use of antihypertensive medication(s). A 12-lead electrocardiogram (32) was used to define left ventricular hypertrophy (33). Participants were defined as current smokers, former smokers, or never smokers by interview. Prevalent stroke at baseline was defined, for exclusion, as a self-reported history of physician-diagnosed stroke. Participants were also asked about use of medications, including aspirin, within the previous 2 weeks (29).

Ascertainment of incident events

Stroke incidence in the ARIC Study was ascertained by contacting participants annually, identifying hospitalizations and deaths occurring during the previous year, and surveying discharge lists from local hospitals and death certificates from state vital statistics offices for potential cerebrovascular events (6, 34–36). When potential strokes were found via selection of records with *International Classification of Diseases, Ninth Revision, Clinical Modification* (37) discharge codes of 430–438 or mention of stroke in the discharge summary, hospital records were copied and sent to a trained nurse for abstraction. Each eligible case was classified by computer algorithm and by expert reviewer, according to criteria adapted from the National Survey of Stroke (38). Differences in diagnosis were adjudicated by another reviewer. Details on quality assurance for ascertainment and classification of events are presented elsewhere (35, 36).

The definition of "ischemic stroke" in this study included validated definite or probable hospitalized embolic or thrombotic strokes. The criteria for classification were based on combinations of symptom type, duration, and severity; results of neuroimaging and other diagnostic procedures; and autopsy evidence (35).

Data analysis

Sex-specific mean baseline values for mean IMT and potential risk factors were compared for persons who suffered incident stroke and those who did not, adjusted for age at baseline, community, and race by analysis of covariance. Sex-specific age- (at baseline), race-, and community-adjusted incidence rates, by level of the categorical risk factors, were computed using Poisson regression (39, 40).

For participants with incident stroke, follow-up was defined as the period between the baseline clinic visit and the date of the first ischemic stroke. For participants with no stroke event, follow-up continued until the date of death or December 31, 1995, or (for the 112 participants lost to follow-up) until the date of last contact.

Cox proportional hazards models were used to estimate the ratios of hazard rates of incident stroke between different levels of mean IMT, adjusting for potentially confounding factors, under the assumption that those ratios were constant over the period of follow-up, given fixed values of other variables in the model (41). The assumption of proportional hazards was checked by testing differences between hazard rate ratios estimated for each of three periods of follow-up (the first 2 years, the next 2 years, and afterwards).

Hazard rate ratios were first estimated from a model adjusting only for age, race, and ARIC community. Variables were entered into the model as linear terms on the log(hazard) scale, as restricted piecewise cubic splines (42), or as categorized variables. The splined models were used to explore nonlinearity in the associations, allowing a cubic association in each of several subintervals of the continuous factor's range but requiring linearity at the beginning and end of the range and requiring that the pieces join smoothly. The subintervals for mean IMT were defined by the 50th, 66.7th, 85th, and 95th sex-specific percentiles (0.65, 0.71, 0.81, and 0.98 mm for women and 0.73, 0.80, 0.94, and 1.14 mm for men).

Next, putative stroke risk factors were added to the model. Interactions between mean IMT and risk factors were evaluated one factor at a time. Finally, the effect on model estimates of random measurement variation in mean IMT (43) was considered by refitting the Cox models after replacing observed mean IMT with a Stein estimate of true mean IMT (44), conditional on predicted mean IMT from sex-specific linear regression of mean IMT on race, community, and age.

RESULTS

The ARIC cohort consists of 15,792 persons. For this analysis, we excluded the Nonwhites in Minneapolis and Washington County and participants from Forsyth County who were neither Black nor White (103 persons altogether). An additional 316 persons were excluded for prevalent stroke, as well as nine with unknown status regarding prevalent stroke, 1,047 with missing information on mean arterial wall thickness, 101 with missing information on diabetes status, and two with no follow-up. This left 7,865 women and 6,349 men for this analysis. Before exclusions, 1,185 potential stroke events occurring through 1995 were investigated; 329 of the events were validated as strokes, 277 ischemic and 52 hemorrhagic (36). There were 199 incident ischemic strokes (90 in women and 109 in men). Median follow-up time was 7.2 years.

Descriptive statistics for the population under study are given in table 1, by incident stroke status. (Summary statistics for the nonstroke group were extremely close to those for the entire population.) Differences in putative risk factor levels generally pointed in the direction of increased predicted risk for persons who eventually had an ischemic stroke. There was no notable difference for aspirin use. Stroke cases had significantly higher mean baseline IMTs (table 1), overall and at each carotid site, than did noncases, by

TABLE 1. Age-, community-, and race-adjusted mean values and proportions for baseline risk factors, by incident ischemic stroke status and gender, Atherosclerosis Risk in Communities Study, 1987–1995

	Females				Males			
	Stroke		No stroke		Stroke		No stroke	
	Mean or proportion	95% confidence interval	Mean or proportion	95% confidence interval	Mean or proportion	95% confidence interval	Mean or proportion	95% confidence interval
Intima-media thickness (mm)								
All-site mean	0.81	0.78, 0.84	0.68	0.65, 0.71	0.84	0.80, 0.88	0.77	0.73, 0.81
Carotid bifurcation	0.92	0.87, 0.97	0.78	0.73, 0.83	0.99	0.94, 1.04	0.90	0.85, 0.95
Common carotid artery	0.70	0.67, 0.73	0.60	0.57, 0.63	0.73	0.70, 0.76	0.66	0.63, 0.69
Internal carotid artery	0.80	0.76, 0.84	0.66	0.62, 0.70	0.80	0.75, 0.85	0.74	0.69, 0.79
Body mass index*	27.5	26.4, 28.7	27.4	27.3, 27.5	27.8	27.1, 28.6	27.3	27.2, 27.4
Fibrinogen (mg/dl)	332.5	319.4, 345.5	305.5	304.1, 306.9	312.5	300.5, 324.5	296.0	294.4, 297.6
Total cholesterol (mg/dl)	236.5	227.8, 245.2	217.9	216.9, 218.8	209.2	201.8, 216.7	210.7	209.7, 211.7
White blood cell count (thousands of cells per mm³)	6.86	6.46, 7.26	6 00	5.96, 6.04	6.63	6.27, 7.00	6.21	6.16, 6.26
Age† (years)	57.1	55.9, 58.3	53.8	53.7, 53.9	57.6	56.5, 58.6	54.5	54.3, 54.6
Hypertension	0.61	0.48, 0.72	0.32	0.31, 0.34	0.55	0.45, 0.66	0.33	0.32, 0.35
Diabetes mellitus	0.30	0.21, 0.41	0.08	0.08, 0.09	0.26	0.18, 0.36	0.09	0.08, 0.10
Current smoking	0.37	0.27, 0.47	0.25	0.24, 0.26	0.39	0.30, 0.48	0.27	0.26, 0.29
Black race‡	0.49	0.39, 0.60	0.27	0.26, 0.28	0.35	0.27, 0.45	0.21	0.20, 0.22
Aspirin use	0.57	0.47, 0.67	0.52	0.51, 0.53	0.43	0.34, 0.52	0.47	0.45, 0.48

* Weight (kg)/height (m)².
† Not adjusted for age.
‡ Not adjusted for race or community.

0.10–0.14 mm for women and 0.06–0.09 mm for men. Adjusted stroke incidence rates (table 2) were higher for higher levels of IMT ($p < 0.02$ for IMT ≥ 1.0 mm and 0.8 mm ≤ IMT < 1.0 mm, relative to IMT < 0.6 mm). There was a clear increase in stroke event rate as mean IMT increased across categories. In each mean IMT tertile, women had clearly and statistically significantly ($p \leq 0.05$) lower adjusted stroke incidence rates than men, but above mean IMTs of 1 mm, the incidence rate for women reached the level for men—both being above 5 per 1,000 person-years, although with few events the confidence intervals were wide.

Table 3 provides the age-, community-, and race-adjusted hazard rate ratios obtained from Cox proportional hazards models. When mean IMT ≥ 1 mm was compared with mean IMT < 1 mm, the hazard rate ratio was 3.3 for women (95 percent confidence interval (CI): 1.9, 5.8) and 2.0 for men (95 percent CI: 1.2, 3.2). The hazard rate ratios between high and low tertiles were also large: 3.8 for women and 2.8 for men. Categorizing mean IMT into subintervals of absolute level indicated a monotonic (graded) relation with incident disease; hazard rate ratios for IMT ≥ 1 mm versus IMT < 0.6 mm were 8.5 for women (95 percent CI: 3.5, 20.7) and 3.6 for men (95 percent CI: 1.5, 9.2). The hazard rate ratio for a 0.18-mm (1 standard deviation) increment of mean IMT, as assessed from a Cox model with linear mean IMT, was significantly elevated for overall mean IMT and for each specific carotid artery site.

To assess the predictive value of IMT for incident ischemic stroke beyond that for potential risk factors, we adjusted IMT hazard rate ratio estimates for these risk factors (table 3). Multiple risk factor-adjusted hazard rate ratios for mean IMT assessed from Cox models with linear mean IMT were lower than those adjusted only for age, community, and race, the reduction being larger for women. The association with IMT remained statistically significant ($p < 0.05$), however. For the models with IMT tertiles, the IMT association

TABLE 2. Sample size, number of events, and age-, community-, and race-adjusted ischemic stroke incidence rates for various levels of baseline intima-media thickness, by gender, Atherosclerosis Risk in Communities Study, 1987–1995

Intima-media thickness	Females (n = 7,865)				Males (n = 6,349)			
	Sample size	No. of events	Incidence rate (per 1,000 person-years)	95% confidence interval	Sample size	No. of events	Incidence rate (per 1,000 person-years)	95% confidence interval
All-site mean								
>95th percentile*	393	16	4.1	2.4, 7.2	317	12	4.6	2.5, 8.5
≤95th percentile	7,472	74	1.3	1.0, 1.8	6,032	97	2.5	2.0, 3.2
Third tertile†	2,619	60	2.6	1.9, 3.7	2,114	65	4.4	3.3, 5.9
Second tertile	2,626	20	1.1	0.7, 1.7	2,120	26	2.0	1.3, 2.9
First tertile	2,620	10	0.7	0.4, 1.3	2,115	18	1.6	1.0, 2.5
≥1.0 mm	347	15	5.1	2.9, 8.9	658	24	5.1	3.2, 8.0
[0.8, 1.0) mm	899	29	3.6	2.3, 5.6	1,494	41	4.0	2.8, 5.7
[0.7, 0.8) mm	1,506	16	1.3	0.8, 2.2	1,670	25	2.4	1.6, 3.6
[0.6, 0.7) mm	2,691	22	1.2	0.7, 1.8	1,716	13	1.3	0.8, 2.3
<0.6 mm	2,422	8	0.6	0.3, 1.2	811	6	1.4	0.6, 3.1
Carotid bifurcation								
Third tertile‡	2,619	56	2.4	1.7, 3.4	2,114	56	3.7	2.7, 5.1
Second tertile	2,626	21	1.1	0.7, 1.7	2,119	35	2.6	1.8, 3.7
First tertile	2,620	13	0.9	0.5, 1.5	2,116	18	1.6	1.0, 2.5
Internal carotid artery								
Third tertile§	2,619	59	2.6	1.9, 3.7	2,114	56	3.9	2.8, 5.3
Second tertile	2,626	20	1.0	0.7, 1.7	2,120	28	2.0	1.4, 3.0
First tertile	2,620	11	0.7	0.4, 1.3	2,115	25	2.0	1.3, 2.9
Common carotid artery								
Third tertile¶	2,619	59	2.5	1.8, 3.6	2,114	69	4.6	3.4, 6.1
Second tertile	2,626	18	1.0	0.6, 1.6	2,120	24	1.9	1.2, 2.8
First tertile	2,620	13	0.9	0.5, 1.6	2,115	16	1.5	0.9, 2.4

* 95th percentile cutpoints were 0.98 mm for women and 1.14 mm for men.
† Second and third tertiles: [0.6070, 0.7057) mm for women and [0.6783, 0.8043) mm for men.
‡ Second and third tertiles: [0.6816, 0.8069) mm for women and [0.7729, 0.9358) mm for men.
§ Second and third tertiles: [0.5733, 0.6794) mm for women and [0.6381, 0.7730) mm for men.
¶ Second and third tertiles: [0.5425, 0.6296) mm for women and [0.5931, 0.6983) mm for men.

TABLE 3. Age-, community-, and race-adjusted hazard rate ratios for incident ischemic stroke obtained from Cox models comparing various levels of baseline intima-media thickness, Atherosclerosis Risk in Communities Study, 1987–1995

Intima-media thickness	Adjusted for age, center, and race				Adjusted for age, center, race, and other factors*			
	Females (n = 7,865)		Males (n = 6,349)		Females (n = 7,865)		Males (n = 6,349)	
	HRR†	95% CI†	HRR	95% CI	HRR	95% CI	HRR	95% CI
All-site mean								
0.18-mm increment	1.60	1.41, 1.81	1.31	1.15, 1.49	1.36	1.16, 1.59	1.21	1.05, 1.39
Second tertile vs. first tertile‡	1.56	0.72, 3.35	1.26	0.69, 2.30	1.58	0.71, 3.52	1.05	0.56, 1.99
Third tertile vs. first tertile	3.83	1.91, 7.67	2.81	1.63, 4.83	2.32	1.09, 4.94	2.24	1.26, 4.00
IMT† > 1 mm (yes/no)	3.31	1.88, 5.81	1.98	1.24, 3.15	2.02	1.11, 3.68	1.78	1.10, 2.88
IMT ≥ 1.0 mm vs. 0.6 mm	8.54	3.52, 20.74	3.64	1.45, 9.15	4.32	1.64, 11.38	2.59	1.00, 6.69
[0.8, 1.0) mm vs. <0.6 mm	6.08	2.69, 13.73	2.87	1.20, 6.87	3.14	1.27, 7.78	2.08	0.85, 5.08
[0.7, 0.8) mm vs. <0.6 mm	2.17	0.92, 5.16	1.70	0.69, 4.19	1.73	0.68, 4.37	1.26	0.50, 3.15
[0.6, 0.7) mm vs. <0.6 mm	1.95	0.86, 4.40	0.95	0.36, 2.50	2.07	0.87, 4.92	0.79	0.29, 2.11
Carotid bifurcation								
0.18-mm increment	1.32	1.20, 1.45	1.17	1.07, 1.27	1.19	1.05, 1.33	1.12	1.02, 1.23
Third tertile vs. first tertile§	2.77	1.48, 5.17	2.36	1.37, 4.09	1.69	0.86, 3.30	2.05	1.14, 3.69
Second tertile vs. first tertile	1.26	0.63, 2.53	1.66	0.94, 2.95	1.22	0.59, 2.52	1.66	0.91, 3.04
Internal carotid artery								
0.18-mm increment	1.28	1.18, 1.39	1.12	1.02, 1.22	1.22	1.10, 1.36	1.06	0.96, 1.17
Third tertile vs. first tertile¶	3.80	1.97, 7.30	1.97	1.21, 3.21	2.45	1.21, 4.99	1.48	0.88, 2.49
Second tertile vs. first tertile	1.49	0.71, 3.11	1.02	0.59, 1.76	1.53	0.71, 3.30	0.90	0.51, 1.57
Common carotid artery								
0.18-mm increment	1.72	1.49, 1.99	1.52	1.28, 1.80	1.32	1.10, 1.58	1.38	1.16, 1.65
Third tertile vs. first tertile#	2.81	1.50, 5.28	3.16	1.80, 5.55	1.65	0.85, 3.19	2.69	1.49, 4.87
Second tertile vs. first tertile	1.08	0.52, 2.21	1.28	0.68, 2 43	0.89	0.42, 1.87	1.22	0.63, 2.36

* Other risk factors: low density lipoprotein cholesterol, high density lipoprotein cholesterol, current smoking, former smoking, hypertension, body mass index, waist:hip ratio, sporting activity, diabetes mellitus, fibrinogen level, left ventricular hypertrophy, and white blood cell count.
† HRR, hazard rate ratio; CI, confidence interval; IMT, intima-media thickness.
‡ Second and third tertiles: [0.6070, 0.7057) mm for women and [0.6783, 0.8043) mm for men.
§ Second and third tertiles: [0.6816, 0.8069) mm for women and [0.7729, 0.9358) mm for men.
¶ Second and third tertiles: [0.5733, 0 6794) mm for women and [0.6381, 0.7730) mm for men.
# Second and third tertiles: [0.5425, 0.6296) mm for women and [0.5931, 0.6983) mm for men.

was also weakened by the addition of the adjusting variables, but it remained significant for overall IMT (though sometimes not at the specific carotid sites).

There were no major violations of the proportional hazards assumptions for mean IMT. The results of tests of differences in IMT hazard rate ratio between periods (the first 2 years, the next 2 years, and afterwards) were not significant for continuous linear IMT or IMT tertiles, though there was a tendency for the hazard rate ratio to be larger in the first two periods than in the third.

Plots from proportional hazards models with splined mean IMT were overlaid with plots from models with linear mean IMT (figure 1), adjusting only for age, race, and community. We plotted the hazard rate ratio comparing the hazard at each mean IMT to the hazard at 0.60 mm. The range for the graphs (but not the fitted models) was limited to 0.6–1.2 mm. In contrast to the linear models (straight dashed lines plotted on the logarithmic scale in figure 1), the splined models suggested that the hazards increased faster at lower levels of IMT. Alternative plots (not shown) of the probability of failure by a fixed time and at fixed covariates showed the same faster rise of risk at lower IMT levels. The departure from linearity was marginally significant ($p = 0.08$ for men and $p = 0.06$ for women). Similar trends were observed in the categorical analysis shown in table 3. In a data-driven additional analysis of this issue, we refitted the Cox models with linear IMT, with IMT restricted to the midrange where the graphs looked linear (0.65–0.80 mm for women and 0.65–0.85 mm for men). The hazard rate ratios for a 0.18-mm difference in IMT calculated from these restricted-range Cox models were very close to those calculated from the average for the splined models over the same restricted range of the hazard rate ratio for a 0.18-mm difference: 2.7–2.8 for women and 2.2–2.4 for men, as compared with 1.60 and 1.31, respectively, for the unrestricted linear models.

The differences in table 3 between men and women in the size of the community-, race-, and age-adjusted association between mean IMT and stroke incidence were statistically significant ($p = 0.05$) for the continuous mean IMT measure, overall and at the internal carotid artery. For the other rows in table 3, the differences were not statistically significant. From the sex-specific models of the interactions of linear mean IMT with the other adjusting variables considered in table 3 (community and, of course, IMT variables not included), only the left ventricular hypertrophy (for both sexes) and waist:hip ratio (for women) interactions were statistically significant at the 0.05 level. The

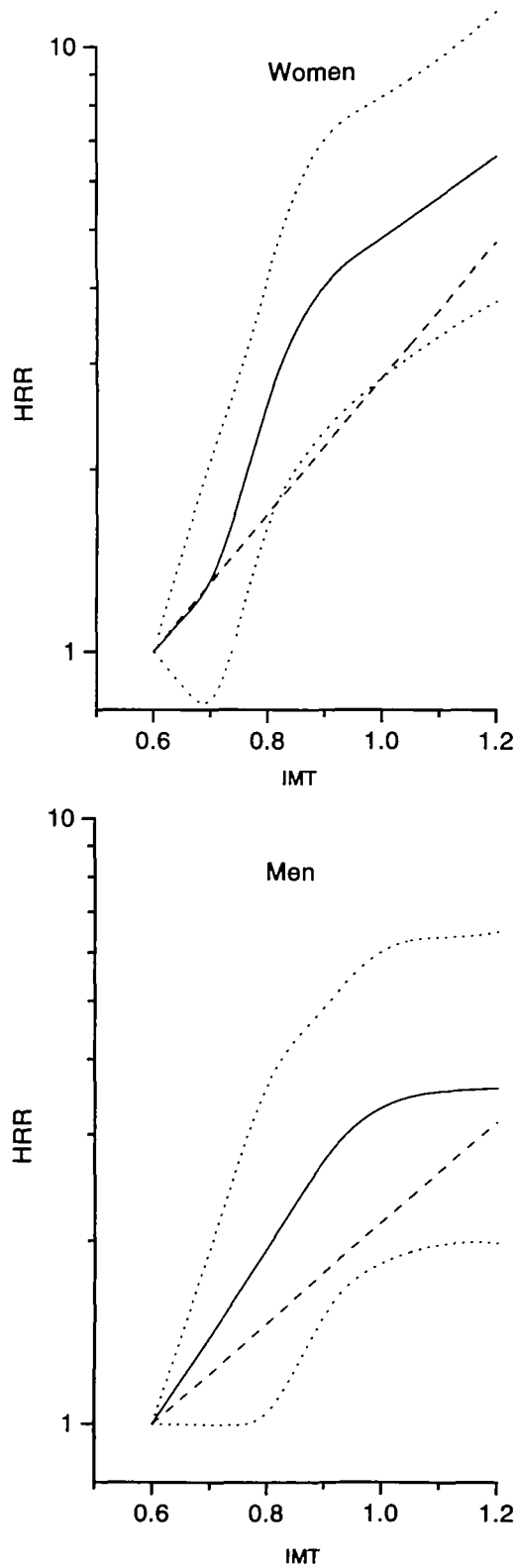

FIGURE 1. Sex-specific hazard rate ratios (HRRs) for incident ischemic stroke according to intima-media thickness (IMT), relative to an IMT of 0.6 mm, Atherosclerosis Risk in Communities Study, 1987–1995. Curves for splined (—) and linear (- - -) IMT values from proportional hazards models are shown. (···, 95% confidence limits for splined model.)

hazard rate ratio for women for a 0.18-mm difference in IMT was 1.73 at the mean waist:hip ratio (0.89), and it was 1.45 at a waist:hip ratio 1 standard deviation above the mean (0.97). The hazard rate ratio for a 0.18-mm difference in IMT was 1.4 times as high for women with left ventricular hypertrophy as for those without it, and 1.9 times higher for men with left ventricular hypertrophy than for those without it.

Cox models with a linear mean IMT term were adjusted for measurement error in mean IMT, assuming a reliability coefficient (r) for mean IMT of either 0.7 or 0.8 (14). For women, the hazard rate ratio for a 0.18-mm increment in mean IMT changed from 1.60 (table 3) to 1.96 for $r = 0.7$ and 1.80 for $r = 0.8$. For men, the table 3 hazard rate ratio of 1.31 went up to 1.47 and 1.40, respectively.

DISCUSSION

As a quantitative indicator of the extent of atherosclerosis, IMT could be expected to be positively associated with incident stroke, a relation that is supported here. Because B-mode ultrasonography is noninvasive, low risk, reliable (14), and valid (8, 45, 46), its use in research applications is of considerable interest, permitting the study of atherosclerosis during its subclinical phase. Because our research protocol for B-mode ultrasonography is standardized and includes neither Doppler capabilities nor the identification of focal areas of disease, our findings probably underestimate the predictive ability of B-mode ultrasonography in clinical settings.

The similarity between the results presented here for ischemic stroke and ARIC results for incident coronary heart disease (2) is remarkable. A graded increase in event rate or hazard rate ratio was seen in both men and women for both ischemic stroke and coronary heart disease, with men having higher event rates at lower levels of IMT and the sex-specific rates being nearly equal at the highest levels of IMT. The spline plots of hazard rate ratio had similar shapes for stroke and coronary heart disease, both increasing faster at lower levels of IMT than at higher levels. The notable difference between the coronary heart disease and stroke associations with IMT was much higher hazard rate ratios for coronary heart disease, though the hazard rate ratios were certainly high for ischemic stroke. The coronary heart disease prediction is not surprising. Carotid wall thickening, like coronary disease, is predominantly atherosclerosis, which is nearly universally found in middle-aged populations in both arterial territories (47). However, stroke has a mixed etiology, some of which is not atherosclerotic. Atherosclerosis is characteristic of the extracranial carotid artery and the larger arteries of the brain, but cerebral ischemic dis-

ease often correlates poorly with large artery disease; and the disease of smaller intracerebral arteries and arterioles is affected by distinct degenerative processes other than atherosclerosis (47–49).

Common to most ischemic strokes is abrupt interruption of blood supply and irreversible damage to brain tissue. The mechanisms of the arterial occlusion vary, however, ranging from cardiogenic embolus (50) to degenerative disease of small-diameter penetrating arteries (51). Of the various mechanisms, in-situ atherosclerosis with superimposed occluding thrombus and artery-to-artery embolization are thought to be common. In the latter, part of an ulcerated, unstable plaque travels through distal branches until it eventually occludes a smaller-sized artery. The origin of an artery-to-artery embolus might be either an extracranial plaque (e.g., in the aorta) or an intracranial plaque (e.g., in the intracranial portion of the internal carotid artery).

Carotid wall thickening, as measured in this study, is not assumed to be a cause of ischemic stroke. With few rare exceptions at the tail of the distribution, intima-media thickening represents neither an ulcerated plaque nor a hemodynamically significant lesion. We therefore assume that mean IMT is a noncausal marker (i.e., a surrogate) of having (or developing) etiologically significant lesions elsewhere. As compared with participants with low IMTs at baseline, those with higher IMTs probably had more advanced atherosclerosis in various segments of the arterial bed—at intracranial and extracranial sites—and therefore were more likely to experience ischemic stroke during follow-up. The fact that the carotid IMT associations in the ARIC Study were nonspecific (i.e., IMT was associated with both stroke and coronary heart disease) lends support to this theory.

Few population studies have investigated carotid IMT as an independent predictor of incident ischemic stroke. The Rotterdam Study (5) used a nested case-control approach among 7,983 persons aged ≥55 years who were followed for less than 4 years (mean = 2.7 years), with 95 strokes of all types. The age- and sex-adjusted odds ratio for stroke was 1.41 (95 percent CI: 1.25, 1.82) for a 0.163-mm difference in common carotid IMT when persons with previous stroke or myocardial infarction were not excluded. When persons with previous stroke or myocardial infarction were excluded, the odds ratio was 1.57 and was higher for men (odds ratio = 1.89) than for women (odds ratio = 1.37), falling to 1.34 for both sexes combined when the analysis was adjusted for multiple risk factors. In the ARIC analysis, when participants with coronary heart disease at baseline were additionally excluded and hazard rate ratios were calculated for a 0.163-mm difference instead of a 0.18-mm difference as in this paper, the age-, sex-, and community-adjusted hazard rate ratios for the common carotid artery were 1.51 for men and 1.67 for women. Thus, the results for incident stroke from the two studies were relatively similar when estimates of effect based on an assumption of linearity of log(hazard) were considered.

The differences between linear and splined models in the estimated size of the association between IMT and stroke (or coronary heart disease) are important. The simpler linear models also indicate a positive statistically significant association, and one might question the stability of the estimates of size of association from the splined models in the range of extreme IMT, where the sample size is smaller or perhaps a selective survival effect is at play. However, it is clear that forcing the log(hazard) model to be linear leads to a sizeable underestimate of the association in the IMT range which includes most of the population, and this is confirmed by the additional linear log(hazard) models over the restricted range where the splined models appear to be linear. The actual stroke hazard rate ratios for a 0.18-mm increase in IMT may be 70–80 percent larger in that middle range of IMT than is predicted from the linear model across the whole range of IMT, but this needs confirmation with a larger number of events.

This study had some limitations. A single mean IMT assessment was used, and correction for the measurement's lack of reliability indicated considerable attenuation of hazard rate ratios if the measurement error was ignored. Furthermore, a considerable amount of ultrasound data was missing, necessitating exclusion of some participants and imputation for most others. However, extensive analyses in the ARIC Study suggest that the mean IMT data were missing at random; for example, missingness at one site was not strongly related to wall thickness at other sites, conditional on the variables used in the imputation process. This justifies the use of the maximum likelihood techniques in the imputation procedure (52). It would not be valid to compute overall mean IMT by averaging only observed sites out of the six, since the sites have different mean thicknesses. Moreover, exclusion of a person entirely because of missing data at any site would be inefficient as well as potentially introduce a selection bias. One alternative to the imputation procedure would be to restrict analysis to the observed data at the common carotid artery, since only 4 percent of persons in this study were missing data on both the left and the right common carotid arteries. An analysis using the mean of the left and right common carotid IMTs yielded hazard rate ratios slightly lower than those

shown in table 3 for the common carotid artery using imputed data (for women, hazard rate ratios were 1.72 and 1.50 from imputed and observed data, respectively, and for men, they were 1.52 and 1.40; statistical significance persisted for analysis with observed data). The ARIC Study's imputed IMT also removes some of the variation between readers as well as the measurement drift over visit 1, and in essence uses data on all observed sites to approximate a missing common carotid artery measurement as opposed to essentially using only one value in place of the mean of two. For these reasons, we think that use of the imputed data more accurately reflects the association being studied.

Another limitation of this study was the low response rate among African Americans, which would have tended to bias the results of the analysis toward a somewhat healthier subgroup of the population, the responders (7)—if indeed the associations considered here differed for responders and nonresponders. Another possible limit to the generalizability of the results is that the four ARIC communities were not a random or representative sample of the US population, although, again, there is no evidence that associations between incident stroke and IMT would show geographic variation within the United States. Loss to follow-up, another potential source of bias, should have had a minimal effect on our results, since only 108 out of more than 12,000 persons were not followed until the occurrence of an incident event, death, or the end of the study period.

Finally, there is always the potential problem of confounding related to variables not considered, although many factors often considered in analyses of stroke probably have their effect partially through atherosclerosis. Examples of such confounders would be socioeconomic factors and dietary factors, and even many of the additional covariates for which we adjusted the data (table 3). Factors related to follow-up, such as carotid endarterectomy, may also affect the association (ignoring this particular variable in follow-up probably biases our estimates toward the null for the IMT-stroke association). However, the effect of these variables on the IMT-stroke association was not the primary interest in the present paper.

The ARIC investigators have obtained data from well standardized measurements in a population-based study of 15,792 persons across four communities. The associations of IMT with potential stroke risk factors have already been firmly established (53–67). This analysis establishes the association of carotid IMT with incident ischemic stroke. After we accounted for the predictive value of other variables, having a mean IMT of 0.8–1.0 mm at baseline was associated with at least a twofold greater hazard rate of subsequent ischemic stroke, and having a mean IMT above 1.0 mm was associated with a three- to fourfold greater hazard rate. To put these numbers into perspective, we note that the hazard rate ratios for hypertension, diabetes, and current smoking (relative to never smoking) were 2.1, 2.5, and 1.3, respectively. We conclude that mean carotid IMT is a useful noninvasive measure that can contribute to the risk stratification of free-living individuals regarding future occurrence of ischemic stroke.

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