

CAROTID-ARTERY INTIMA AND MEDIA THICKNESS AS A RISK FACTOR FOR MYOCARDIAL INFARCTION AND STROKE IN OLDER ADULTS

DANIEL H. O'LEARY, M.D., JOSEPH F. POLAK, M.D., M.P.H., RICHARD A. KRONMAL, PH.D.,
TERI A. MANOLIO, M.D., M.H.S., GREGORY L. BURKE, M.D., M.S., AND SIDNEY K. WOLFSON, JR., M.D.,
FOR THE CARDIOVASCULAR HEALTH STUDY COLLABORATIVE RESEARCH GROUP

ABSTRACT

Background The combined thickness of the intima and media of the carotid artery is associated with the prevalence of cardiovascular disease. We studied the associations between the thickness of the carotid-artery intima and media and the incidence of new myocardial infarction or stroke in persons without clinical cardiovascular disease.

Methods Noninvasive measurements of the intima and media of the common and internal carotid artery were made with high-resolution ultrasonography in 5858 subjects 65 years of age or older. Cardiovascular events (new myocardial infarction or stroke) served as outcome variables in subjects without clinical cardiovascular disease (4476 subjects) over a median follow-up period of 6.2 years.

Results The incidence of cardiovascular events correlated with measurements of carotid-artery intima-media thickness. The relative risk of myocardial infarction or stroke increased with intima-media thickness ($P < 0.001$). The relative risk of myocardial infarction or stroke (adjusted for age and sex) for the quintile with the highest thickness as compared with the lowest quintile was 3.87 (95 percent confidence interval, 2.72 to 5.51). The association between cardiovascular events and intima-media thickness remained significant after adjustment for traditional risk factors, showing increasing risks for each quintile of combined intima-media thickness, from the second quintile (relative risk, 1.54; 95 percent confidence interval, 1.04 to 2.28), to the third (relative risk, 1.84; 95 percent confidence interval, 1.26 to 2.67), fourth (relative risk, 2.01; 95 percent confidence interval, 1.38 to 2.91), and fifth (relative risk, 3.15; 95 percent confidence interval, 2.19 to 4.52). The results of separate analyses of myocardial infarction and stroke paralleled those for the combined end point.

Conclusions Increases in the thickness of the intima and media of the carotid artery, as measured noninvasively by ultrasonography, are directly associated with an increased risk of myocardial infarction and stroke in older adults without a history of cardiovascular disease. (N Engl J Med 1999;340:14-22.)

©1999, Massachusetts Medical Society.

HIGH-RESOLUTION carotid ultrasonography has been used to obtain measurements of the thickness of the intima and media of the carotid arteries. Previous studies have shown cross-sectional associations between common-carotid-artery intima-media thickness and cardiovascular risk factors,¹⁻³ the prevalence of cardiovascular disease,²⁻⁴ and the involvement of other arterial beds with atherosclerosis.^{5,6} Changes in common-carotid-artery intima-media thickness have also been adopted as a surrogate end point for determining the success of interventions that lower the levels of low-density lipoprotein cholesterol.⁷⁻⁹ There are only a few studies showing an association between increased carotid-artery intima-media thickness and new myocardial infarction or stroke.¹⁰⁻¹³

We investigated the hypothesis that carotid-artery intima-media thickness is associated with the incidence of myocardial infarction and stroke in adults 65 years of age or older without preexisting cardiovascular disease who are living in the community. We also hypothesized that carotid-artery intima-media thickness is a predictor of these events after traditional cardiovascular risk factors have been controlled for.

METHODS

Subjects and Study Design

The study subjects were participants in the Cardiovascular Health Study, a prospective, multicenter study of men and women 65 years of age or older that was sponsored by the National Heart, Lung, and Blood Institute.¹⁴ Between June 1989 and May 1990, 5201 participants were enrolled from random samples of Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh. The study was approved by the institutional review boards at the clinical sites and the coordinating center at the University of Washington, and all the participants provided written informed consent. A detailed description of the recruitment methods has been published elsewhere.¹⁵ Ninety-four percent of the members of this first cohort were white, and most of the rest were black. A

From the Department of Radiology, Tufts–New England Medical Center, Boston (D.H.O.); the Department of Radiology, Brigham and Women's Hospital, Boston (J.E.P.); the Department of Biostatistics, University of Washington, Seattle (R.A.K.); the Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, Md. (T.A.M.); the Department of Public Health Sciences, Bowman Gray School of Medicine, Winston-Salem, N.C. (G.L.B.); and the Department of Surgery, University of Pittsburgh, Pittsburgh (S.K.W.). Address reprint requests to the CHS Coordinating Center, Century Sq., 1501 4th Ave., Suite 2025, Seattle, WA 98101, or to daniel.oleary@es.nmc.org.

second cohort of 687 black participants was enrolled between June 1992 and June 1993, three years after the enrollment of the original Cardiovascular Health Study cohort. Of the 5888 participants, 1389 were eliminated from the analyses because they had cardiovascular disease at enrollment (997 with cardiac disease, 249 with cerebrovascular disease, and 143 with both) and 30 (7 of whom also had cardiac disease) did not undergo carotid ultrasonography, leaving a sample of 4476 participants.

The base-line examination included a medical history taking, physical examination, laboratory testing, and assessment of cardiovascular-disease status. The study design, quality-control procedures, laboratory methods, and blood-pressure measurement have been previously reported.^{13,16-27} The algorithms for classifying new myocardial infarctions and strokes have also been published.^{27,28} Myocardial infarctions and strokes were ascertained by questions at annual visits and interim telephone interviews every six months, reporting of events by participants, and use of Medicare hospital records. Discharge summaries and diagnoses were obtained for all hospitalizations. For all potential new myocardial infarctions or strokes, additional information, including results of cardiac-enzyme measurements, serial electrocardiography, cranial computed tomography, and cerebral magnetic resonance imaging, was collected from medical records. Interviews were conducted with surviving participants or, for fatal events, from witnesses or proxies. All data on events were reviewed and initially classified by local physicians at the field centers. Final classification of all events was determined by a committee of Cardiovascular Health Study investigators after a review of the medical records.

The carotid arteries were evaluated with high-resolution B-mode ultrasonography.²⁹ One longitudinal image of the common carotid artery and three longitudinal images of the internal carotid artery were acquired. Measurements were made at a central reading center by readers blinded to all clinical information. Measurements were made from stored digital images when the black cohort was enrolled three years later, so that the same readers were used for all readings. The maximal rather than the mean intima-media thickness was used as the key variable after a statistical investigation of the strength of the associations between risk factors and intima-media thickness.

The many measures of intima-media thickness were summarized in two variables, one for the common carotid artery and one for the internal carotid artery. The maximal intima-media thickness of the common carotid artery and of the internal carotid artery was defined as the mean of the maximal intima-media thickness of the near and far wall on both the left and right sides. The number of measurements that were available for averaging thus ranged from 1 to 4 for the common carotid artery and 1 to 12 for the internal carotid artery. A composite measure that combined the maximal common-carotid-artery intima-media thickness and maximal internal-carotid-artery intima-media thickness was obtained by averaging these two measurements after standardization (subtraction of the mean and division by the standard deviation for the measurement).³⁰ The Spearman correlations between all the readings at base line and all the readings performed by separate readers three years later were 0.75, 0.86, and 0.84 for the common carotid artery, internal carotid artery, and combined measure, respectively.

Statistical Analysis

Preexisting cardiac disease was defined as documented symptomatic myocardial infarction, angina, coronary-artery bypass surgery, or coronary-artery angioplasty. Preexisting cerebrovascular disease was defined as a history of stroke, transient ischemic attack, or carotid endarterectomy. Participants with a history of cardiac disease or cerebrovascular disease were excluded so that we could study asymptomatic persons without clinical symptoms or signs of cardiovascular disease.

All analyses were performed with SPSS/Windows statistical software.³¹ The Cox proportional-hazards regression model was used to estimate the relative risk of new myocardial infarction,

stroke, and the combined end point. Quintiles of carotid-artery measures and the continuous version of these variables were used in these analyses. Data on subjects were censored after death from any cause and after the last follow-up visit.

We evaluated the effect of traditional risk factors on any observed associations between carotid intima-media thickness and a given cardiovascular outcome with use of Cox proportional-hazards models selected by a stepwise strategy applied to the following variables (with P=0.10 necessary to enter a variable into the model): carotid-artery intima-media thickness, age, sex, race, presence or absence of atrial fibrillation, systolic and diastolic pressure, history of diabetes, history of smoking, history of hypertension, and low-density lipoprotein and high-density lipoprotein cholesterol levels. A variable that was entered into a model for a given outcome was kept in all three models in order to permit a direct comparison between models. The interaction between sex and the wall-thickness variables was tested in all the models. We also evaluated the relative importance of intima-media thickness (as a continuous variable) as compared with traditional risk factors in Cox proportional-hazards models both without adjustment for age and sex and with adjustment for these variables. The comparison of models was based on the Wald statistic, which has an asymptotic chi-square distribution.

RESULTS

The base-line characteristics of the 4476 study participants are given in Table 1. The mean age of the participants at entry was 72.5 years, and 38.8 percent were men. Blacks made up 15.2 percent of the sample. The median follow-up was 6.2 years (maximum, 7). There were 267 new myocardial infarctions, 284 new strokes, and 496 participants who had a new myocardial infarction or stroke. Fifty-five

TABLE 1. CHARACTERISTICS OF THE 4476 STUDY PARTICIPANTS AT ENROLLMENT.

CHARACTERISTIC	VALUE*
Age (yr)	72.5±5.5
Male sex (%)	38.8
Black race (%)	15.2
Atrial fibrillation (%)	3.0
Diabetes (%)	12.9
Hypertension (%)	39.9
Current smoker (%)	12.2
Pack-years of smoking†	36.8±26.2
Blood pressure (mm Hg)	
Systolic	136.3±21.5
Diastolic	71.1±11.3
Cholesterol (mg/dl)‡	
LDL	129.8±35.5
HDL	55.6±15.8
Intima-media thickness (mm)	
Common carotid artery	1.03±0.20
Internal carotid artery	1.37±0.55

*Plus-minus values are means ±SD.

†Pack-years of smoking are for those who had ever smoked.

‡LDL denotes low-density lipoprotein, and HDL high-density lipoprotein. To convert values to millimoles per liter, multiply by 0.02586.

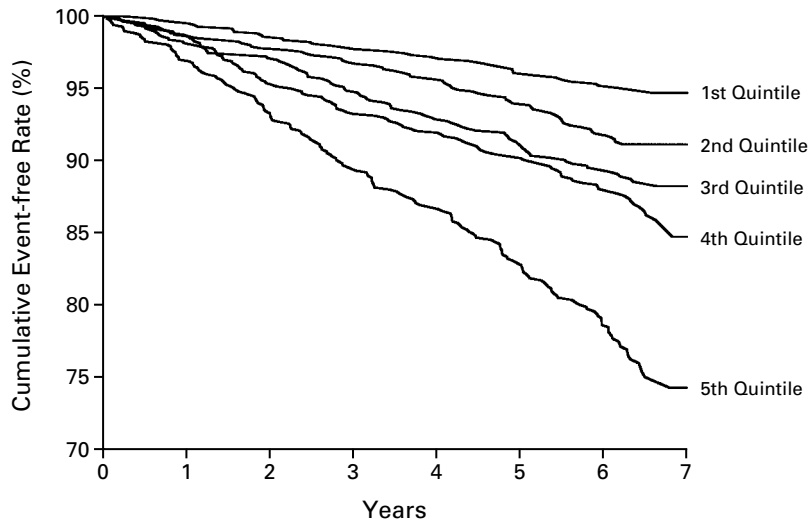


Figure 1. Unadjusted Cumulative Event-free Rates for the Combined End Point of Myocardial Infarction or Stroke, According to Quintile of Combined Intima-Media Thickness.

The estimated cumulative rate of the combined end point for the fifth quintile of the combined measure was over 25 percent at seven years, as compared with a cumulative rate of less than 5 percent for the first quintile.

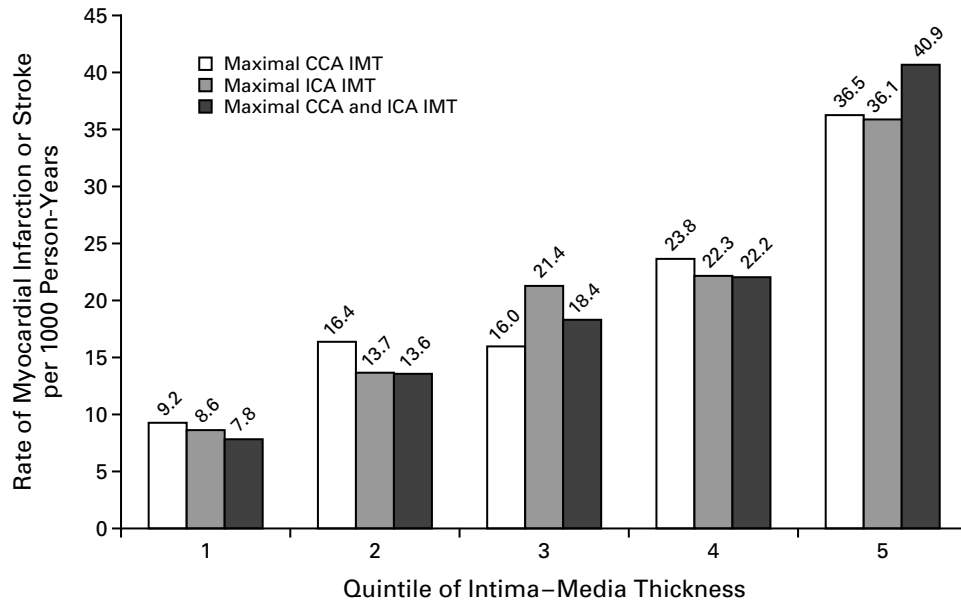


Figure 2. Unadjusted Incidence of Myocardial Infarction or Stroke According to Quintile of Carotid-Artery Intima-Media Thickness.

The yearly incidence of the combined end point of myocardial infarction or stroke increased with increasing quintiles of each of the measures of intima-media thickness (IMT). The rates were similar for quintiles of common-carotid-artery (CCA) intima-media thickness and internal-carotid-artery (ICA) intima-media thickness, but the gradient of increasing risk was slightly less pronounced than for the combined measure.

TABLE 2. RELATIVE RISK OF THE COMBINED END POINT OF STROKE OR MYOCARDIAL INFARCTION AS A FUNCTION OF THE COMMON-CAROTID-ARTERY AND INTERNAL-CAROTID-ARTERY INTIMA-MEDIA THICKNESS EXPRESSED AS QUINTILES AND AS A CONTINUOUS VARIABLE.*

VARIABLE	No. OF EVENTS (STROKE OR MI)/ No. AT RISK	RELATIVE RISK (95% CI)		
		UNADJUSTED	ADJUSTED FOR AGE AND SEX	ADJUSTED FOR AGE, SEX, AND OTHER RISK FACTORS†
Maximal CCA IMT				
<0.87 mm	47/897	1.00	1.00	1.00
0.87–0.96 mm	84/906	1.79 (1.25–2.55)	1.61 (1.13–2.31)	1.49 (1.04–2.14)
0.97–1.05 mm	80/891	1.70 (1.18–2.44)	1.44 (1.00–2.08)	1.29 (0.89–1.86)
1.06–1.17 mm	118/888	2.59 (1.85–3.63)	2.05 (1.46–2.89)	1.76 (1.24–2.48)
≥1.18 mm	167/894	3.98 (2.88–5.51)	2.85 (2.04–3.99)	2.22 (1.58–3.13)
Per 1 SD (0.20 mm) increase		1.47 (1.37–1.57)	1.35 (1.25–1.45)	1.27 (1.17–1.38)
P value		<0.001	<0.001	<0.001
Maximal ICA IMT‡				
<0.90 mm	43/894	1.00	1.00	1.00
0.91–1.10 mm	72/896	1.59 (1.09–2.32)	1.52 (1.04–2.22)	1.78 (1.13–2.81)
1.11–1.39 mm	108/895	2.43 (1.71–3.47)	2.15 (1.51–3.07)	1.95 (1.24–3.05)
1.40–1.80 mm	109/895	2.60 (1.82–3.69)	2.13 (1.49–3.04)	1.88 (1.20–2.96)
≥1.81 mm	163/895	4.22 (3.02–5.91)	3.20 (2.27–4.51)	2.47 (1.59–3.85)
Per 1 SD (0.55 mm) increase		1.51 (1.40–1.64)	1.37 (1.27–1.49)	1.30 (1.20–1.41)
P value		<0.001	<0.001	<0.001
Maximal CCA and ICA IMT (average, standardized)				
1st quintile	40/895	1.00	1.00	1.00
2nd quintile	70/895	1.71 (1.16–2.53)	1.60 (1.08–2.36)	1.54 (1.04–2.28)
3rd quintile	93/896	2.33 (1.60–3.37)	2.03 (1.40–2.94)	1.84 (1.26–2.67)
4th quintile	109/895	2.84 (1.98–4.08)	2.27 (1.57–3.29)	2.01 (1.38–2.91)
5th quintile	184/895	5.27 (3.75–7.43)	3.87 (2.72–5.51)	3.15 (2.19–4.52)
Per 1 SD increase		1.58 (1.48–1.69)	1.44 (1.34–1.55)	1.36 (1.25–1.47)
P value		<0.001	<0.001	<0.001

*MI denotes myocardial infarction, CI confidence interval, CCA common carotid artery, IMT intima-media thickness, and ICA internal carotid artery.

†The risk factors were systolic and diastolic blood pressure, presence or absence of atrial fibrillation, pack-years of smoking, and history of diabetes. There were 4464 participants included in this analysis.

‡For one participant who had a myocardial infarction, the ICA IMT measurement was missing, but the CCA IMT measurement was obtained.

participants had both a myocardial infarction and a stroke, but only the event that occurred first was used for the analysis of the combined end point.

Figure 1 shows the cumulative event-free rates with respect to the combined end point according to quintiles of intima-media thickness. The estimated cumulative rate of the combined end point for the highest quintile of the combined wall-thickness measure was over 25 percent at seven years, as compared with a cumulative rate of less than 5 percent for the lowest quintile. The yearly incidence of the combined end point of myocardial infarction or stroke increased with increasing quintiles for each of the measures of intima-media thickness (Fig. 2). The rates were similar for quintiles of common-carotid-artery intima-media thickness and internal-carotid-artery intima-media thickness, but the gradient of increasing risk was slightly less pronounced than for the combined measure.

In a Cox proportional-hazards regression, the combined measure of intima-media thickness was

significantly associated with the risk of the combined end point after adjustment for age and sex ($P < 0.001$ by the test for trend), with persons in the highest quintile having a risk that was 3.9 times as great as that of persons in the lowest quintile (Table 2). The risk associated with the combined measure of intima-media thickness remained significant ($P < 0.001$ by the test for trend), although slightly reduced in magnitude, after adjustment for systolic and diastolic blood pressure, pack-years of smoking, and the presence or absence of atrial fibrillation and diabetes. Similar results were observed for the individual measures of intima-media thickness, but with somewhat smaller relative risks (Table 2).

Cox proportional-hazards models using the intima-media thickness as a continuous variable also showed strong associations with the combined event. The age- and sex-adjusted relative risks associated with a change of 1 SD in the intima-media thickness of the common carotid artery, internal carotid artery, and the two combined were similar, with a 35 to 44

TABLE 3. RELATIVE RISK OF MYOCARDIAL INFARCTION AS A FUNCTION OF THE COMMON-CAROTID-ARTERY AND INTERNAL-CAROTID-ARTERY INTIMA-MEDIA THICKNESS EXPRESSED AS QUINTILES AND AS A CONTINUOUS VARIABLE.*

VARIABLE	No. OF EVENTS/ No. AT RISK	RELATIVE RISK (95% CI)		
		UNADJUSTED	ADJUSTED FOR AGE AND SEX	ADJUSTED FOR AGE, SEX, AND OTHER RISK FACTORS†
Maximal CCA IMT				
<0.87 mm	22/897	1.00	1.00	1.00
0.87-0.96 mm	47/906	2.12 (1.28-3.52)	1.92 (1.16-3.19)	1.79 (1.08-2.98)
0.97-1.05 mm	41/891	1.85 (1.10-3.11)	1.58 (0.94-2.67)	1.40 (0.83-2.38)
1.06-1.17 mm	66/888	3.06 (1.89-4.95)	2.39 (1.47-3.91)	2.07 (1.27-3.39)
≥1.18 mm	91/894	4.50 (2.82-7.17)	3.17 (1.96-5.12)	2.46 (1.51-4.01)
Per 1 SD (0.20 mm) increase		1.46 (1.33-1.60)	1.33 (1.21-1.48)	1.24 (1.12-1.38)
P value		<0.001	<0.001	<0.001
Maximal ICA IMT‡				
<0.90 mm	19/894	1.00	1.00	1.00
0.91-1.10 mm	34/896	1.68 (0.96-2.95)	1.54 (0.88-2.70)	1.55 (0.89-2.73)
1.11-1.39 mm	58/895	2.93 (1.74-4.92)	2.45 (1.46-4.13)	2.30 (1.36-3.88)
1.40-1.80 mm	70/895	3.74 (2.25-6.20)	2.95 (1.77-4.93)	2.68 (1.60-4.48)
≥1.81 mm	85/895	4.84 (2.94-7.96)	3.52 (2.12-5.84)	3.00 (1.80-5.01)
Per 1 SD (0.55 mm) increase		1.57 (1.42-1.74)	1.43 (1.28-1.59)	1.34 (1.20-1.50)
P value		<0.001	<0.001	<0.001
Maximal CCA and ICA IMT (average, standardized)				
1st quintile	18/895	1.00	1.00	1.00
2nd quintile	33/895	1.75 (0.98-3.12)	1.62 (0.91-2.88)	1.58 (0.89-2.81)
3rd quintile	52/896	2.88 (1.69-4.93)	2.46 (1.43-4.22)	2.20 (1.28-3.78)
4th quintile	62/895	3.56 (2.10-6.01)	2.78 (1.63-4.73)	2.45 (1.44-4.19)
5th quintile	102/895	6.30 (3.82-10.41)	4.51 (2.69-7.55)	3.61 (2.13-6.11)
Per 1 SD increase		1.60 (1.46-1.76)	1.46 (1.32-1.61)	1.36 (1.23-1.52)
P value		<0.001	<0.001	<0.001

*CI denotes confidence interval, CCA common carotid artery, IMT intima-media thickness, and ICA internal carotid artery.

†The risk factors were systolic blood pressure, diastolic blood pressure, history of diabetes, and pack-years of smoking. There were 4463 participants included in this analysis.

‡For one participant who had a myocardial infarction, the ICA IMT measurement was missing, but the CCA IMT measurement was obtained.

percent increase in risk, and remained significant after adjustment for risk factors. Comparison of the chi-square statistics showed that the combined measure of intima-media thickness was a stronger predictor than the individual measures.

We examined the strength of the associations with myocardial infarction alone as the outcome. The results for myocardial infarction paralleled those for the combined end point. Although the intima-media thickness of both the common and internal carotid arteries was associated with the risk of myocardial infarction, the relative risks associated with greater common-carotid-artery intima-media thickness tended to be lower than those associated with greater internal-carotid-artery intima-media thickness and with greater combined intima-media thickness (Table 3). Increases of 1 SD in common-carotid-artery, internal-carotid-artery, and combined thickness were associated with 33 to 46 percent increases in risk after adjustment for age and sex.

In contrast, the common-carotid-artery intima-

media thickness and the combined measure were better predictors of stroke than the internal-carotid-artery intima-media thickness (Table 4). An increment of 1 SD in wall thickness was associated with a 33 to 43 percent increase in risk after adjustment for age and sex and a 25 to 33 percent increase in risk after adjustment for additional factors ($P < 0.001$ for all comparisons).

Adding a term for interaction between intima-media thickness and sex to the above models did not result in any significant effect in any of the models ($P > 0.20$ for all comparisons).

Cox proportional-hazards models, with the intima-media thickness as a continuous variable, showed strong associations between the combined outcome and traditional risk factors as well as the intima-media thickness (Table 5). The age- and sex-adjusted relative risks associated with an increase of 1 SD in the combined measure of intima-media thickness were at least as strong as those associated with traditional risk factors (Table 5).

TABLE 4. RELATIVE RISK OF INCIDENT STROKE AS A FUNCTION OF THE COMMON-CAROTID-ARTERY AND INTERNAL-CAROTID-ARTERY INTIMA-MEDIA THICKNESS EXPRESSED AS QUINTILES AND AS A CONTINUOUS VARIABLE.*

VARIABLE	NO. OF EVENTS/ NO. AT RISK	RELATIVE RISK (95% CI)		
		UNADJUSTED	ADJUSTED FOR AGE AND SEX	ADJUSTED FOR AGE, SEX, AND OTHER RISK FACTORS†
Maximal CCA IMT				
<0.87 mm	29/897	1.00	1.00	1.00
0.87-0.96 mm	46/906	1.57 (0.98-2.49)	1.40 (0.88-2.23)	1.33 (0.83-2.12)
0.97-1.05 mm	47/891	1.65 (1.04-2.62)	1.38 (0.86-2.20)	1.21 (0.76-1.93)
1.06-1.17 mm	60/888	2.09 (1.34-3.26)	1.66 (1.06-2.60)	1.39 (0.88-2.18)
≥1.18 mm	102/894	3.86 (2.55-5.83)	2.76 (1.80-4.24)	2.13 (1.38-3.28)
Per 1 SD (0.20 mm) increase		1.49 (1.37-1.62)	1.37 (1.25-1.51)	1.28 (1.16-1.42)
P value		<0.001	<0.001	<0.001
Maximal ICA IMT‡				
<0.90 mm	30/894	1.00	1.00	1.00
0.91-1.10 mm	43/896	1.36 (0.85-2.16)	1.35 (0.84-2.15)	1.34 (0.84-2.14)
1.11-1.39 mm	61/895	1.98 (1.28-3.07)	1.81 (1.16-2.80)	1.69 (1.09-2.62)
1.40-1.80 mm	50/895	1.67 (1.06-2.62)	1.38 (0.87-2.18)	1.22 (0.77-1.93)
≥1.81 mm	100/895	3.66 (2.43-5.50)	2.82 (1.85-4.28)	2.35 (1.55-3.57)
Per 1 SD (0.55 mm) increase		1.47 (1.33-1.63)	1.33 (1.19-1.48)	1.25 (1.12-1.39)
P value		<0.001	<0.001	<0.001
Maximal CCA and ICA IMT (average, standardized)				
1st quintile	26/895	1.00	1.00	1.00
2nd quintile	44/895	1.68 (1.03-2.72)	1.58 (0.97-2.57)	1.50 (0.92-2.43)
3rd quintile	48/896	1.84 (1.14-2.97)	1.62 (1.00-2.61)	1.37 (0.85-2.22)
4th quintile	59/895	2.34 (1.47-3.71)	1.87 (1.17-2.99)	1.57 (0.98-2.51)
5th quintile	107/895	4.57 (2.98-7.02)	3.37 (2.16-5.25)	2.57 (1.64-4.02)
Per 1 SD increase		1.57 (1.43-1.71)	1.43 (1.29-1.57)	1.33 (1.20-1.47)
P value		<0.001	<0.001	<0.001

*CI denotes confidence interval, CCA common carotid artery, IMT intima-media thickness, and ICA internal carotid artery.

†The risk factors were systolic blood pressure, history of hypertension, presence or absence of atrial fibrillation, and history of diabetes. There were 4466 participants included in this analysis.

‡For one participant (who did not have a stroke) the ICA IMT measurement was missing.

TABLE 5. COMPARISON OF THE ASSOCIATIONS OF INDIVIDUAL RISK FACTORS WITH THE COMBINED EVENT OF STROKE OR MYOCARDIAL INFARCTION IN COX PROPORTIONAL-HAZARDS MODELS WITH AND WITHOUT ADJUSTMENT FOR AGE AND SEX.*

RISK FACTOR	UNADJUSTED	RELATIVE RISK ADJUSTED FOR THE THREE VARIABLES SHOWN (95% CI)						
	RELATIVE RISK							
Age (per 5.5 yr)	1.50	1.33	1.51	1.39	1.50	1.50	1.48	1.48
Sex (men vs. women)	1.65	1.34	1.46	1.59	1.45	1.51	1.51	1.55
Combined IMT measure (per 1 SD)	1.58	1.44 (1.33-1.55)						
Diastolic blood pressure (per 11.3 mm Hg)	1.24		1.26 (1.15-1.37)					
Systolic blood pressure (per 21.5 mm Hg)	1.48			1.39 (1.28-1.51)				
Pack-years of smoking (per 25 pack-yr)	1.14				1.14 (1.05-1.24)			
LDL and HDL cholesterol (per 1 SD)	1.16					1.16 (1.06-1.26)		
Diabetes (yes vs. no)	2.19						2.11 (1.70-2.62)	
Atrial fibrillation (yes vs. no)	1.78							1.61 (1.07-2.42)

*CI denotes confidence interval, IMT intima-media thickness, LDL low-density lipoprotein, and HDL high-density lipoprotein.

DISCUSSION

We have previously reported on the positive associations between cardiovascular risk factors and carotid-artery intima-media thickness.^{2,29} We have also shown that a measurement that combined common-carotid-artery and internal-carotid-artery intima-media thicknesses was more strongly associated with the prevalence of cardiovascular disease and with traditional risk factors than either variable used alone.³⁰ We now report a positive association between carotid-artery intima-media thickness and the incidence of new myocardial infarction and stroke in adults 65 years of age or older who did not have a history of cardiovascular disease. We have shown that the intima-media thickness is a strong predictor of both myocardial infarction and stroke and that the risk gradients are similar. The combined measure of common-carotid-artery and internal-carotid-artery intima-media thickness was a better predictor of events than either thickness measure taken alone. When statistical adjustment was made for traditional cardiovascular risk factors, carotid-artery intima-media thickness remained a significant predictor of cardiovascular events. The strength of the associations between intima-media thickness and outcome was at least as strong as the associations seen with traditional risk factors.

Four other studies have explored the possible association between carotid-artery intima-media thickness and the incidence of cardiovascular events.¹⁰⁻¹³ Three of these studies reported results using measurements of the common carotid artery. Salonen and Salonen, in a study of 1257 middle-aged Finnish men, observed an association between common-carotid-artery intima-media thickness and cardiac events. This observation was based on a one-year follow-up and a total of 24 events.¹⁰ Because the definitions of high-risk categories in their study were different from those we used, direct comparison of our results with theirs is not possible.

The Rotterdam Elderly Study was a single-center, prospective study of disease and disability in the elderly involving 7983 subjects 55 years of age or older.³² They performed a case-control study in a subgroup of their population that showed an association between common-carotid-artery intima-media thickness and the risk of myocardial infarction and stroke.¹¹ The Rotterdam investigators did not find a consistent relative risk of myocardial infarction, whereas we found that the risk of myocardial infarction increased in a monotonic fashion with increasing intima-media thickness. They included subjects with angina, transient ischemic attack, and other manifestations of cardiovascular disease at entry, whereas we excluded such subjects. The inclusion of subjects with symptomatic cardiovascular disease may explain why the Rotterdam investigators were unable to show a strong association between common-carotid-

artery intima-media thickness and the risk of myocardial infarction, whereas we show a strong risk gradient. The differences between their study and ours may be explained by the larger number of subjects and the longer duration of follow-up in our study. Moreover, our results extend their findings by showing that internal-carotid-artery intima-media thickness is as good a predictor as common-carotid-artery intima-media thickness, and the combination of the two is statistically superior to either one.

The subjects of the Atherosclerosis Risk in Communities Study were 15,792 middle-aged men and women, 45 to 64 years of age and living in four separate areas of the United States, who were followed for four to seven years for the incidence of cardiac disease.¹² Although it reported only far-wall measurements, the Atherosclerosis Risk in Communities Study also used a combined measure of common-carotid-artery and internal-carotid-artery intima-media thicknesses. Although they did not report on the associations with stroke, the investigators found a similar association between intima-media thickness and cardiac disease in a younger population.¹² Hodis et al. also found an association between intima-media thickness and coronary events in a study of men who had undergone coronary-artery bypass graft surgery and were followed for an average of 8.8 years.¹³

In our study, which assessed whether noninvasive measurements have any predictive power with respect to subsequent cardiovascular events, we were aware that carotid-artery intima-media thickness is strongly associated with cardiovascular risk factors.^{2-5,29,33,34} Despite this association, we have shown that the carotid-artery intima-media thickness is a strong predictor of new cardiovascular events even after statistical adjustment for other risk factors. This finding has clinical significance, particularly with regard to the elderly. Calculated risk profiles have been proposed for use in identifying persons at high risk for myocardial infarction³⁵ and for stroke.³⁶ However, borderline elevation of multiple risk factors is common in the elderly, and the association between risk factors and cardiovascular disease may weaken in the later years of life.^{37,38} Therefore, it may be difficult for clinicians to identify older patients with subclinical cardiovascular disease on the basis of classic risk factors. Increased intima-media thickness, an indicator of subclinical disease, may reflect the consequences of past exposure to risk factors. The addition of measurements of intima-media thickness to cardiovascular risk equations may help identify asymptomatic persons who would benefit from aggressive preventive measures.

This strategy, if applied to populations similar to our cohort, would require combined measurements of common-carotid-artery and internal-carotid-artery intima-media thickness at the far and near walls of the arteries. The internal-carotid-artery intima-

media measurements, because of the way they are performed, probably reflect the presence of focal plaque and may thus be more representative of risk-factor exposure.³⁹ This may explain in part the added predictive power of combined measurements of the common and internal carotid arteries. Similarly, near-wall measurements are also useful, since far-wall measurements had a significantly weaker association with outcomes ($P < 0.001$) than the combined near- and far-wall measurements (analyses not shown).

Measurements of carotid-artery intima-media thickness were as strong predictors of events as the traditional risk factors. After adjustment for conventional risk factors, the combined measure of intima-media thickness was the variable most strongly associated with the risk of cardiovascular events. An increase of 1 SD in combined intima-media thickness was associated with a relative risk of 1.36 for the combined end point of myocardial infarction or stroke after adjustment for age, sex, and the other risk factors. In contrast, in the same model an increase in age of 1 SD (5.5 years) was associated with a relative risk of 1.34, and an increase in systolic blood pressure of 1 SD (21.5 mm Hg) with a relative risk of 1.21. The relative strength of the associations between events and intima-media thickness, as compared with the association between events and other traditional risk factors, suggests that intima-media thickness is by itself as powerful a predictor of cardiovascular events as the traditional risk factors.

Variability in measurement of the intima-media thickness might have affected our results. The strong correlations between replicate readings of the intima-media thickness (Spearman coefficients of 0.75 to 0.86) are similar to those already published.^{2,4,5,11-13,30} Any increase in the precision of the measurements as a result of technological improvements might increase their predictive power for cardiovascular events.

We conclude that the intima-media thickness of the common carotid artery and the internal carotid artery is strongly associated with the risk of myocardial infarction and stroke in asymptomatic older adults. Measurements of carotid-artery intima-media thickness retain predictive power with respect to new cardiovascular events even after traditional risk factors for cardiovascular events have been taken into consideration; moreover, such measurements seem more powerful predictors than these same risk factors.

Supported in part by contracts (NO1-HC85079 through NO1-HC85086) with the National Heart, Lung, and Blood Institute.

REFERENCES

1. Poli A, Tremoli E, Colombo A, Sirtori M, Pignoli P, Paoletti R. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients: a new model for the quantitation and follow-up of preclinical atherosclerosis in living human subjects. *Atherosclerosis* 1988;70:253-61.
2. O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. *Stroke* 1992;23:1752-60.
3. Mannami T, Konishi M, Baba S, Nishi N, Terao A. Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japanese city: the Suita study. *Stroke* 1997;28:518-25.
4. Bots ML, Breslau PJ, Briet E, et al. Cardiovascular determinants of carotid artery disease: the Rotterdam Elderly Study. *Hypertension* 1992;19:717-20.
5. Burke GL, Evans GW, Riley WA, et al. Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke* 1995;26:386-91.
6. Allan PL, Mowbray PI, Lee AJ, Fowkes FG. Relationship between carotid intima-media thickness and symptomatic and asymptomatic peripheral arterial disease: the Edinburgh Artery Study. *Stroke* 1997;28:348-53.
7. Blankenhorn DH, Selzer RH, Crawford DW, et al. Beneficial effects of colestipol-niacin therapy on the common carotid artery: two- and four-year reduction of intima-media thickness measured by ultrasound. *Circulation* 1993;88:20-8.
8. Furberg CD, Adams HP Jr, Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation* 1994;90:1679-87.
9. Hodis HN, Mack WJ, LaBree L, et al. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med* 1996;124:548-56.
10. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler Thromb* 1991;11:1245-9.
11. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation* 1997;96:1432-7.
12. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. *Am J Epidemiol* 1997;146:483-94.
13. Hodis HN, Mack WJ, LaBree L, et al. The role of carotid artery intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 1998;128:262-9.
14. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991;1:263-76.
15. Tell GS, Fried LP, Hermanson BH, Manolio TA, Newman AB, Borhani NO. Recruitment of adults 65 years and older as participants in the Cardiovascular Health Study. *Ann Epidemiol* 1993;3:358-66.
16. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study. *J Clin Epidemiol* 1992;45:683-92.
17. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499-502.
18. von Claus A. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. *Acta Haematol* 1957;17:237-46.
19. Gardin JM, Wong ND, Bommer W, et al. Echocardiographic design of a multicenter investigation of free-living elderly subjects: the Cardiovascular Health Study. *J Am Soc Echocardiogr* 1992;5:63-72.
20. Furberg CD, Manolio TA, Psaty BM, et al. Major electrocardiographic abnormalities in persons aged 65 years and older (the Cardiovascular Health Study). *Am J Cardiol* 1992;69:1329-35.
21. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS. Orthostatic hypotension in older adults: the Cardiovascular Health Study. *Hypertension* 1992;19:508-19.
22. Newman AB, Sutton-Tyrrell K, Vogt MT, Kuller LH. Morbidity and mortality in hypertensive adults with a low ankle/arm blood pressure index. *JAMA* 1993;270:487-9.
23. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. *Circulation* 1993;88:837-45.
24. Herbert V, Lau KS, Gottlieb CW, Bleicher SJ. Coated charcoal immunoassay of insulin. *J Clin Endocrinol Metab* 1965;25:1375-84.
25. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979;28:1039-57.
26. Mittlemark MB, Psaty BM, Rautaharju PM, et al. Prevalence of cardiovascular disease among older adults: the Cardiovascular Health Study. *Am J Epidemiol* 1993;137:311-7.
27. Price TR, Psaty B, O'Leary D, Burke G, Gardin J. Assessment of cerebrovascular disease in the Cardiovascular Health Study. *Ann Epidemiol* 1993;3:504-7.
28. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertain-

ment of cardiovascular events: the Cardiovascular Health Study. *Ann Epidemiol* 1995;5:278-85.

29. O'Leary DH, Polak JF, Wolfson SK Jr, et al. Use of sonography to evaluate carotid atherosclerosis in the elderly: the Cardiovascular Health Study. *Stroke* 1991;22:1155-63.
30. O'Leary DH, Polak JF, Kronmal RA, et al. Thickening of the carotid wall: a marker for atherosclerosis in the elderly? *Stroke* 1996;27:224-31.
31. SPSS for Windows, release 8.0. Chicago: SPSS, 1998.
32. Hofman A, Grobbee DE, de Jong PTVM, van den Ouweland EA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
33. Heiss G, Sharrett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. *Am J Epidemiol* 1991;134:250-6.
34. Kuller L, Borhani N, Furberg C, et al. Prevalence of subclinical atherosclerosis and cardiovascular disease and association with risk factors in the Cardiovascular Health Study. *Am J Epidemiol* 1994;139:1164-79.
35. Anderson KM, Wilson PWF, Odell PM, Kannel WB. An updated coronary risk profile: a statement for health professionals. *Circulation* 1991;83:356-62.
36. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke* 1991;22:312-8.
37. Stamler J, Wentworth DN, Neaton JD. Is the relationship between serum cholesterol and risk of death from coronary heart disease continuous and graded? Findings in 356,222 primary screenings of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986;256:2823-8.
38. Benfante R, Yano K, Hwang LJ, Curb JD, Kagan A, Ross W. Elevated serum cholesterol is a risk factor for both coronary heart disease and thromboembolic stroke in Hawaiian Japanese men: implications of shared risk. *Stroke* 1994;25:814-20.
39. Wilson PWF, Hoeg JM, D'Agostino RB, et al. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. *N Engl J Med* 1997;337:516-22.