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A Negative Carotid Plaque Area Test Is Superior to Other Noninvasive Atherosclerosis Studies for Reducing the Likelihood of Having Underlying Significant Coronary Artery Disease

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Objective—Coronary calcium score (CCS), carotid plaque area (CPA), intima-media thickness (IMT), and C-reactive protein (CRP) are independent predictors of cardiovascular prognosis. Although each test may enhance risk stratification, their comparative abilities to screen for underlying coronary stenoses in individual patients is less established.

Methods and Results—Forty-two patients who had a 16-slice coronary computed tomography angiogram (CTA) performed were invited to have CPA, IMT, and CRP measured. CPA was defined as the sum of all the cross-sectional areas of each plaque >1 mm in diameter found in all carotid vessels bilaterally. CCS and the number plus degree of stenotic coronary arteries were determined by CTA. The presence of clinically significant coronary artery disease (CAD) was defined as the existence of any stenosis ≥50%. CTA identified clinically significant CAD in 43% of the patients. CPA >0 was more sensitive (72%) and specific (58%) than a CCS >0 (58% and 55%) for identifying CAD. A "clean" carotid artery (CPA=0) provides a superior negative predictive value (74%) and likelihood ratio of a negative test (0.48) than all other studies, in particular versus a CCS=0 (65% and 0.72). The areas under the receiver-operator curves for CPA and CCS in relation to any CAD were similar (0.640 versus 0.675). Carotid IMT and CRP performed poorly compared with CPA and CCS. For detecting CAD in only the left main or left anterior descending artery, the negative predictive value and likelihood ratio of a negative test remained superior for CPA (87% and 0.33) compared with CCS (80% and 0.56). In our population with a prevalence of these coronary lesions of 30%, the post-test probability in any patient with a negative CPA result is reduced to 10%.

Conclusion—CPA determination is superior to CCS, IMT, and CRP in its ability to reduce the likelihood of clinically significant underlying CAD in patients of varying cardiac risk. (***Arterioscler Thromb Vasc Biol***. 2006;26:656-662.)

Key Words: coronary calcium ■ coronary artery disease ■ computed tomography angiography ■ atherosclerosis

High sensitivity C-reactive protein (CRP),[1,2] carotid intima-media thickness (IMT),[3,4] and coronary calcium score (CCS)[5,6] are independent predictors of future cardiovascular events. Obtaining these tests may improve risk stratification in intermediate-risk patients determined by Framingham risk score.[7] IMT and CCS are considered markers of underlying atherosclerotic burden, whereas CRP provides pathophysiological information regarding the degree of systemic inflammation.[1] Nevertheless, some studies suggest that CRP can also predict the presence of coronary artery disease (CAD).[1] Combining anatomic with functional tests may even further enhance risk stratification.[8]

Although not promoted as a means to identify the presence of coronary stenoses,[7,9] CCS is correlated to the extent of underlying atherosclerosis.[10–15] However, even a CCS of 0 does not eliminate the possibility of future cardiovascular events,[5,6,16] nor does it rule out the existence of underlying significant coronary stenoses or myocardial ischemia.[10–15] The imperfect ability of CCS to identify CAD is not surprising given the pathobiology of atherosclerosis, because vulnerable lipid-rich coronary lesions may not be calcified in the earlier stages of disease. It is likely that the prognostic strength of a high CCS[5,6] is caused primarily by its correlation with the extent of underlying atherosclerotic burden throughout the coronary vasculature[10,11] and not to the identification of calcium within any particular individual lesion.[9] The inability of CCS testing to identify patients (particularly young people) with clinically significant minimally or noncalcified (yet potentially vulnerable) coronary plaques is a significant limitation.

Carotid plaque area (CPA) has also been shown to be an independent predictor of future cardiovascular risk[17,18] and for the presence of CAD.[19] In general, carotid plaque is a superior predictor of underlying coronary atherosclerosis than IMT.[20] Although IMT weakly correlates with the extent of CAD, it is more strongly related to age, hypertension, and vascular hypertrophy of the media. CPA provides direct information regarding extracoronary atherosclerosis per se, a process that differs from the factors that chiefly determine IMT. In addition, CPA does not have the same shortcomings of noncalcified atherosclerosis detection or radiation exposure that limits CCS. Its major limitation for heart disease prediction is that it relies on a presumed strong biological correlation of atherosclerosis between the carotid and coronary vasculature. Therefore, carotid IMT, CPA, and CCS provide anatomic information about differing biological processes within the vascular wall and/or insight into the degree of atherogenesis at various stages of disease.

With these factors in mind, we sought to compare the predictive ability of multiple noninvasive tests to detect and/or rule out "clinically significant" coronary artery disease. Few studies have compared multiple modalities within the same population of patients.[13] In addition, no study has compared the results of these tests to those of the new technology of multidetector coronary computed tomography angiography (CTA). The pretest probability (prevalence) of CAD significantly alters the clinical applicability of any screening test. Most studies have used invasive coronary angiography as the reference standard, thereby creating a selection bias toward higher-risk patients with a much greater pretest probability of CAD (eg, patients with chest pain, positive stress tests, or known CAD).[10–15] By using noninvasive CTA as the reference standard, we were able to investigate the screening ability of these tests among a cohort of patients with a wider degree of coronary risk more typical of outpatient practice. A particular focus was to investigate the ability of CPA versus CCS measurement to identify a patient cohort with a reduced likelihood of having clinically significant CAD.

Methods

This project was approved by the Institutional Review Board of the University of Michigan Medical School. All individuals recruited to the study were patients seen in the outpatient cardiology clinics for management of cardiovascular risk factors. Any of such patients who had a CTA performed for clinical purposes as determined by the physician between 2002 and 2004 were invited to take part in this study. There were no exclusion criteria for entering the study among patients who had the CTA performed. However, no patient had a previous history of any type of coronary or carotid revascularization.

Recruited patients then had a carotid duplex ultrasound performed at the outpatient diagnostic vascular unit of the University of Michigan, which is accredited by the Intersocietal Commission for the Accreditation of Vascular Laboratories. Carotid IMT and CPA were obtained by methods previously described.[21] Briefly, a 7.5-mHz linear array transducer connected to a Powervision ultrasound device (Toshiba, Inc, Tustin, Calif) was used. All analyses were measured with longitudinal carotid images with the probe at a 90-degree angle from blood flow (eg, effort was made to eliminate oblique image acquisition). The technician measured IMT on-screen using electronic calipers with the distal 1 cm of the common carotid artery zoomed to give a clear IMT image. IMT was defined as the distance between the media-adventitia and the intima-lumen interface. The single largest IMT site within the distal 1 cm of both the near and far walls of the bilateral common carotid arteries were averaged (4 values) to provide a single final IMT value. No patient had a significant plaque at this segment of IMT measurement in the common carotid. CPA was determined as the sum cross-sectional area of all carotid plaques (>1.1 mm thickness) in all carotid vessels (common, internal, external, and bulb) bilaterally. Each longitudinal plaque image and degree of stenosis was corroborated against axial images to assure accurate imaging (to reduce overestimation or underestimation of plaque size). When a plaque was found, the technician traced the image manually in longitudinal view. The ultrasound computer directly provided plaque cross-sectional area. Blood was drawn during the same visit for CRP and analyzed as previously described in the University of Michigan clinical chemistry laboratory.[22] All tests were performed within a 6-month period.

Cardiac CT

Each patient had CCS and then 16-row multidetector CTA on a LightSpeed 16 or Pro CT Scanner (GE Medical Systems, Milwaukee, Wis). All scans were evaluated by the same radiologist who provided standardized reporting of the CCS and the percent stenoses of each coronary artery. The CCS was from cardiac apex to base using prospective EKG-triggered 16-row ECG-triggered sequential images at 75% of the R-R interval, 2.5-mm section thickness, and 0.4- to 0.5-second gantry rotation time at 120 kVp and 320 mA. Before scanning, patients with a heart rate $\geq$65 beats $\cdot$ min^{-1} were treated with oral, and when necessary, intravenous metoprolol as required to achieve a heart rate <65 beats $\cdot$ min^{-1} to optimize CTA imaging and reduce motion artifact. A contrast timing bolus was performed to obtain the optimal scan delay using 20 mL of the non-ionic iso-osmolar intravenous contrast agent, iodixanol (Visipague 320; Nycomed, Amersham NJ), administered through an Angiocath in an antecubital vein at a rate of 4 mL per second, with the region of interest placed in the aortic root. The individualized delay used was peak enhancement time at the aortic root plus 3 seconds. For coronary CTA, a total of 100 mL iodixanol was administered at 4 mL/second during a single breath-hold CT acquisition was then performed using retrospective ECG gating and a 0.625×16 detector configuration, gantry rotation speed was 0.4 to 0.5 seconds, pitch was 0.2 to 0.3 depending on heart rate, 120 kVp and 440 to 800 mA. Retrospective 0.625-mm reconstructions were performed at 70%, 75%, and 80% of the R-R interval at 0.625-mm slice thickness routinely, with additional reconstructions at additional increments of the R-R interval if necessary.

Smart Score software on a GE Advantage Windows workstation version 4.1 (GE Medical Systems, Milwaukee, Wis) was used for CCS quantification to obtain the Agatson Score Equivalent for a multidetector CT acquisition. For analysis of the coronary arteries, examinations were interpreted on a GE Advantage Windows workstation version 4.1 or 4.2 by a single radiologist using Card IQ Analysis II software. Curved reformats, maximum intensity projections, and the lumen view for analysis of individual coronary arteries (right coronary artery, left main, left anterior descending, and circumflex coronaries) for the presence or absence of atherosclerotic plaque, which was classified as calcified or noncalcified. The severity of all stenoses were reported to the nearest 10th percent diameter stenosis.

Statistical Analyses

Descriptive statistics were reported as the group mean and standard deviation. Framingham Risk Scores were calculated using the on-line program (http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof). Differences in group mean values were compared using an independent samples t test. The χ^2 analysis was used to evaluate differences between categorical variables. A level of significance of $P<0.05$ was used for all tests. Sensitivity, specificity, and negative predictive value for the detection of coronary atherosclerosis were determined for CPA, IMT, CRP, and CCS, with atherosclerosis being defined as a stenosis $\geq$50% from CTA as the reference standard. Receiver-operator curves, c-statistics, and Pearson correlation coefficients (log-normalized data for CCS), and all other statis-

TABLE 1.   Patient Characteristics

	Total Cohort Mean±SD (n=42)	With CAD Mean±SD (n=18)	Without CAD Mean±SD (n=24)	P
Age, y	57±8	62±7	52±7	<0.001
Male/Female, n	34/8	15/3	19/5	0.734
Body mass index, kg/m^2	28.0±3.7	27.8±4.0	28.3±3.4	0.710
Body weight, kg	86±14	87±15	84±14	0.599
Cardiovascular family history, n	24 (57%)	9 (50%)	15 (63%)	0.418
Coronary artery disease history, n	10 (24%)	7 (39%)	3 (13%)	0.047
Current smoker, n	1 (2%)	1 (6%)	0	0.243
Systemic hypertension, n	20 (48%)	13 (72%)	7 (29%)	0.006
Hyperlipidemia (history), n	34 (81%)	15 (83%)	19 (79%)	0.734
Medication usage				
Aspirin	32 (76%)			
Nonstatin lipid-lowering drug	2 (4%)			
Statin	21 (50%)			
ACEI or ARB	12 (28%)			
Systolic blood pressure, mm Hg	123±10	126±11	121±9	0.127
Diastolic blood pressure, mm Hg	73±9	69±8	75±10	0.031
Total cholesterol, mg · dL^{-1}	195±57	191±58	198±58	0.701
High-density lipoprotein, mg · dL^{-1}	46±15	58±17	58±19	1.000
Low-density lipoprotein, mg · dL^{-1}	113±43	110±49	115±39	0.719
Triglycerides, mg · dL^{-1}	125±66	112±47	135±77	0.275
C-reactive protein, mg · L^{-1}	2.2±2.6	2.0±2.0	2.3±3.0	0.694
*Framingham risk score, %	10±4	13±7	7±6	0.007
Coronary calcium, Agatson score equivalent	118±239	226±321	37±99	0.010
Carotid intima-media thickness, mm	0.84±0.28	0.86±0.32	0.82±0.26	0.668
Carotid plaque area, mm^2	23.2±31.2	28.8±29.9	18.9±32.0	0.314

Positive family history is equal to first-degree relative with documented cardiovascular disease or event before ages 55 (male relative) or 65 (female relative).

Hypertension denotes previous diagnosis of elevated blood pressure and/or currently on antihypertensive medication.

Hyperlipidemia history denotes previous diagnosis of elevated serum lipoproteins and/or currently on lipid-lowering medications.

CAD denotes coronary artery disease defined by any lesion ≥50% in any vessel as determined by CT angiography.

P values determined by independent samples *t* tests.

*Calculated Framingham risk score. This value assumes a score of 20% for patients with the diagnosis of coronary heart disease or disease risk equivalents before CTA testing.

ACEI indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

tical analyses were performed with SPSS 12.0 (SPSS Incorporated, Chicago, Ill).

Results

Forty-two patients had all tests performed. The reasons for CTA testing were to evaluate known CAD (n=10), risk stratification in moderate-risk to high-risk patients without established coronary disease (n=23), a strong family history of premature heart disease (n=7), and valvular abnormalities (n=2). The clinical characteristics of the study patients are displayed in Table 1. Twenty-four, 8, and 10 patients had Framingham Risk Scores between 0% and 9%, 10% and 19%, and ≥20%, respectively. Among the tests, only CCS significantly differed between subjects with versus those without CAD determined by CTA. After adjustment for age, the differences in diastolic blood pressure, CCS, and Fra-

mingham Risk Score remained significant (*P* all <0.05). Eighteen patients (43%) had clinically significant CAD on CTA; 13 patients (31%) had clinically significant CAD in the left main and/or anterior descending arteries.

Among all study parameters, only CCS (*r*=0.42, *P*=0.006) and CPA (*r*=0.43, *P*=0.004) were significantly correlated to the Framingham Risk Score. CPA, CRP, and CCS were not correlated with each other; however CPA was correlated to CIMT (*r*=0.39, *P*=0.009). No parameter was significantly related to CRP. Figures 1 and 2 show the data regarding each test's ability to correctly categorize patients according to the presence or absence of underlying CAD. For both definitions, CPA of 0 had the lowest false-negative rate for excluding coronary disease compared with all other tests.

The performance accuracy of the tests is demonstrated in Table 2. The sensitivity and negative predictive value for both
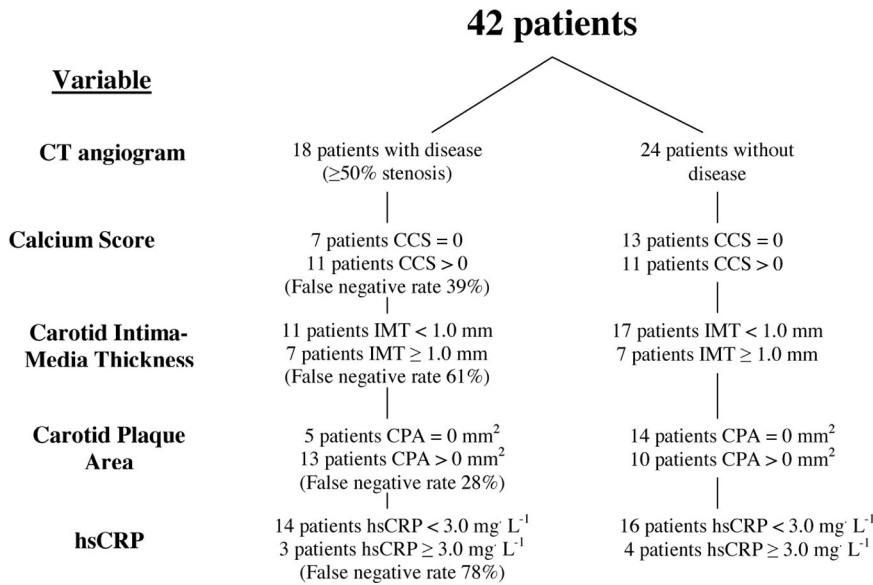
42 patients

Variable		

CT angiogram

18 patients with disease
(≥50% stenosis)

24 patients without
disease

Calcium Score

7 patients CCS = 0
11 patients CCS > 0
(False negative rate 39%)

13 patients CCS = 0
11 patients CCS > 0

Carotid Intima-
Media Thickness

11 patients IMT < 1.0 mm
7 patients IMT ≥ 1.0 mm
(False negative rate 61%)

17 patients IMT < 1.0 mm
7 patients IMT ≥ 1.0 mm

Carotid Plaque
Area

5 patients CPA = 0 mm^2
13 patients CPA > 0 mm^2
(False negative rate 28%)

14 patients CPA = 0 mm^2
10 patients CPA > 0 mm^2

hsCRP

14 patients hsCRP < 3.0 mg·L^{-1}
3 patients hsCRP ≥ 3.0 mg·L^{-1}
(False negative rate 78%)

16 patients hsCRP < 3.0 mg·L^{-1}
4 patients hsCRP ≥ 3.0 mg·L^{-1}

Figure 1. Characteristics of patients with and without disease, as defined as a ≥50% stenosis in any vessel on the CT angiogram.

definitions of CAD were greatest for CPA among all tests. Both a CPA and CCS >0 were not very specific for having significant coronary disease. However, CPA had a superior likelihood ratio of a negative test compared with CCS. With a prevalence of having a 50% lesion in either the left anterior descending or the main artery equal to 30% (13 of 42 patients), then the likelihood (odds) of having such lesions (post-test probability) would only be 10% in any patient with a CPA test result of 0, a reduction of 67%. For CAD defined as ≥70% lesions in the left main or anterior descending artery, a CPA-O reduces the likelihood by >90%. The receiver-operator curves and c-statistics for identifying any 50% coronary artery lesion by CTA were similar for both CPA and CCS (Figure 3). The results of all testing (eg, sensitivity) were not enhanced by combining CPA and CCS findings. The negative predictive values for CPA and CCS were both 80% when CAD was defined as ≥70% stenosis by CTA. The negative predictive value for any left main and/or

anterior descending artery stenosis ≥70% was 93% for CPA and 95% for CCS. Given the poor accuracies of CRP and IMT, we evaluated the positive predictive values and likelihood ratios of a positive test only for CPA and CCS. The positive predictive values of CPA and CCS for identifying a significant coronary lesion were 78% and 82%, respectively. The likelihood ratios of a positive test were 1.73 and 1.33, respectively.

Discussion

Few studies have directly compared the ability of multiple noninvasive tests for atherosclerosis to predict the presence of underlying CAD in the same patients.[13] The salient findings of this study are that a negative CPA test was superior to a CCS of 0 in reducing the likelihood of having significant underlying coronary atherosclerosis in a population of patients of varying cardiovascular risk. Second, a "clean" carotid artery had a strong negative predictive value (87%)

42 patients

Variable		

CT angiogram

13 patients with ≥50% stenosis
in left main or LAD

29 patients without
disease

Calcium Scoring

4 patients CCS = 0
9 patients CCS > 0
(False negative rate 31%)

16 patients CCS = 0
13 patients CCS > 0

Intima-Media
Thickness

10 patients IMT < 1.0 mm
3 patients IMT ≥ 1.0 mm
(False negative rate 77%)

18 patients IMT < 1.0 mm
11 patients IMT ≥ 1.0 mm

Carotid Plaque
Area

2 patients CPA = 0 mm^2
11 patients CPA > 0 mm^2
(False negative rate 15%)

13 patients CPA = 0 mm^2
16 patients CPA > 0 mm^2

hsCRP

9 patients hsCRP < 3.0 mg·L^{-1}
4 patients hsCRP ≥ 3.0 mg·L^{-1}
(False negative rate 69%)

21 patients hsCRP < 3.0 mg·L^{-1}
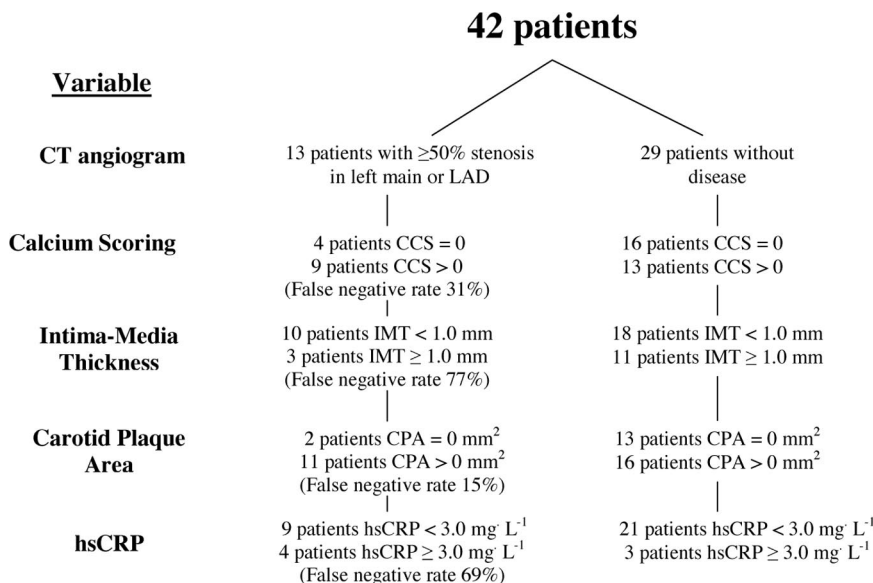3 patients hsCRP ≥ 3.0 mg·L^{-1}

Figure 2. Characteristics of patients dichotomized by the presence of a stenosis ≥50% in only the left main or left anterior descending (LAD) coronary artery determined by CT angiography.

TABLE 2.   Ability of Each Test to Detect Coronary Artery Disease Defined as (A) the Presence of Any Coronary Artery Stenosis ≥50% Determined by CT Angiography Found in Any Coronary Vessel or (B) the Presence of Any Coronary Artery Stenosis ≥50% Determined by CT Angiography in Only the Left Main or Left Anterior Descending Arteries

	Sensitivity (%)		Specificity (%)		Negative Predictive Value (%)		Negative Likelihood Ratio	
Test	A	B	A	B	A	B	A	B
Coronary calcium score (CCS)	61	69	54	55	65	80	0.72	0.56
Carotid intima-media thickness (CIMT)	39	23	71	62	61	64	0.86	1.24
High-sensitivity C-reactive protein (hsCRP)	18	31	80	88	53	70	1.0	0.78
Carotid plaque area (CPA)	72	85	58	45	74	87	0.48	0.33

Sensitivity and specificity are calculated for CCS >0, CIMT ≥1.0 mm, hsCRP ≥3.0 mg·dL^{-1}, CPA>0 mm^2.

Negative predictive value and likelihood ratio of a negative test are calculated for CCS=0, CIMT <1.0 mm, hsCRP <3.0 mg·dL^{-1}, and CPA=0 mm^2.

for significant left main and/or left anterior descending coronary artery disease. Despite only a moderate specificity of an abnormal result, a CPA of 0 was capable of reducing the post-test probability of these lesions by 67%. Third, although previously validated to predict clinical outcomes, both carotid IMT and CRP were poor predictors of coronary stenoses. CRP was not correlated to any anatomic measurement of atherosclerosis. These findings confirm that this "functional" inflammatory marker is likely a superior predictor of future events, not underlying atherosclerotic burden.[5] Finally, whereas both CPA and CCS were significantly correlated to the Framingham risk score, their nonsignificant inter-association was weak. Therefore, these tests may be providing different biological information, although combining

results did not improve CAD risk prediction in this small study.

Recent studies corroborate that CCS is an independent predictor of future cardiovascular risk beyond the information provided by clinical risk scores.[5,6] The value of a CCS measurement likely lies in its ability to correlate with the extent of underlying coronary atherosclerosis by histopathology and invasive angiography.[10–15] A very low CCS is associated with a low likelihood of stress-induced coronary ischemia in patients with and without chest pain.[14] However, myocardial infarctions and significant coronary disease can occur in patients with little to no coronary calcium.[10–16] A CCS of 0 is not an infallible marker of low absolute coronary risk and it does not meaningfully lower event rates in
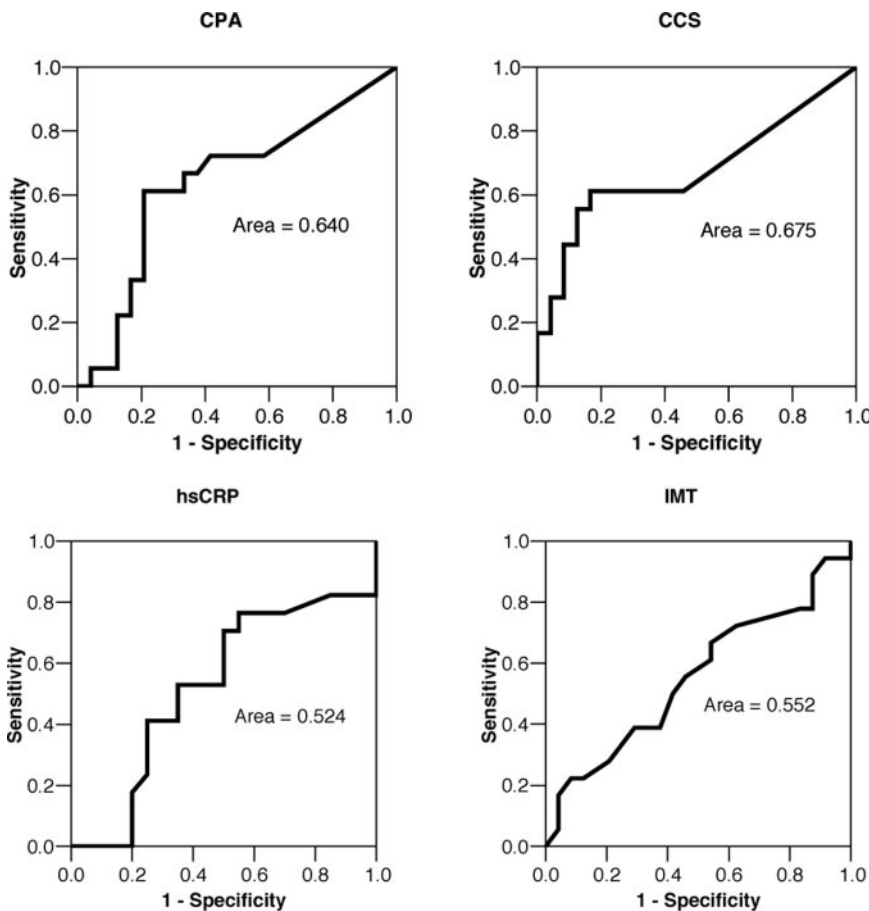

Figure 3. Receiver operator curves for identifying coronary artery disease for each individual test.

high-risk patients (eg, those with Framingham scores >15% to 20%).[6] Other limitations are test cost, exposure to radiation, and the limited availability of equipment. Nevertheless, CCS did correlate in our study, as in others,[5] with Framingham risk scores. It also significantly differed between patients with versus those without underlying coronary lesions and had an overall C-statistic similar to CPA. This latter fact suggests that taking both sensitivity and specificity into account, CPA and CCS perform similarly. However, the sensitivity, specificity, and negative predictive value to predict coronary lesions were all slightly inferior to that of CPA (Table 2). Most importantly from a clinical utility standpoint, a negative CPA test result was superior to a CCS of 0 in ruling out underlying CAD.

CPA and IMT are both independently related to cardiovascular prognosis.[3,4,17–19] Carotid and coronary atherosclerosis are known to be correlated[23]; however, carotid IMT may be less strongly associated with coronary disease than CPA for many reasons.[20] Thus, it is not surprising that CPA outperformed CIMT. The relatively poor predictive value of IMT is in accord with a recent publication in which CCS was also found to be superior to IMT.[13] However, CPA was not reported in this previous study and therefore the most relevant and useful information derived from carotid ultrasound testing for predicting coronary disease was not evaluated. It is possible that had the authors also included a measure of carotid plaque a much stronger predictive value of CPA over IMT (and akin to CCS) may have been found. As CPA can identify any noncalcified atherosclerotic plaque with an axial resolution accuracy of <0.1 mm, it is likely a more sensitive test superior for recognizing earlier lesion formation than CCS, which relies on identifying calcification in plaques that develop with the evolution of plaque over time.[20] Our results show that although both CCS and CPA are similarly related to Framingham Risk Score, a "clean" carotid (CPA=0) has a superior ability to rule out significant coronary stenoses than a negative CCS of 0. Given the pathobiology of coronary atherosclerosis and the fact that many unstable/vulnerable lesions may not be calcified, it is also not surprising that clinically meaningful coronary lesions can go undetected by CCS measurement.[10–15] This likely explains the moderately superior performance of CPA compared with CCS. The ease of measuring CPA and the fact that it is faster, less expensive, and without the risk of radiation exposure makes it attractive as a screening tool. The major limitation of CPA testing is that it relies on the presumption of a high biological correlation between atherosclerosis in 2 different vascular beds. This is the most likely explanation for its false-negative rate of 15% to 28% for detecting 50% coronary lesions. Therefore, even a CPA of 0 is not an infallible indicator of the absence of obstructive CAD. However, our results parallel those of the only other study of which we are aware that evaluated the negative predictive value of the absence of carotid plaque for ruling out CAD (88%).[24]

Our results suggest that in patients with a wide spectrum of underlying cardiovascular risk, a screening CPA test of 0 can reduce the likelihood (post-test probability) of having significant high-risk lesions (left main, left anterior descending) to ≈10%. A "clean" carotid test could potentially be able to screen out patients from requiring additional more invasive, risky, or burdensome tests. A larger study with a cohort of patients from a variety of pretest risk levels, with and without symptoms suggestive of angina, is required to confirm this initial observation. Nevertheless, these promising results suggest that CPA may be a reasonably effective screening tool supporting the rationale for larger investigations.

This study has several limitations. There were no functional ischemic assessments of the patients and the clinical significance of any identified 50% coronary lesion is not known. However, this threshold is what has been commonly used in previous reports.[10–15] If a more stringent cutoff value of 70% stenosis were used (as this is more likely to be associated with cardiac ischemia), the negative predictive values for both tests improve to 80%. For any left main or left anterior descending artery 70% lesion, this value increases to 93% (CPA) and 95% (CCS). Few patients were found to have this degree of stenoses (7/42), thus a 50% lesion was chosen as the primary outcome. Although we enrolled patients with a wide range of estimated cardiovascular risk (24 low, 8 intermediate, 10 high), all individuals were recruited from a single outpatient cardiology clinic. This may have resulted in a selection bias that reduces the external validity of our results compared with the population as a whole. However, because the noninvasive CTA was used instead of coronary angiography, the present study likely suffers less from this problem than previous publications.[10–15] The study design actually allowed us to enroll a much broader spectrum of patients with a wider variety of pretest CAD probability. We also recognize that the use of CTA, instead of coronary angiography, as the gold standard comparator may present other limitations. Nevertheless, most recent publications support the high degree of accuracy of adequately performed CTA studies (80% to 90% sensitivity) for correctly identifying clinically meaningful coronary stenoses (>50%) within major epicardiac vessels.[25] In fact, it could be argued that the CTA is "oversensitive" and falsely identifies lesions at the 50% level. This could possibly explain the modestly inferior ability of CCS to rule out coronary lesions in this study as compared with some previous angiographic studies.[10–15] Nonetheless, both CPA and CCS results were compared with the same CTA findings and suffered from this same limitation that may have reduced their absolute degrees of accuracy compared with studies that used conventional angiography. This limitation, however, would not have contributed to altering their comparative abilities to predict CAD. It is also possible that the capabilities of CTA to characterize vessel wall anatomy beyond assessment of only the arterial lumen (eg, conventional angiograms) may actually make it a superior test for identifying very early coronary atherosclerosis or stenoses missed by angiograms (ie, because of outward remodeling). Hence, it is conceivable that the less robust ability of a CCS of 0 to rule out coronary lesions in our study is a more accurate refection of its true performance. The prognostic abilities of CTA versus conventional angiography have not been reported and future studies may settle this issue. Because of the small number of patients in this study, we were limited in our ability to assess the performance of CCS and CPA at multiple threshold values of normalcy (or to assess

each test by result mean and/or by percentiles) and therefore chose to focus on the predictive value of "negative" test results. No other threshold values provided useful discriminatory power in this small sample size. We also could not account for the effect of previous medication usage on CPA or CCS. However, antiatherosclerotic medications (eg, statins) alter CPA, CIMT, and CCS in parallel fashions and therefore do not bias the results to favor the accuracy one particular test to identify the presence of CAD. In addition, the goal of this study was to assess the accuracy of these tests among a wide variety of patients regardless of medication status. Finally, we could not provide follow-up data regarding patient outcomes. Much larger observations, such as the Multiethnic Study of Atherosclerosis, will be able to compare the prognostic accuracy of carotid plaque, IMT, and CCS in the same patients. In the meantime, our results support the notion that the simpler, less expensive, and less risky ultrasound test for CPA may prove to be at least equal to CCS.

This small study suggests that a "clean" carotid is modestly superior to a negative coronary calcium test for identifying patients without significant underlying coronary lesions. A CPA of 0 reduces the likelihood of a 70% left anterior descending artery or left main obstruction by >90%. It is possible that a screening CPA assessment may be able to significantly reduce the need for additional or invasive testing in borderline-risk patients because of its relatively high-negative predictive value. Further studies are warranted in a larger population of patients both with and without chest pain and at various cardiovascular risk levels to corroborate this finding.

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