

Relationship Between Coronary Artery Calcification and Other Measures of Subclinical Cardiovascular Disease in Older Adults

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Background—In the Cardiovascular Health Study, subclinical cardiovascular disease (CVD) predicted CVD events in older adults. The extent to which this measure or its components reflect calcified coronary disease is unknown.

Methods and Results—Coronary artery calcium (CAC) was assessed with electron beam tomography in 414 participants without clinical CVD and examined using cut points ($CAC \geq 400$ and $CAC \geq 800$) and the $\log(CAC)$; 274 had subclinical CVD by ankle-arm index, ECG, or carotid ultrasound. Cut points for subclinical disease as previously defined in the Cardiovascular Health Study were examined as well as continuous measures to produce receiver operating characteristic curve curves. A low ankle-arm index was highly specific for a high CAC score. The internal carotid artery intima-media thickness was most strongly correlated with CAC ($r=0.30$) and was significantly related to both CAC cut points and to the $\log(CAC)$ score independently of all other measures.

Conclusions—In these community-dwelling older adults without clinical CVD, internal carotid artery intima-media thickness was most closely related to CAC. However, 17.5% of those with a $CAC \geq 400$ would be missed in the ascertainment of subclinical atherosclerosis using the previously published composite of subclinical atherosclerosis. Prospective follow-up will determine whether the CAC score improves prediction of CVD events over other noninvasive measures. (*Arterioscler Thromb Vasc Biol.* 2002;22:1674-1679.)

Key Words: coronary artery calcification ■ ultrafast CT scan ■ carotid wall thickness
■ subclinical cardiovascular disease ■ ankle-arm index

Coronary artery calcium (CAC) assessed by electron beam tomography (EBT) is a measure of calcified atherosclerotic plaque and correlates with the extent of underlying atherosclerosis. Although the relationship between angiographically defined coronary stenoses and EBT-detected calcified lesions is imprecise, higher CAC scores are associated with a greater likelihood of obstructive coronary disease. A total score of >400 has been shown to be a sensitive cut point for flow abnormalities on exercise stress myocardial perfusion computerized tomography (SPECT) scanning,¹ and a highly specific cut point for at least one coronary artery with a $\geq 70\%$ stenosis on angiography.² Although the early results from middle-aged, high-risk adults suggest that higher CAC scores predict cardiovascular disease (CVD) events,³⁻⁶ the utility of CAC scanning in asymptomatic elderly people is unknown.⁷

Ongoing epidemiological studies of cardiovascular risk have shown that several other measures of the extent of vascular disease, such as carotid wall thickness,^{8,9} ankle-arm

index (AAI),¹⁰ and electrocardiographic abnormalities¹¹⁻¹⁴ are independent predictors of CVD outcomes. Few studies have noninvasive measures in all of these vascular beds in comparison with CAC in an asymptomatic population of older adults. In the Rotterdam Coronary Calcification Study, several measures (common carotid artery wall thickness, carotid plaque, AAI, and aortic calcification) were found to be significantly associated with CAC.¹⁵ Two other recent studies discuss correlations between carotid disease and CAC. Davis et al¹⁶ found that those with any CAC had a higher mean maximal intima-media wall thickness measured at 12 carotid artery locations (near and far wall measurements of the internal carotid, common carotid, and carotid bifurcations) in young men and women. In symptomatic men aged 50 to 75 years of age, Arad et al¹⁷ found correlations between CAC and carotid artery calcium and between coronary stenosis and carotid intima-media thickness (IMT). The relative merits of noninvasive measures and traditional risk factors will ultimately need to be evaluated in relationship to

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CVD outcomes. However, cross-sectional comparisons of noninvasive measures of disease can help to determine the extent to which these measures might overlap in predicting future events. We have shown that there is a wide range of scores in a subset of older adults in Cardiovascular Health Study (CHS) with no evidence of either clinical or other subclinical disease by previous criteria.¹⁸ In this report, we describe the extent to which these previous measures of subclinical disease were associated with high levels of CAC in a cohort of community-dwelling older adults with no previous history of clinical CVD.

Methods

CHS is an ongoing cohort study established in 1989 to determine the relationship of cardiovascular risk factors to incident CVD in older adults.^{19,20} Between May 1998 and June 2000, 614 (84%) of 727 participants seen in Pittsburgh, Pennsylvania at the final examination underwent EBT scanning.^{21,22} Nonparticipants were too ill or could not travel (61%), had died after the last clinic visit (16%), or refused (23%). All gave informed consent for the protocol, which was approved by the Institutional Review Board of the University of Pittsburgh.

CAC

CAC was assessed using an Imatron C-150 scanner using the Agatston scoring method²³ as previously described.¹⁸ For this analysis, a CAC score cut point of 400 was chosen because it has been shown to be associated with angiographic obstruction with at least one significant stenosis² and flow abnormalities by SPECT.¹ The cut point of 800 was also examined as an approximation of the 80th percentile in our study population for those without clinical CVD. Because the carotid wall thickness criteria was based on the 80th percentile, this allowed a more direct comparison between these two measures.

Demographic and Cardiovascular Risk Factors

Age was assessed at the time of the EBT scan (1998 to 2000), and cardiovascular risk factor data from the 1998 to 1999 clinic visit were used. Because past levels of risk factors may have contributed to calcium deposition over time, additional analyses using 1992 to 1993 clinic visit data were performed, but relationships (or lack of relationships) between risk factors and CAC score did not change. Systolic and diastolic blood pressures were measured according to a standard protocol. Hypertension was defined as systolic blood pressure >160 mm Hg or seated blood pressure average diastolic >95 mm Hg or self-reported hypertension and use of antihypertensive medication. Diabetes was defined as present if the participant used insulin or oral hypoglycemics or if glucose level exceeded 126 mg/dL (7.0 mmol/L). Cigarette smoking was reported as ever (past and current use) versus never because there were few current smokers; total smoking exposure also was assessed by pack-years.²⁴ All blood was collected and analyzed at the time of baseline examination according to laboratory methods previously described.²⁵

Definitions of Clinical and Other Subclinical CVD

This analysis focuses on the 414 participants without prevalent clinical CVD as ascertained at the time of the EBT scan using adjudicated baseline and events data. Prevalent clinical CVD included those who had coronary artery bypass surgery or percutaneous transluminal angioplasty, history of myocardial infarction, treated angina, congestive heart failure, stroke or transient ischemic attack, carotid surgery, peripheral vascular bypass surgery, angioplasty, or physician-diagnosed intermittent claudication. Baseline self-reporting was validated by medical records.²⁶ Events occurring after baseline were evaluated every 6 months²⁷ through phone call or clinic visit, followed by review of medical records and informant interview and adjudicated by committee. We previously reported clinical CVD prevalence in 205 of the 614 participants using baseline

adjudicated data and adjudicated follow-up data through 1996 to 1997, approximately 2 years before the scan. Updating this to include more recent adjudications through the time of the scan, we now report clinical CVD in 215 participants.

In those patients with no history of clinically diagnosed CVD events, subclinical CVD status was assessed in 1998 to 1999. Subclinical disease was defined as an AAI <0.90, internal carotid or common carotid intima-media wall thickness (ICA IMT and CCA IMT, respectively) greater than the CHS population 80th percentile (ICA IMT \geq 1.81 mm, and CCA IMT \geq 1.18 mm), carotid stenosis >25%, and major ECG abnormalities. Also included were those patients with a positive Rose questionnaire for angina or intermittent claudication.²⁸ The 80th percentile cut points used in this analysis were established from 1992 to 1993 data, and they were retained because they were shown to be predictive of clinical CVD events.⁸ Of the 414 participants used in this analysis, all three measures of carotid disease were available for 378 participants, AAI data were available for 390 participants, and ECG data were available for 394 participants. The relationship of each carotid measure to coronary calcium was examined first, then a composite variable for carotid disease was defined as an ICA IMT or CCA IMT greater than the 1992 to 1993 80th percentile value or carotid stenosis greater than 25%. Major ECG abnormalities included ventricular conduction defects, left ventricular hypertrophy, first-degree atrio-ventricular block, or atrial fibrillation, ST-T abnormalities, or major Q-wave abnormalities.²⁹ Echocardiographic abnormalities were not measured concurrently with the other measures.

Statistical Analysis

The sensitivity and specificity of subclinical disease measures to detect a high CAC score was obtained from separate 2 \times 2 tables in the 414 without clinical CVD. Receiver operating characteristic curve (ROC) analyses were used to assess whether one subclinical disease measure (ICA IMT, CCA IMT, AAI, ECG abnormality) was a better balance of sensitivity and specificity than another in predicting a high CAC score. Both the continuous and categorical forms of these other subclinical measures were used to produce a number relating to the area under a curve by plotting sensitivity against 1-specificity rates. The resultant area can range from 0 to 100%, with higher rates indicating higher rates of true-positive results with minimal false-positive results (the balance of sensitivity and specificity). Logistic regression was used to determine the association between other subclinical measures and a high CAC (defined using cut points of 400 then 800). The log of the calcium score was used in linear regression models assessing the association between the calcium score and the continuous measures of carotid wall thickness and AAI adjusting for other CVD risk factors selected resulting from univariate associations with CAC scores in this population in previous analyses^{21,22} (age at scan, gender, race, body mass index, diabetes, smoking history and pack-years, cholesterol, hypertension). Gender and race interactions were tested with each of the other subclinical disease measures, but no significant interactions were found. Separate models were designed using each individual measure of other subclinical disease to predict either a high CAC score (cut point of 400 or 800) or the log of the CAC score. Final models included gender, age at scan, and race along with stepwise selection of CVD risk factors. Significance was defined by a $P < 0.05$.

Results

The participants in this study had no history of clinical CVD at the time of the EBT scan ($n = 414$). They were of mean age 79.9 years (range 70 to 97 years), similar in men and women. CAC scores ranged from 0 to 4151, and the median was higher in men (386.5) than in women (165.6). Men were more likely to have major ECG abnormalities and men had a higher mean CCA IMT. Results of ECG, AAI, and carotid ultrasound assessment indicated the presence of other subclinical

TABLE 1. Prevalence of Subclinical Atherosclerosis by Various Measures in Those Without Clinical CVD, The CHS Study of Arterial Calcification in the Elderly

	CAC Score Cut Points						P
	Overall N=414	CAC=0 n=46 (11%)	CAC 1–99 n=106 (25.6%)	CAC 100–399 n=106 (25.6%)	CAC 401–800 n=75 (18.1%)	CAC ≥800 n=81 (19.6%)	
Men, n (%)	150 (36.2)	11 (23.9)	33 (31.1)	33 (31.1)	31 (41.3)	42 (51.6)	0.005
Age at scan, mean±SD, y	79.9±4.0	78.1±3.1	79.6±4.0	79.6±4.0	79.9±3.9	81.7±3.7	
Other subclinical disease measures							
Cut points for measures, n (%) with							
Low AAI, n=390	7 (18.2)	2 (4.6)	16 (15.5)	23 (22.8)	19 (27.5)	11 (15.1)	0.018
Major ECG abnormalities, n=394	142 (36.0)	14 (31.8)	37 (35.9)	29 (29.0)	27 (37.5)	35 (46.7)	0.183
Carotid artery stenosis>25%, n=378	101 (26.7)	3 (7.7)	15 (15.0)	28 (28.3)	25 (35.2)	30 (43.5)	<0.0001
ICA>80th percentile (>1.81 mm), n=380	118 (31.1)	1 (2.6)	19 (18.8)	32 (32.3)	36 (50.0)	30 (43.5)	<0.0001
CCA>80th percentile (>1.18 mm), n=383	96 (25.1)	7 (18.0)	21 (20.6)	24 (24.0)	25 (34.7)	19 (27.1)	0.204
Presence of any of above, n=386	274 (71.0)	22 (53.7)	63 (61.8)	71 (71.0)	58 (82.9)	60 (82.2)	0.0006
Continuous measures, mean±SD							
ICA IMT, mm	1.61±0.86	1.13±0.34	1.42±0.83	1.60±0.77	1.90±0.92	1.90±0.98	<0.0001
CCA IMT, mm	1.09±0.23	1.04±0.21	1.04±0.17	1.09±0.21	1.14±0.26	1.13±0.29	0.023

atherosclerosis by these measures alone in 274 of 414 participants with CAC measures (Table 1).

Using the cut point measures to define a high CAC, the sensitivity, specificity, and positive predictive values of these other measures of subclinical disease was calculated, and multivariate models were constructed to assess the areas under ROC curves (Table 2). The composite measure of carotid disease was more sensitive than any one carotid disease measure (61.2% for a CAC≥400 and 55.9% for a CAC≥800). Each of the carotid wall thickness measures and the AAI were highly specific but not sensitive. Specificity for the AAI was 83.5% for CAC≥400 and 81.1% for CAC≥800, but sensitivity was 21.1% for CAC≥400 and 15.1% for CAC≥800. The presence of major ECG abnormalities was intermediate, being neither sensitive nor specific. The combination measure of atherosclerosis, defined as abnormal in any of these other subclinical measures, was the most sensitive but least

specific: 82.5% and 82.2% sensitivity, respectively, for CAC≥400 and CAC≥800 and 35.8% and 31.6% specificity, respectively for the cut points. The positive-predictive value (PPV) of each measure illustrates that about half of those found to have subclinical atherosclerosis by these other measures have a CAC score≥400. Multivariate logistic regression models using the cut point form of these other measures of subclinical atherosclerosis and adjusting for age, gender, race, pack-years of smoking, cholesterol, and hypertension produced ROC analyses showing that the areas under the curve (AUC) for each model were quite uniform for these measures (all between 0.70 and 0.78). Age, male gender, white race, and pack-years of smoking were all independent predictors of a high CAC (either cut point). ICA IMT also was independently predictive of a CAC≥400, resulting in significant associations between a high CAC and both the composite carotid and overall composite disease measure. Only carotid stenosis >25%

TABLE 2. Sensitivity and Specificity of Subclinical CVD Measures in Those Without Clinical CVD to Detect Coronary Calcium, the CHS Arterial Calcification in the Elderly study, N=414

Subclinical CVD Measure	CAC≥400 N=156				CAC≥800 (N=81)			
	Sensitivity	Specificity	PPV	AUC	Sensitivity	Specificity	PPV	AUC
ICA IMT>80th percentile, n=118	46.8	78.2	55.9	0.74*	43.5	71.7	25.4	0.77
CCA IMT>80th percentile, n=96	31.0	78.4	45.8	0.70	27.4	75.4	19.8	0.75
Carotid stenosis>25%, n=101	39.3	80.7	54.5	0.72*	43.5	77.0	29.7	0.77*
Any carotid disease, n=182	61.2	59.4	46.7	0.73*	55.9	53.6	20.9	0.77
AAI<0.9, n=71	21.1	83.5	42.3	0.71	15.1	81.1	15.5	0.77
Major ECG abnormality, n=142	42.2	67.6	43.7	0.71	46.7	66.5	24.7	0.77
Low AAI, major ECG abnormality, or either carotid IMT>80th percentile, n=274	82.5	35.8	43.1	0.73*	82.2	31.6	21.9	0.76

Age, gender, race, and smoking independently predictive of CAC level in each model shown.

*Indicates measure is independently predictive of CAC level at $P<0.01$ level.

TABLE 3. Logistic Regression Models Using Carotid and AAI Measures in Continuous Form for Those Without Clinical CVD, the CHS Arterial Calcification in the Elderly Study, N=414

	CAC \geq 400 (N=156)				CAC \geq 800 (N=81)			
	OR	95% CI	P	AUC	OR	95% CI	P	AUC
ICA IMT	1.63	1.22–2.17	0.001	0.73	1.15	0.82–1.62	0.419	0.76
CCA IMT	2.89	1.02–8.19	0.046	0.71	1.22	0.34–4.39	0.764	0.75
AAI	0.63	0.18–2.26	0.481	0.71	6.76	1.22–37.3	0.029	0.77
All three measures in model								
ICA IMT	1.63	1.16–2.21	0.005	0.74	1.30	0.89–1.91	0.18	0.78
CCA IMT	1.18	0.36–3.88	0.783		1.26	0.27–5.82	0.77	
AAI	0.94	0.23–3.80	0.925		10.19	1.64–63.34	0.013	

was also associated independently with a CAC \geq 800 (in addition to age, gender, race, and smoking).

We then used the continuous form of the carotid artery and AAI data to repeat the steps done for the cut point analyses. Each carotid artery wall thickness measure, but not the AAI, was independently related to a CAC score of \geq 400 (ICA IMT odds ratio (OR)=1.625, 95% confidence interval (CI) 1.22 to 2.17, $P=0.0011$; CCA IMT OR=2.89, 95% CI 1.02 to 8.19, $P=0.046$; Table 3). The AUC for these measures was found to be 0.73 and 0.71 for the ICA IMT and CCA IMT, respectively. The AAI was significantly predictive of a CAC score \geq 800 (AAI OR=6.76, 95% CI 1.22 to 37.3, $P=0.029$) with an AUC of 0.77. When all subclinical disease markers were examined simultaneously, only the ICA IMT was independently predictive of a CAC \geq 400 (OR=1.60, 95% CI 1.16 to 2.21, $P=0.0047$) and only the AAI was significantly related to a CAC \geq 800 (OR=10.19, 95% CI 1.64 to 63.34, $P=0.0128$).

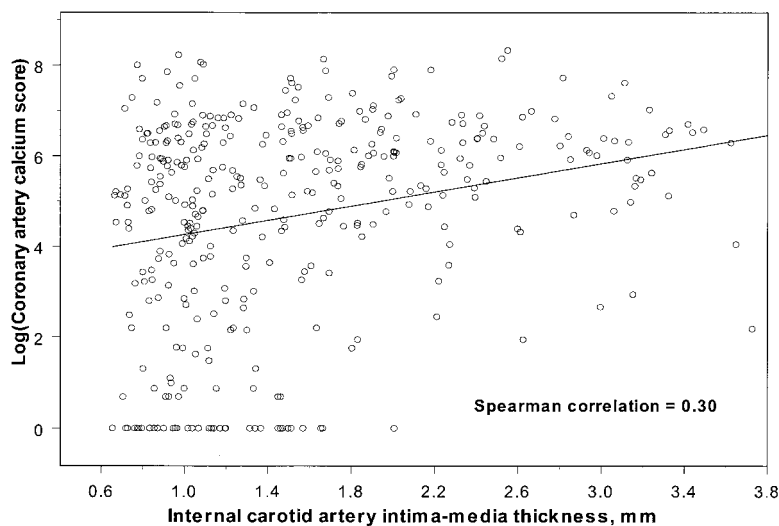
Each of the carotid measures were positively correlated with the continuous form of the CAC score with the ICA having the strongest correlation (Spearman correlations for ICA IMT and CAC: $r=0.30$, $P<0.0001$; CCA IMT and CAC: $r=0.12$, $P<0.02$; carotid stenosis $>25\%$: $r=0.27$, $P<0.0001$). The high CAC scores across the continuum of ICA IMT are shown in Figure 1, and this pattern was seen in each of the carotid measures as well as the AAI. Of note, no

participant with an ICA IMT >1.8 mm had a CAC score of 0. The AAI and CAC were modestly and inversely correlated ($r=-0.10$, $P=0.059$). Smoking exposure (pack-years) was also significantly correlated with the CAC score ($r=0.19$, $P=0.0001$). Additionally, these measures were significantly correlated with each other.

The AAI, ICA IMT, and CCA IMT were entered as continuous variables in separate linear regression models to examine the strength of relationships between each measure and the log(CAC score), adjusting for other CVD risk factors (Table 4). In models containing only one of the subclinical disease measures (AAI, ICA IMT, or CCA IMT measures), each measure, along with age at scan, male gender, white race, and pack years of smoking was independently predictive of the log(CAC score). In a model containing all three measures, the ICA IMT ($\beta=0.55$, $P=0.0002$) and the AAI ($\beta=-1.28$, $P=0.047$) continued to be independently predictive of the log(CAC score) in addition to pack-years of smoking ($\beta=0.0118$, $P=0.039$), male gender ($\beta=1.17$, $P<0.0001$), and white race ($\beta=1.36$, $P<0.0001$).

Discussion

This study has found that 38% of older adults without any history of clinical CVD can have extensive CAC (score \geq 400) and that previous measures of subclinical vascular disease failed to detect 40 to 75% of participants with



Scatterplot of the log of the CAC score and the internal carotid IMT (in mm) for those without clinical CVD in the CHS Pittsburgh cohort (n=414).

TABLE 4. Results of Linear Regression Models Using Other Subclinical Vascular Disease Measures to Predict the Log(CAC Score) for Those Without Clinical CVD, The CHS Arterial Calcification in the Elderly Study, n=414.

Model/Variable	Model R ²	Parameter Estimate (β)	SE	95% CI	P
AAI model	0.20	-1.59	0.619	-2.81, -0.37	0.011
ICA model	0.23	0.62	0.139	0.35, 0.90	<0.0001
CCA model	0.19	1.11	0.511	0.11, 2.12	0.030
Overall model					
AAI	0.25	-1.28	0.645	-2.55, -0.01	0.047
ICA IMT		0.55	0.151	0.26, 0.86	0.0002
CCA IMT		0.16	0.544	-0.91, 1.23	0.773

Each model included age at scan, gender, race, body mass index, total cholesterol, presence of hypertension or diabetes, history of smoking and pack-years smoked as explanatory variables.

high CAC scores using any one measure. Although all of these disease measures are correlated, 17.5% (n=25/143) of those with a CAC \geq 400 would be missed in the ascertainment of subclinical atherosclerosis using a composite of these other measures (a low AAI, major ECG abnormalities, or increased carotid artery IMT). The composite measure of carotid disease by ultrasound was the most sensitive in detecting a high score whereas the presence of a low AAI was most specific. The combination of measures (carotid, AAI, ECG) improved sensitivity with a loss of specificity.

Although these other measures of subclinical disease have been shown to be independent predictors of CVD events, they only predict about 75% of incident CVD events.³⁰ It is possible that a proportion of the other 25% of cases may have come from a subgroup with coronary or aortic calcification (disease not detected by the current subclinical disease composite score). Twenty-four percent (n=30/124) of those without clinical or subclinical disease had a CAC score \geq 400 and about 13% (16/124) had scores over 800. Whether individuals with a high level of coronary artery calcium would benefit from being identified is not yet known, as it is unclear whether any summary measure of subclinical disease will provide incremental benefit for predicting events over traditional risk factors alone.⁷ In older adults, high CAC scores are not well predicted by their traditional risk factors.²¹ Noninvasive testing might prove to be especially useful in such a population of older adults.³¹ Importantly, our data suggest that these other measures of subclinical atherosclerosis identify only a portion of people with coronary artery disease and that those with high CAC scores are most likely to be older white men with smoking history. Studies of the predictive value of CAC screening should specifically consider its utility for subgroups who seem to be at intermediate risk by other risk assessments.³² In our study, ongoing follow-up will show whether just the presence of a high coronary calcium score alone predicts CVD events in late life.

Lower extremity arterial disease was found to be very specific for a higher CAC score; most of those with low AAI can be assumed to have extensive coronary artery disease. Of the carotid measures, the ICA IMT was more strongly related to the CAC score, suggesting that it may capture atherosclerosis more directly than the CCA IMT. The CCA IMT may be more reflective of medial hypertrophy, secondary to hyper-

tension than to atherosclerosis per se.³³ Our data would lend support to these observations. To test whether calcium deposition was uniform in different vessels in the same person, Arad et al¹⁷ explored the relationship of calcium scores to plaque volumes in the carotid and coronary arteries. A relationship was identified between peripheral artery atherosclerosis and coronary calcium but not between a composite carotid wall thickness measure (ICA and CCA IMTs) and carotid calcification. This indicates that coronary calcium scans may present new information to a clinician regarding total atherosclerotic burden.

An important limitation is that this study is a cross-sectional view of the sensitivity and specificity of subclinical disease measures to detect high levels of CAC, which have been associated with ischemic threshold, rather than cardiovascular events. The risk of CVD events has been shown to increase continuously across the range of CAC.³⁴ In these analyses we sought to provide data that can be compared with published CHS articles, but additional work is needed to compare these measures, particularly the continuous measures of internal carotid wall thickness and CAC as predictors of clinical cardiovascular outcomes. Prospective data also are needed to determine whether the risk of high CAC might be attenuated with age. All of these measures have associated costs and the relative predictive value of each will need to be directly compared with risk stratification based on traditional risk factor algorithms.^{35,36}

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