Clinical Correlates of Carotid Artery Atherosclerosis in African Americans: Ethnic and Geographic Disparities

By

Meisam Moghbelli

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William Sollecito

Date

Adolfo Correa

Date
Abstract:

Objectives We evaluated whether carotid intima-media thickness (CIMT) and the presence or absence of plaque improved coronary heart disease (CHD) risk prediction when added to traditional risk factors.

Background Traditional cardiovascular disease (CVD) risk prediction schemes need further improvement as the majority of the CVD events occur in the intermediate risk groups. On an ultrasound scan, CIMT and presence of plaque are associated with CVD, and therefore could potentially help improve CHD risk prediction.

Methods Risk prediction models (overall, and in men and women) considered included traditional risk factors (TRF) only, TRF plus CIMT, TRF plus plaque, and TRF plus CIMT plus plaque presence. Predictivity was established by calculating the area under the curve (AUC). Cox proportional hazards models were used to estimate 10-year CHD risk for each risk model. Observed events were compared with expected events, and, the net reclassification index (NRI) was calculated.

Results Overall, the CIMT plus TRF plus plaque model provided the most improvement in AUC in the overall sample. Similarly, the CIMT plus TRF plus plaque model had the best net reclassification index of 9.9% in the overall population. However, comparison of TRF and CIMT and plaque with TRF and CIMT or TRF and plaque only resulted in statistically non-significant changes of the statistical test.

Conclusions Adding plaque and CIMT to TRF improve CHD risk prediction in the Jackson Heart Study (JHS). We hope that our study will shed further light on which patients to identify
for further risk factor modification and or medical treatment and further intervention to reduce
the burden of cardiovascular disease, and its overall impact in our population.
Introduction

Cardiovascular disease (CVD) is a major cause of death and disability in developed countries, and increasingly in the developing world as well. Although CVD mortality rates have declined over the past four decades in the United States, it remains responsible for about one third of all deaths in individuals over 35. (1,2) It has been estimated that one half of all middle aged men and one third of all middle aged women in the United States will develop some manifestation of CVD in their lifetime. (3)

The goal of our paper is to discuss cardiovascular disease prevalence, incidence, established environmental, biological, and demographic risk factors for the development of CVD, and to discuss an available imaging modality and appropriateness of using this modality for primary and secondary prevention of CVD. We will also briefly discuss mortality and temporal trends in this challenging disease that has become a large socioeconomic burden on developed, and now even developing countries.

Later, we will also discuss the use of an imaging modality, measurement of carotid IMT thickness, in a group of selected patients, and if the addition of this imaging data assisted clinicians in the risk prediction when added to traditional risk factor models.

Population based epidemiologic data, such as that from the Framingham Heart Study (8,9), provides the best assessment of the risk factors that contribute to the development of CVD, as well as the way it evolves, progresses, and causes major cardiovascular events. Epidemiologic data also provides critical information regarding targets for the primary and secondary prevention of CVD.

Cardiovascular disease currently accounts for nearly half of noncommunicable diseases, which have overtaken communicable diseases as the world’s major disease burden. CVD is
now the leading global cause of death, accounting for 17.3 million deaths per year, a number that is only expected to grow to over 24 million by 2030. (12)

Economists predict that the cost of not investing in CVD prevention and treatment could amount to as much as $47 trillion worldwide in the next 25 years. This loss is potentially avoidable, as the World Health Organization (WHO) prescribed interventions only cost $11-$13 billion annually (6). As almost 80% of cardiovascular deaths occur in developing countries, the economic consequences will be more severe as well. (figure 1)

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**Figure 1** Crude Data: Proportion of Deaths Due to CVD by Country Income Level CVD = cardiovascular disease. 

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Lawrence J. Laslett, Peter Alagona Jr., Bernard A. Clark III, Joseph P. Drozda Jr., Frances Saldivar, Sean R. W... 

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CVD is responsible for 10% of disability adjusted life years (DALY) in developing countries, and for 8% of DALY’s in developed countries (8). This economic loss is worse in developing countries where CVD affects a high proportion of working age adults (9).

Much of the information related to risk of cardiovascular events is developed from national survey data and from observational cohorts. The 2010 Heart Disease and Stroke Statistics update of the American Heart Association reported that 17.6 million people in the US have 10.2 million have coronary heart disease with increasing prevalence with age for both women and men (2). A 2009 report that used NHANES data showed that myocardial infarction prevalence was significantly greater in men than women between 1988 to 1994 and from 1999 to 2004. (9) However there were trends toward a decrease in men and an increase in women.

Databases like NHANES that rely on self reported CV events from health interviews probably underestimate the true burden of CVD. Silent ischemia, which accounts for up to 75% of all ischemic episodes (5) may only be brought to light on an exercise treadmill stress test or other clinical testing.

Data from 44 years of follow up in the original Framingham Study cohort and 20 years of surveillance of their offspring has allowed us to determine the incidence of initial coronary and vascular events (8-10).

In the United States, autopsy data have documented a reduced prevalence of CVD over time in both the general population and military personnel. A number of major CV risk factors declined between 1960 and 2000: percent of total population with total serum cholesterol greater than 240 declined from 34 percent to 17 percent, and hypertension, defined as systolic blood pressure of greater than 140 with diastolic of equal or greater than 90, decreased from
31 to 15 percent. Also, smoking as a proportion of the total population declined from 39 to 26 percent.

Many individuals in the general population have one or more risk factors for CVD, and over 90 percent of CV events occur in individuals with at least one risk factor. The absence of major risk factors predicts a much lower risk of CVD.

Atherosclerosis is responsible for almost all cases of CVD. This process begins with fatty streaks that are first seen in adolescence, which progress into plaques in adulthood, and culminate in thrombotic occlusions later in life.

A variety of factors are associated with an increased risk for atherosclerotic plaque, which have been well validated in both the Framingham and the NHANES cohorts. (Table 1)

Table 1:

<table>
<thead>
<tr>
<th><strong>Positive risk factors</strong></th>
<th><strong>Negative risk factors</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: male ≥ 45, female ≥ 55 or premature menopause without estrogen replacement therapy</td>
<td>HDL cholesterol ≥ 60 mg/dL (1.55 mmol/L)</td>
</tr>
<tr>
<td>Family history of premature coronary heart disease: definite myocardial infarction or sudden death before age 55 years in male first-degree relative and before age 65 in female first-degree relative</td>
<td><em>Confirmed by measurements on several occasions.</em></td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td><em>If the HDL cholesterol level is ≥ 60 mg/dL, subtract one risk factor.</em></td>
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Risk factor assessment is useful in adults to guide therapy and intervention for dyslipidemia, hypertension, diabetes, and other CV risks.

A precise estimate of the prevalence of CVD remains elusive, but the prevalence of identified risk factors has changed over time with increased awareness and changes in diet and lifestyle. A comparison of results from sequential NHANES surveys has shown the prevalence of obesity, defined as BMI greater than 30 kg/m2, increased dramatically in the United States from 15 to 30 percent between 1960 and 2000, with an associated increase in diagnosed diabetes, from 1.8 to 5.0 percent in the total population. In the obese population this change was most prominent (2.9 to 10.1 percent) (19)

These changes are associated with the increases in the use of lipid lowering pharmacologic agents and antihypertensive medications. Various socioeconomic factors, including where a person lives, his or her education, occupation, and income, or a combination of these, have been associated with an increased risk of CVD, and cardiovascular mortality. (21, 22)

**Imaging Techniques**

Over the past decades, significant efforts have been made to develop imaging techniques for atherosclerosis, with the hope that this imaging could serve as a surrogate for cardiovascular disease. Autopsy studies have indicated that atherosclerosis precedes the occurrence of clinical cardiovascular events. Therefore imaging to detect early atherosclerosis is potentially predictive of future cardiovascular events. It can also potentially be used to evaluate cardiovascular drug efficacy. One of the best-validated methods for atherosclerotic imaging is carotid intima media thickness (IMT) measurement. (8-11)
Carotid IMT can be measured in a variety of methods, including MRI and ultrasound, however there is a greater body of experience and data with ultrasound. (12)

Carotid arteries can be visualized at high resolution with B-mode ultrasound using linear array transducers for superficial and vascular structures with frequency ranges between 5 to 15 MHz. The resolution obtained is at 0.44mm laterally and 0.25mm laterally. IMT measurements can then be obtained from the near and far walls from the distal common carotid arteries, the carotid bifurcation, and the proximal internal carotid segments of both the right and left side. CIMT is therefore often a composite of intima media thickness measurements of various segments and angles. (13-15)

For CIMT measurements, longitudinal images of the carotid arteries are obtained in which the leading edges of the lumen-intima and media-adventitia interfaces of the arterial wall represent intima-media complex. Typically normal common carotid CIMT at age 10 is 0.4-0.5mm, while form the fifth decade of life this can progress to 0.8mm, or more. (16,17)

Since the arterial walls are sub millimeter structures, performing these measurements requires expertise and experience, and standardized image acquisition is paramount. Standardized ultrasound equipment and protocols need to be used. Image analysis should be done using standardized protocols.

The indications that have been mentioned for CIMT measurement include screening for atherosclerosis, risk stratification for future cardiovascular disease related events, and assessment of drug efficacy. (18-21)

Cardiovascular risk prediction in asymptomatic individuals is based on risk scores. Guidelines have based risk assessment on the use of multivariate risk models; their ability to predict future cardiovascular events has limitations. (3,4) A high percentage of CV events occur in patients
who are actually classified as low or intermediate risk. (5) CIMT has also been proposed as a potential tool to aid cardiovascular risk stratification as it compromises a direct measure of atherosclerosis that is associated with future cardiovascular events, and is a safe, inexpensive, and widely available technique (6).

In patients without a history of known cardiovascular disease (CVD), measurements of CIMT of various segments result in modest but statistically significant increases in net reclassification improvement when added to risk estimates based on traditional risk factors or risk models. (18-21).

Whether this improvement translates into measurable health benefits has not been established. Numerous prospective epidemiological studies have shown that CIMT is a predictor of future cardiovascular events independent of traditional risk factors. Two systemic reviews and meta analyses have reviewed both the one time and serial use of CIMT for CVD risk prediction (7,8).

In the ARIC study of 13,145 participants without known CVD mean IMT of all segments did show an improvement in reclassification of 7.1 percent in all subjects and 16.7 percent in subjects at intermediate risk. (9) The addition of presence of plaque (defined as maximum CMIT>1.5mm) to traditional risk factors increased the net reclassification improvement by 7.7 percent in all subjects and 17.7 percent in subjects at intermediate risk (9).

The 2010 American College of Cardiology /American Heart Association guidelines for the assessment of CVD in asymptomatic adults gives a level IIa recommendation for utilizing CIMT in cardiovascular risk evaluation in intermediate risk patients (5). No further recommendations were made regarding the use of CIMT in low risk patients, high-risk patients, or those with established CVD.

CIMT has also frequently been utilized in clinical trials to test the efficacy of cardiovascular drugs. While CIMT has been used as a surrogate end point to monitor the effects of therapy in
clinical trials, modification of therapy based on CIMT results has not been shown to alter clinical endpoints.

**Jackson Heart Study**

Ethnic and geographic disparities in cardiovascular disease (CVD) mortality, morbidity and risk factors are well documented. One intersection of ethnic and geographic disparities occurs in Mississippi, where in 2002, African Americans had age-adjusted CVD mortality rates 38% (women) and 88% (men) greater than the national average (7). The Jackson Heart Study (JHS), a community based, observational study of African Americans living in the Jackson, Mississippi statistical metropolitan area, provides an opportunity to study the natural history of CVD in this especially vulnerable population.

The JHS is a large, community-based, observational study whose participants were recruited from urban and rural areas of the three counties from the state of Mississippi (Hinds, Madison and Rankin) that make up the Jackson Miss, metropolitan statistical area (MSA). Participants were enrolled from each of 4 recruitment pools: random, 17%; volunteer, 22%; currently enrolled in the Atherosclerosis Risk in Communities (ARIC) Study, 30% and secondary family members, 31%. Institutional Review Board (IRB) for the Jackson heart Study has been obtained and is currently on file at Jackson State University, and the University of North Carolina IRB approval was deemed to be unnecessary by expedited IRB review.

Ethnic differences in subclinical disease burden have also been documented, although these patterns are not always congruent with disparities in CVD mortality, morbidity and risk factors noted above. In the Cardiovascular Health Study (8), for example, African American women had a higher prevalence of clinical cardiovascular disease than white women even though the prevalence of a composite measure of subclinical disease was similar in these two groups.
Ethnic differences were apparent, however, among the individual components of the composite subclinical disease measure: African Americans had significantly lower ankle/brachial blood pressures, significantly greater common carotid artery wall thickness and a higher prevalence of major ECG abnormalities, while white participants had a much higher prevalence of carotid artery stenosis. The JHS provides a unique opportunity to better understand the relationship between important CVD risk factors, the development of subclinical atherosclerosis, and the manifestation of clinical cardiovascular disease events in an ethnic minority population.

One widely recognized measure of subclinical atherosclerosis collected during the baseline JHS examination is carotid artery intimal-medial thickness (IMT). Previous studies have consistently shown that CIMT is correlated with traditional CVD risk factors (9, 10, 11) and with both prevalent CVD (19) and incident CVD (13, 19). Importantly, however, although the relationships with prevalent and incident CVD were demonstrated in ethnically diverse cohorts and included statistical adjustment for ethnicity, none of these studies have focused specifically on these relationships in an ethnic minority.

**Methods**

Recruitment was limited to non-institutionalized adult African Americans 35-84 years old, except in the family cohort where those 21 to 34 years of age were eligible. The final cohort of 5,301 participants includes 6.59% of all African American Jackson MSA residents aged 35-84 (N=76,426, US Census 2000). Major components of each exam include medical history, physical examination, blood/urine analyses and interview questions on areas such as: physical activity; stress, coping and spirituality; racism and discrimination; socioeconomic position; and access to health care. At 12-month intervals after the baseline clinic visit (Exam 1), participants are contacted by telephone to: update information; confirm vital statistics; document interim medical
events, hospitalizations, and functional status; and obtain additional sociocultural information. Questions about medical events, symptoms of cardiovascular disease and functional status are repeated annually. Ongoing cohort surveillance includes abstraction of medical records and death certificates for relevant International Classification of Diseases (ICD) codes and adjudication of nonfatal events and deaths.

We describe the relationships between the three major carotid ultrasound outcomes available in JHS: average IMT across the common carotid, bifurcation and internal carotid arteries, average common carotid artery IMT, and presence of carotid plaque, and to describe the relationships of each ultrasound outcome to demographic factors including age, gender and SES and also to clinical parameters with established relationships to CVD events. The specific clinical correlates examined include parameters related to the domains of blood pressure, diabetes, lipid metabolism, obesity, smoking history and renal function.

We excluded individual with prior cardiovascular events, or with missing CVD data, missing C-IMT data, missing information on traditional risk factors for CVD, which provided us with our sample size of 13,741 individuals for the analysis.

The ultrasound procedure, in brief, consists of a GE 3000DISA system and images were recorded and stored on hard drive for archiving purposes. The C-IMT was assessed in three segments, average IMT across the common carotid, bifurcation and internal carotid arteries. At each of the segments, 11 measurements of the far wall were attempted, in 1 mm increments. The mean of the measurements across these segments of both right and left sides was calculated. Trained readers adjudicated plaque presence or absence when 2 of the 3 following criteria were met: abnormal wall thickness defined as C-
IMT>1.5mm, abnormal plaque shape with protrusion into the lumen, or loss of alignment with adjacent arterial wall boundary, and abnormal wall texture defined as brighter echoes than adjacent boundaries. An average common carotid artery IMT, and presence or absence of carotid plaque also noted on data collection sheets. For the presence or absence of plaque, intra-reader agreement was associated with a Cohen’s kappa coefficient statistic of 0.79 (which measures degree of agreement on a scale of 0 to 1), while the intra-reader agreement was 0.61, which suggests agreement of readers beyond chance. (35)

Incident CVD events included definite or probable myocardial infarction (MI), silent MI between exam 1 and 2 as indicated by electrocardiograms, definite CVD death, or a clinical need for revascularization procedure.

Interviews with next of kin and questionnaires completed by physicians and medical examiners or coroners were used to collect information on deaths, and review and abstraction of hospital records were used to collect information on possible fatal and nonfatal myocardial infarctions (MIs). Events were classified using standardized criteria. (15)

The analyses were then performed in the entire study sample, and then by gender, age, systolic blood pressure, antihypertensive medication use, total cholesterol, high-density lipoprotein cholesterol (HDL-C), diabetes, and smoking status.

Statistical analysis was performed using IMB SPSS Statistics software. Using Cox-proportional hazards, the 10 year CVD risk for each of the models was calculated, and individuals classified into 0-5% (low risk), 5-10% (low to intermediate risk), 10-20% (intermediate to high risk), and greater than 20% (high risk). Then we found a number of individuals who changed risk groups. We then estimated the integrated discrimination improvement, which is the difference in an R squared like statistic between the traditional models. (32-34) We then calculated the net
reclassification index (NRI), which examines the net effect of adding a marker to the risk prediction scheme using statistical calculations. NRI and IDI were then calculated for the follow up period and confidence intervals were established. (Table 2)

**Results**

The 25th and 75th percentile C-IMT of our total population were 0.66mm and 0.93mm for men and 0.61 and 0.9 mm in women, respectively. Atherosclerotic plaque presence increased from 14.6% in the overall study population with a C-IMT<25th percentile to 26.9% in those with a C-IMT between 25-75th percentile, to 67.3% in those with a C-IMT>75th percentile. When divided by risk groups, plaque prevalence increased from 23% in the 0-5% risk group, to 35.7% in the 5-10% risk group, to 48.9% in the 10-20% risk group, to 56.4% in the >20% risk group.

Over a mean follow up period of 10.1 years, there were 1803 cardiovascular events. Using statistical analysis utilizing adjusted area under the curve, we determined the CVD incidence rate per 1,000 person years in the various C-IMT categories taking into account the absence, or presence, of plaque as described above. In all risk categories, the presence of plaque was associated with a higher incidence of CV events.
Discussion

CVD risk prediction models based on traditional risk factors noted in table 1 have formed the basis for the clinical practice of CVD prevention, however they remain far from optimal. Several authors have looked at adding biomarkers to improve cardiovascular risk prediction, and others have even examined utilizing genetic markers. (35) Imaging tests such as carotid Doppler ultrasound, and coronary calcium scoring offer other options that could be used in improving CVD risk prediction, though there is limited data using statistical methodology that have evaluated whether the addition of imaging studies to risk models can improve CVD risk prediction. Here we show that in the study population, C-IMT to measure the presence and thickness of plaque can improve CVD risk prediction, especially in specific groups of patients. Plaque presence seemed to have a more profound effect in improving risk prediction if women than men for unclear reasons. Current guidelines suggest that individuals with a 0-10% predicted 10 year risk are considered low in risk, however evidence has shown even in this group there appears to be spectrum of risk, therefore 5-20% 10 year estimated risk should be considered the intermediate risk group. This was the reason we divided our low risk group into 0-5% and 5-10% estimated risk groups, and it was in this group that our results showed statistical significance.

Conclusions

In summary, our data suggests that adding CIMT and plaque information improves CVD risk prediction, and as with other markers, the addition of C-IMT and plaque information appears to be most valuable in the intermediate risk groups, particularly in the 5-10% and 10-20%
estimated risk group. The overall improvement in risk prediction appears to be equivalent to other contemporary markers.

In our analyses we show that the mere presence of plaque without any quantification helped improve CVD risk prediction.

In the future, improved imaging technology may enable us to reliably quantify plaque volume, which will likely only further improve our ability to risk stratify CVD.

The strengths of the study include the use of contemporary statistical methodology, the long follow up of our subjects, and the number of incident CVD events accrued over the time period. The study did face limitations as well, as we have not accounted for changes in the risk factors over the time period in the analysis, or changes in the medications used during the time period. However this is similar to any other risk prediction model that has been described. We also did not account for the potential difference between plaque presence in one versus multiple arterial beds. Several individuals had missing C-IMT data, and we cannot determine how that dataset would have impacted the results. Also of clinical importance, there is no reliable clinical data that shows whether treating individuals by this strategy based on the identification of higher risk will prevent incident cardiovascular events though this would be an expected result.

Cardiovascular prevention efforts are receiving growing attention in an effort to offset the increasing burden of CVD, as well as to stem rising healthcare costs by developing strategies to modify risk factors associated with CVD.

The debate still continues regarding which approach has the greatest impact on reducing CVD morbidity and mortality: better control of CVD risk factors, or the use of medical interventions (36).
We hope that our study will shed further light on this topic by identifying patients that would benefit from further risk stratification and/or treatment. However, further research needs to be done to better determine indeed what patients would further benefit from risk stratification, in order to equitably distribute use of limited resources.

Disclaimer: statistics support provided by A. Alexander.
<table>
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<th>Model</th>
<th>Overall</th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>TRF vs. TRF+CIMT (95% CI)</td>
<td>NRI (%)</td>
<td>Clinical NRI (%)</td>
<td>NRI (%)</td>
</tr>
<tr>
<td></td>
<td>7.1 (2.2, 10.6)</td>
<td>16.7 (9.3, 22.4)</td>
<td>8.9 (3.4, 15.1)</td>
</tr>
<tr>
<td>TRF vs. TRF+plaque (95% CI)</td>
<td>7.7 (2.3, 11.4)</td>
<td>17.7 (10.9, 24.7)</td>
<td>4.2 (0.2, 12.2)</td>
</tr>
<tr>
<td>TRF vs. TRF+CIMT+plaque (95% CI)</td>
<td>9.9 (3.8, 13.5)</td>
<td>21.7 (13.4, 28.2)</td>
<td>8.9 (4.1, 17.1)</td>
</tr>
<tr>
<td>TRF+CIMT vs. TRF+CIMT+plaque (95% CI)</td>
<td>2.8 (−1.2, 6.4)</td>
<td>10.6 (3.8, 16.5)</td>
<td>0.03 (−2.6, 6.3)</td>
</tr>
<tr>
<td>TRF+plaque vs. TRF+CIMT+plaque (95% CI)</td>
<td>2.1 (−1.1, 5.3)</td>
<td>7.9 (2.6, 13.3)</td>
<td>4.8 (−0, 10)</td>
</tr>
</tbody>
</table>

Table 2: Net Reclassification Index using various comparison models in the overall sample
References


*intima-media thickness to assess progression and regression of atherosclerosis.*


