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Relation of Carotid Intima-Media Thickness to Cardiovascular Events in Black Americans (From the Jackson Heart Study)

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Abstract

Although several prospective studies have reported independent relationships between carotid intima-media thickness (CIMT) and risk of incident cardiovascular diseases (CVD) among primarily non-African American (AA) cohorts, the utility of CIMT values for the prediction of incident coronary heart disease and stroke events in blacks remain unclear. At the baseline examination (2000–2004) of the Jackson Heart Study (JHS), AA adults 21–94 years of age (mean 54) underwent bilateral far-wall CIMT measurement (mean 0.76 mm). Incident CVD events were then assessed over 7–11 years of follow-up (2000–2011) from samples of 2,463 women (107 CVD events) and 1,338 men (64 CVD events) who were free of clinical CVD at baseline. Each 0.2 mm increase in CIMT was associated with age-adjusted incident CVD hazard ratios of 1.4 (95% confidence interval: 1.2, 1.5) for women and 1.3 (1.1, 1.6) for men. Classification accuracy improved only slightly when comparing multivariable models that used traditional risk factors alone versus models that added CIMT: C-statistics 0.837 (0.794, 0.881) versus 0.842 (0.798, 0.886) in women and 0.754 (0.683, 0.826) versus 0.763 (0.701, 0.825) in men. Similarly, risk-reclassification was only mildly improved by adding CIMT: Net Reclassification Index (NRI) 0.13 ($p = 0.05$) and 0.05 ($p = 0.50$) for women and men, respectively; Integrated Discrimination Improvement (IDI) 0.02 ($p = 0.02$) and 0.01 ($p = 0.26$) for women and men, respectively. In conclusion, CIMT was associated with incident CVD but provided modest incremental improvement in risk reclassification beyond traditional risk factors in a community-based AA cohort.

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Keywords

carotid intima-media thickness; cardiovascular disease; prognosis

Among African Americans, heart disease and stroke are the first and third leading causes of death, respectively, with atherosclerosis serving as the root cause of the majority of cardiovascular events.[1] Non-invasive ultrasound to measure atherosclerosis in the carotid arteries has been utilized as a measure of cardiovascular risk in clinical practice and large prospective studies.[2–7] However, the association between carotid atherosclerosis and incident cardiovascular diseases (CVD) has been derived from predominately white study populations.[8–15] Data on the risk reclassification of individuals using carotid intima-media thickness (CIMT) for incident CVD events (including both stroke and coronary heart disease) is limited, particularly among African Americans, with current prevention guidelines citing inconsistent relationships between CIMT and CVD events.[16] We assessed whether CIMT was associated with incident CVD events in African Americans using the population-based Jackson Heart Study (JHS).

METHODS

The Jackson Heart Study (JHS) is the largest single-site, epidemiological population-based study of African Americans and was designed to better understand the etiology of cardiovascular, renal and respiratory diseases among a community-based cohort of African Americans in Jackson, Mississippi. A total of 5,301 adults aged between 21 to 94 years were recruited between September 2000 and March 2004.[17] Of the 5,301 participants, 681 (12.8%) were excluded from the current analyses due to preexisting cardiovascular disease (410 with coronary heart disease, 161 with stroke, and 110 with both), 226 (4.3%) missing CIMT measures, 428 (8.1%) with missing other risk factor data, and 165 (3.1%) aged younger than 30 or older than 80 years (Supplementary Figure). Among the JHS cohort, 22% were also included in the Atherosclerosis Risk in Communities study.[17]

Traditional risk factors (TRFs) were prospectively collected, including age, gender, body mass index, current cigarette smoking status, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), medication use, and hypertension and diabetes status. The ascertainment of carotid intima-media thickness (CIMT) was performed according to the JHS protocol.[17] Briefly, an electrocardiography-gated, B-mode, and spectral steered Doppler with an integrated recorder ultrasound was used to obtain the carotid artery images using a 7.5 MHz linear-array transducer. CIMT was measured in millimeters and scan images were obtained bilaterally (right and left sides) for both carotid artery walls (far and near walls) at 3 segments of the carotid artery: common carotid artery (CCA), bifurcation of the carotid artery (BCA), and internal carotid artery (ICA). The scanned values of all segments (ICAs, BCAs or CCAs), angles (anterior, lateral or posterior), sides (right or left) and walls (far or near) of carotid artery were recorded. Mean CIMT was calculated as the average of far-wall values across both right and left sides at the CCA, BCA, and ICA segments, as measured at end-diastole (at the R wave) in gated still frames.

Adverse clinical events occurring between September 2000 and December 2011 were ascertained and validated, as previously described.[18] An incident CVD event was defined as a new myocardial infarction, stroke, or fatal coronary heart disease event. Crude CVD incident rates were calculated by quartiles of CIMT. Cox proportional-hazards regression models were used to estimate hazard ratio (HR) and associations of categorical and continuous CIMT values with incident CVD events for both the overall cohort and stratified by gender. Interactions between TRFs and CIMT were also investigated. Only significant TRFs were retained in the TRF-only models. For evaluating the added predictive ability of CIMT as a new marker, Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) methods were used.[19,20] The NRI reclassification table is to quantify correct movement in three risk categories (upwards for events and downwards for non-events by adding CIMT to the TRF-only models), and the IDI is for assessing improvement of sensitivity without sacrificing specificity. Overall, C-statistics were calibrated to 5-year survival probabilities from gender-specific TRF-only Cox models. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics of the 3,801 participants are presented in Table 1. Over a median follow-up duration of 9 years (>33,500 person-years), we identified 339 deaths (201 in women) and 171 new CVD cases (107 in women; 92 were new stroke cases). The crude mortality rate was 10.1 per 1,000 person-years and the crude incident rate for adverse CVD events was 5.1 (2.7 for incident stroke, and 2.7 for incident coronary heart disease). Participants in the highest CIMT quartile had the largest crude incident CVD rates for both men and women, 10.7 and 9.8, respectively; this association was supported in age-adjusted models for women (Table 2) as were associations of continuous CIMT (per 0.2 mm increase) for both men and women.

In the final models (TRF + CIMT as a continuous variable), age, LDL cholesterol and diabetes status were significant risk factors for men, whereas age, current smoking status, diabetes status and systolic blood pressure were for women. Adjusted for traditional risk factors, CIMT was independently associated with incident cardiovascular events (Table 3). Adding a term for interaction between age and gender did not result in significant effect in any of the models. The use of the common carotid artery IMT resulted in similar hazard rate ratios and C-statistics as the composite CIMT measure. Reclassifications for participants with and without new CV events are summarized in Table 4.

Reclassification improved slightly by adding CIMT to the TRF-only model with net gains for those 7 men (7.8%, NRI = 0.05, p = 0.50) and 16 women (11.2%, NRI = 0.13, p = 0.05) who suffered CVD events. The IDI were 0.01 (p = 0.26) for men, and 0.02 (p = 0.02) for women, respectively.

DISCUSSION

The role of CIMT for the prediction of CVD risk remains highly debated. There are no large-scale studies assessing the prognostic value of CIMT among African Americans.[13]

Within the current study, the largest to systematically assess the prognostic value of CIMT in an African American screening cohort, we demonstrated the following important observations. First, CIMT, defined herein as the mean of the far wall measurements of the common carotid, carotid bifurcation and internal carotid artery, was independently associated with incident CVD events in a predominately low-risk, middle-aged African American cohort without baseline CVD. Of note, when comparing common carotid IMT to more extensive measures of CIMT, there was no difference in results, similar to prior studies in non-African Americans. Secondly, the overall C-statistics, NRI and IDI indicated that CIMT modestly improved risk prediction of an incident CVD when added to TRFs in multivariable models in both men and women in the JHS population. The observed gender-related differences in risk reclassification are hypothesis generating and require further study.

The implications of these finding are numerous. First, the results serve as the largest prospective assessment of CIMT and risk prediction in an African American population. Among participants with significantly elevated CIMT, CVD risk is significantly increased, confirming similar findings in non-African populations. The results extend prior reports showing that CIMT may more precisely identify individual CVD risk and guide the application of preventive medications among lower-risk African Americans. However, similar to the results of the Multi-Ethnic Study of Atherosclerosis, CIMT only modestly improved risk reclassification as compared to age and TRFs, suggesting that CIMT may be a marker to predict a new CVD event, but that the majority of African American participants will not be reclassified using CIMT.[21] Specifically, we noted that the strongest risk factor for the development of incident CVD was that related to chronologic aging among the JHS African-American participants.

The current study is not without limitations. First, the study was performed within a single geographical area, which may limit generalizability. Additionally, while the follow-up period was relatively long compared to many prognostic studies, 9.0 years is shorter than the 10-year period for which the Framingham risk score is calculated; and this may decrease the overall power of our observations. Additionally, carotid plaque was not systemically assessed. Prior studies have shown that the inclusion of carotid plaque into CVD risk prediction models may significantly improve accuracy beyond measurement of CIMT alone. Finally, the impact of statins, anti-hypertensive and anti-platelet medications during the ascertainment period is unknown.

Despite these limitations, our study provides relatively large-scale evidence that black American participants with severely elevated CIMT have significantly increased risk for incident hard CVD events, extending prior studies performed in predominately white populations. While the proportion of individuals reclassified was relatively low, risk prediction in women was significantly improved with the addition of CIMT. Carotid IMT may be useful in identifying asymptomatic individuals at very high CVD risk in whom aggressive preventive therapies and therapeutic lifestyle changes should be applied.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics

Characteristics	All (N = 3,801)	Men (N = 1,338)	Women (N = 2,463)	p-value
Age (years) at baseline visit	54.2 ± 11.5	53.4 ± 11.5	54.6 ± 11.5	< 0.01
Education less than high school	561 (14.8%)	207 (15.5%)	354 (14.4%)	0.362
Body mass index (kg/cm^2)	31.7 ± 7.1	29.8 ±6.1	32.7 ± 7.4	< 0.01
Current smoking status	456 (12.0%)	227 (17.0%)	229 (9.3%)	< 0.01
Diastolic blood pressure (mm Hg)	79.4 ± 10.3	82.4 ± 10.4	77.7 ± 9.9	< 0.01
Systolic blood pressure (mm Hg)	126.2 ± 17.6	127.6 ± 17.2	125.5 ± 17.7	< 0.01
Total cholesterol (mg/dl)	200.4 ± 39.5	198.1 ± 39.4	201.6 ± 39.5	< 0.01
High density lipoprotein cholesterol (mg/dl)	52.3 ± 14.5	46.4 ± 12.5	55.5 ± 14.5	< 0.01
Low density lipoprotein cholesterol (mg/dl)	127.8 ± 36.6	130.1 ± 36.9	126.6 ± 36.4	< 0.01
Diabetes mellitus	643 (16.9%)	199 (14.9%)	444 (18.0%)	< 0.01
Hypertension	1,775 (46.7%)	606 (45.3%)	1,169 (47.5%)	0.200
Mean carotid intima media thickness (mm), far-wall	0.760 ± 0.210	0.792 ± 0.208	0.743 ± 0.208	< 0.01

Values in table are mean (± standard deviation) or N (%)

Table 2

Unadjusted and Age-Adjusted Hazard Ratios for Incident Cardiovascular Events by Gender According to Quartile of Mean Carotid Intima-Media Thickness

Men (N = 1,338)				Women (N = 2,463)			
Mean Carotid Intima Media Thickness (mm)	**Events / Persons at Risk**	**Unadjusted Hazard Ratio (95% Confidence Interval)**	**Age-Adjusted Hazard Ratio (95% Confidence Interval)**	**Mean Carotid Intima-Media Thickness (mm)**	**Events / Persons at Risk**	**Unadjusted Hazard Ratio (95% Confidence Interval)**	**Age-Adjusted Hazard Ratio (95% Confidence Interval)**
Quartile 1: 0.431 – 0.649	10/324	reference	reference	Quartile 1: 0.415 – 0.607	8/607	reference	reference
Quartile 2: 0.650 – 0.754	8/327	0.8 (0.3 – 2.0)	0.6 (0.2 – 1.6)	Quartile 2: 0.608 – 0.696	18/598	2.3 (1.0 – 5.3) *	1.5 (0.7 – 3.6)
Quartile 3: 0.755 – 0.879	16/319	1.7 (0.7 – 3.6)	1.0 (0.4 – 2.3)	Quartile 3: 0.697 – 0.819	29/587	3.7 (1.7 – 8.1) *	1.9 (0.9 – 4.3)
Quartile 4: 0.880 – 1.919	30/304	3.2 (1.6 – 6.5) *	1.5 (0.7 – 3.4)	Quartile 4: 0.820 – 2.749	52/564	6.8 (3.2 – 14.4) *	2.6 (1.2 – 5.7) *
p-value for trend		< 0.01	0.13	p-value for trend		< 0.01	< 0.01
Per 0.2 mm increase	N/A	1.5 (1.3 – 1.8) *	1.3 (1.1 – 1.6) *	Per 0.2 mm increase	N/A	1.6 (1.5 – 1.8) *	1.4 (1.2 – 1.5) *

* p<0.05

Table 3

Hazard Ratios and C-Statistics in Cox Proportional Hazards Models to Predict Incident Cardiovascular Events

Variables	Univariate Cox Model Hazard Ratios (95% CI)			Multivariate TRF + CIMT Cox Model Hazard Ratios (95% CI)		
	Men	Women	Overall	Men	Women	Overall
Carotid intima-media thickness (mm)	8.9 (4.0 – 19.9) *	10.6 (6.6 – 17.0) *	10.2 (6.7 – 15.4) *	4.3 (1.6 – 11.6) *	4.2 (2.3 – 7.7) *	3.6 (2.1 – 6.0) *
Age (years) at baseline visit	1.9 (1.5 – 2.3) *	2.3 (1.9 – 2.8) *	2.1 (1.8 – 2.4) *	1.5 (1.2 – 1.9) *	1.8 (1.4 – 2.3) *	1.7 (1.4 – 2.0) *
Body mass index (kg/m^2)	1.0 (0.8 – 1.2)	0.9 (0.8 – 1.1)	0.9 (0.8 – 1.0)			
Current smoking status (yes or no)	1.5 (0.8 – 2.7)	1.9 (1.1 – 3.2) *	1.7 (1.2 – 2.5) *		2.7 (1.6 – 4.6) *	2.1 (1.4 – 3.2) *
Diastolic blood pressure (mmHg)	0.9 (0.8 – 1.1)	1.0 (0.9 – 1.1)	1.0 (0.9 – 1.1)			
Systolic blood pressure (mmHg)	1.3 (1.1 – 1.4) *	1.4 (1.3 – 1.5) *	1.4 (1.3 – 1.5) *		1.2 (1.1 – 1.4) *	1.2 (1.1 – 1.3) *
Total cholesterol (mg/dL)	0.8 (0.7 – 1.0)	1.3 (1.2 – 1.5) *	1.1 (1.0 – 1.2)			
High density lipoprotein cholesterol (mg/dL)	1.1 (0.9 – 1.3)	1.0 (0.8 – 1.1)	1.0 (0.9 – 1.1)			
Low density lipoprotein cholesterol (mg/dL)	0.8 (0.7 – 1.0)	1.3 (1.1 – 1.5) *	1.1 (1.0 – 1.2)	0.8 (0.6 – 1.0)		
Diabetes status (yes or no)	3.1 (1.8 – 5.1) *	2.8 (1.9 – 4.1) *	2.8 (2.1 – 3.9) *	2.2 (1.3 – 3.7) *	1.9 (1.3 – 2.9) *	2.0 (1.5 – 2.8) *
Hypertension status (yes or no)	2.4 (1.4 – 4.1) *	2.3 (1.5 – 3.5) *	2.3 (1.7 – 3.2) *			

Variables	C-Statistics (95% CI) After calibrated with 5-year survival probabilities		
Carotid intima-media thickness (mm)	.650 (.557 – .743)	.723 (.657 – .789)	.697 (.643 – .751)
Age (years)	.728 (.639 – .817)	.758 (.701 – .814)	.746 (.697 – .795)
Significant traditional risk factors **	.754 (.683 – .826)	.837 (.794 – .881)	.802 (.762 – .841)
Final model=carotid intima-media thickness + significant traditional risk factors **	.763 (.701 – .825)	.842 (.798 – .886)	.805 (.768 – .843)

CIMT, carotid intima-media thickness; TRF, traditional risk factors;

* p-value < 0.05

** Significant traditional risk factors included in the Cox models for men = age, diabetes status and LDL cholesterol

Significant traditional risk factors included in the Cox models for women and for overall = age, diabetes status, current smoking status, and systolic blood pressure

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Table 4

Risk Reclassification Before and After Adding Carotid Intima-Media Thickness to Predict an Incident Cardiovascular Event

		Risk Categories* after adding Carotid Intima-Media Thickness			
Risk Categories* before adding Carotid Intima-Media Thickness		**Low Risk***	**Medium Risk***	**High Risk***	**Correctly Reclassified**
Men (N = 1,338)					
Participants with a cardiovascular event (n= 64)		***47 (73.4%)***	***13 (20.3%)***	***4 (6.3%)***	
Low Risk	49 (76.6%)	45 (91.8%)			
Medium Risk	14 (21.9%)		9 (64.3%)		
High Risk	1 (1.6%)			1 (100.0 %)	0 (0%) ---
Participants without a cardiovascular event		***1,178 (92.5%)***	***91 (7.1%)***	***5 (0.4 %)***	
Low Risk	1,186 (93.1%)	1,158 (97.6%)			
Medium Risk	85 (6.7%)		61 (71.8%)		
High Risk	3 (0.2%)			1 (33.3%)	
Women (N= 2,463)					
Participants with a cardiovascular event (n = 107)		***69 (64.5%)***	***28 (26.2%)***	***10 (9.3 %)***	
Low Risk	74 (69.2%)	66 (89.2%)			
Medium Risk	31(29.0%)		20 (64.5%)		
High Risk	2 (1.8%)			1 (50.0%)	
Participants without a cardiovascular event		***2,196 (93.2%)***	***137 (5.8%)***	***23 (1.0%)***	
Low Risk	2,186 (92.8%)	2,148 (98.3%)			
Medium Risk	153 (6.5%)		96 (62.7%)		
High Risk	17 (0.7%)				

*Risk reclassification categories – low risk (less than 6%), medium-risk (6% to 15%), and high-risk (greater than 15%)