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Cardiac Imaging

Prognostic Value of Multidetector Coronary Computed Tomographic Angiography for Prediction of All-Cause Mortality

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Objectives The purpose of this study was to examine the association of all-cause death with the coronary computed tomographic angiography (CCTA)-defined extent and severity of coronary artery disease (CAD).

Background The prognostic value of identifying CAD by CCTA remains undefined.

Methods We examined a single-center consecutive cohort of 1,127 patients ≥45 years old with chest symptoms. Stenosis by CCTA was scored as minimal (<30%), mild (30% to 49%), moderate (50% to 69%), or severe (≥70%) for each coronary artery. Plaque was assessed in 3 ways: 1) moderate or obstructive plaque; 2) CCTA score modified from Duke coronary artery score; and 3) simple clinical scores grading plaque extent and distribution. A 15.3 ± 3.9-month follow-up of all-cause death was assessed using Cox proportional hazards models adjusted for pretest CAD likelihood and risk factors. Deaths were verified by the Social Security Death Index.

Results The CCTA predictors of death included proximal left anterior descending artery stenosis and number of vessels with ≥50% and ≥70% stenosis (all $p < 0.0001$). A modified Duke CAD index, an angiographic score integrating proximal CAD, plaque extent, and left main (LM) disease, improved risk stratification ($p < 0.0001$). Patients with <50% stenosis had the highest survival at 99.7%. Survival worsened with higher-risk Duke scores, ranging from 96% survival for 1 stenosis ≥70% or 2 stenoses ≥50% ($p = 0.013$) to 85% survival for ≥50% LM artery stenosis ($p < 0.0001$). Clinical scores measuring plaque burden and distribution predicted 5% to 6% higher absolute death rate (6.6% vs. 1.6% and 8.4% vs. 2.5%; $p = 0.05$ for both).

Conclusions In patients with chest pain, CCTA identifies increased risk for all-cause death. Importantly, a negative CCTA portends an extremely low risk for death. (J Am Coll Cardiol 2007;50:1161–70) © 2007 by the American College of Cardiology Foundation

Cardiovascular disease remains the leading cause of morbidity and mortality in the world. Because efficacious therapies exist to reduce cardiovascular events, it is vital to identify individuals at high risk for adverse outcomes.

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Noninvasive evaluation of symptomatic patients to further stratify risk beyond traditional cardiac risk factor scoring has primarily relied on stress nuclear myocardial perfusion imaging and echocardiography (1). The recent introduction of multidetector coronary computed tomographic angiography (CCTA) offers a novel noninvasive approach for evaluation of coronary and cardiac structure and function (2,3). Current-generation CT scanners permit high diagnostic accuracy for detection of and high negative predictive value to exclude obstructive coronary lesions (4).

To date, the prognostic value of CCTA in patients presenting with chest symptoms is only beginning to be examined (5,6). Therefore, the goal of the present study was to determine whether use of CCTA as the primary noninvasive imaging modality in the evaluation of patients presenting with chest symptoms would offer incremental prognostic value for prediction of all-cause mortality.

Methods

Patients. We evaluated 1,127 consecutive patients ≥45 years of age from January 2004 to February 2005 who presented with chest symptoms (pain, tightness, palpita-

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Abbreviations and Acronyms

CAD = coronary artery disease

CCTA = coronary computed tomographic angiography

tions, and dyspnea), thought not to represent acute coronary syndromes, for which CCTA coronary angiography was the primary diagnostic imaging modality. Patients were referred for evaluation by CCTA for a variety of indications, including evaluation of symptoms, signs of cardiac disease (abnormal rest or stress test), or asymptomatic patients with peripheral arterial disease, cerebrovascular disease, or multiple coronary artery disease (CAD) risk factors. Symptoms included typical angina, atypical angina, dyspnea, or excessive fatigue. Patients classified by Diamond et al. as nonanginal chest pain were placed into the atypical angina group (7). Pretest likelihood of CAD was determined based on criteria from the American College of Cardiology/American Heart Association guidelines on stable chest pain, with patients grouped as having a low likelihood (<30%), intermediate likelihood (30% to 69%), or high likelihood (>70%). Of the 1,127, 30% were classified with low, 50% with intermediate, and 20% with high CAD likelihood. Patients were referred from outpatient clinics (66%), inpatient wards (20%), and the emergency department (14%). All patients were in normal sinus rhythm and were capable of the breath hold needed for CCTA.

Patients with heart rates >70 beats/min were given 5-mg intravenous metoprolol at 5-min intervals to a total dose of 25 mg. If the patient's heart rate did not drop below 70 beats/min, CCTA was performed at the lowest heart rate.

Before the initiation of the scan, we prospectively collected information on the presence of categoric cardiac risk factors in each individual. Systemic arterial hypertension was defined as a documented history of high blood pressure or treatment with antihypertensive medications. Diabetes mellitus was defined by diagnosis of diabetes made previously by a physician and/or use of insulin or oral hypoglycemic agents. Dyslipidemia was defined as known but untreated dyslipidemia or current treatment with lipid-lowering medications. A positive smoking history was defined as current smoking or cessation of smoking within 3 months of testing. Family history of coronary heart disease was determined by patient query.

Scan protocol and image reconstruction. All scans were performed with a 16-slice multidetector CT scanner (Lightspeed Pro 16, GE Healthcare, Milwaukee, Wisconsin). Imaging of a test bolus of contrast was performed at 2 mm superior to the take-off of the left main coronary artery for precise timing of contrast injection. During the CCTA angiography acquisition, 100-ml iodinated contrast (Isovue 370, Bracco Diagnostics, Princeton, New Jersey) was injected followed by a 50-ml saline flush. Monophasic contrast-enhanced CCTA of the chest was performed, with initiation of the scan at the apices of the lung and termination of the scan at the level of the diaphragm. Contrast timing was performed to optimize uniform contrast enhancement of the coronary arteries. The scan parameters were: 16 × 0.625 mm collimation, tube voltage 120 mV, effective 400 to 650 mA. Estimated radiation doses ranged from 10 to 25 mSv.

Helical scan data were obtained with retrospective electrocardiographic gating. Images were reconstructed immediately after completion of the scan in a consistent manner to identify motion-free coronary artery images. Electrocardiographically gated datasets were reconstructed at 70%, 75%, and 80% of the cardiac cycle after the QRS complex to identify central diastole, with additional datasets reconstructed at 40%, 45%, and 50% of the cardiac cycle to identify central early diastole. Optimal phase reconstruction was assessed by comparison of different phases, and the phase with the least amount of coronary artery motion was chosen for analysis. Multiple phases were used for image interpretation if minimal coronary artery motion was different for different arteries. The CCTAs were evaluated on 2-dimensional maximum intensity projections in oblique cardiocentric views that focused on coronary arterial segments for optimal viewing. Two orthogonal thin maximal intensity projection cardiocentric views approximating traditional coronary angiography angles were used for the left anterior descending, left circumflex, and right coronary artery circulations. Three-dimensional rotation was performed, when necessary, to focus on diagonal and marginal branch vessels.

For CCTAs with suboptimal image quality, multiphase reconstruction was employed for additional points within the cardiac cycle for identification of phases with the least amount of cardiac motion artifact. In other cases, multisector reconstruction algorithms were employed to optimize image quality. Three-dimensional views using curved multiplanar reformation and short-axis cross-sectional viewing techniques were additionally used to enhance detection of obstructive coronary plaque, if necessary. In all individuals, irrespective of image quality, every arterial segment was scored. If a coronary artery segment was uninterpretable even despite these multiple techniques, the unevaluable segment was scored similarly to the most proximal segment which was evaluable.

Noninvasive CCTA analyses. All scans were analyzed by a cardiologist with experience interpreting several thousand CCTA scans. Coronary segments were visually scored for the presence of coronary plaque. The coronary artery tree was divided into 16 separate segments based on a modified AHA classification (left main artery; proximal, mid, and distal left anterior descending artery; proximal, mid, and distal diagonal/intermediate branch; proximal, mid and distal left circumflex artery; proximal, mid, and distal obtuse marginal branch; and proximal, mid, and distal right coronary artery) (8). In cases where multiple diagonal or obtuse marginal branches were present, plaque was graded based on the branch with the largest luminal diameter and/or serving the largest area of myocardium.

In each coronary artery segment, coronary atherosclerosis was defined as tissue structures >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. Coronary artherosclerotic lesions were quantified for stenosis by visual estimation. Stenosis was graded as none or very mild (<30% estimated obstruction of coronary luminal diameter), mild (30% to 49% estimated obstruction of coronary luminal diameter), moderate (50% to 69% estimated obstruction of coronary luminal diameter), or severe (≥70% estimated obstruction of coronary luminal diameter). Percentage obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque (Fig. 1). In instances in which plaque was highly calcified, 2-dimensional oblique images were also viewed without maximal intensity projection at 0.625-mm isotropic voxel resolution to minimize partial volume averaging artifact of calcium.

Currently, no standardized protocol exists for the grading of coronary plaque by CCTA. Therefore, coronary arteries by CCTA were assessed by 3 distinct methods. Two traditional angiographic predictors of mortality were used: 1) the presence of obstructive lesions in major epicardial vessel distributions; and 2) a modified Duke prognostic CAD index. Additionally, simple and intuitive clinical coronary plaque scores were created which can be easily used into daily practice.

First, CCTA scans were assessed to detect obstructive plaque reducing coronary luminal diameter in major epicardial vessels. The CCTA scans were analyzed by identification of the number of the 3 major epicardial vessels (left anterior descending artery, left circumflex artery, and right coronary artery) exhibiting moderate (≥50% obstruction of coronary luminal diameter) or severe (≥70% obstruction of coronary luminal diameter) plaque. Individuals exhibiting moderate or severe coronary plaque in diagonal branches or obtuse marginal branches were considered to possess moderate or severe coronary plaque in the left anterior descending artery and left circumflex artery territory, respectively. Individuals were also categorized based on moderate or severe obstruction of coronary luminal diameter of the left main artery.

Second, we applied the previously reported Duke prognostic CAD index (9,10), which details the expected 5-year survival by the extent and severity of angiographic CAD, to the CCTA scans. The score comprises 16 angiographic subsets that are assigned prognostic weights from 0 to 100. Five-year cardiovascular survival is inversely proportional to the prognostic weight; that is, higher scores are associated with lower survival. We used a modified Duke prognostic CAD index to further assess prognosis in patients with <50% stenosis. From our cohort, we identified the following subsets: 1) <50% stenosis (n = 430); 2) ≥2 stenoses

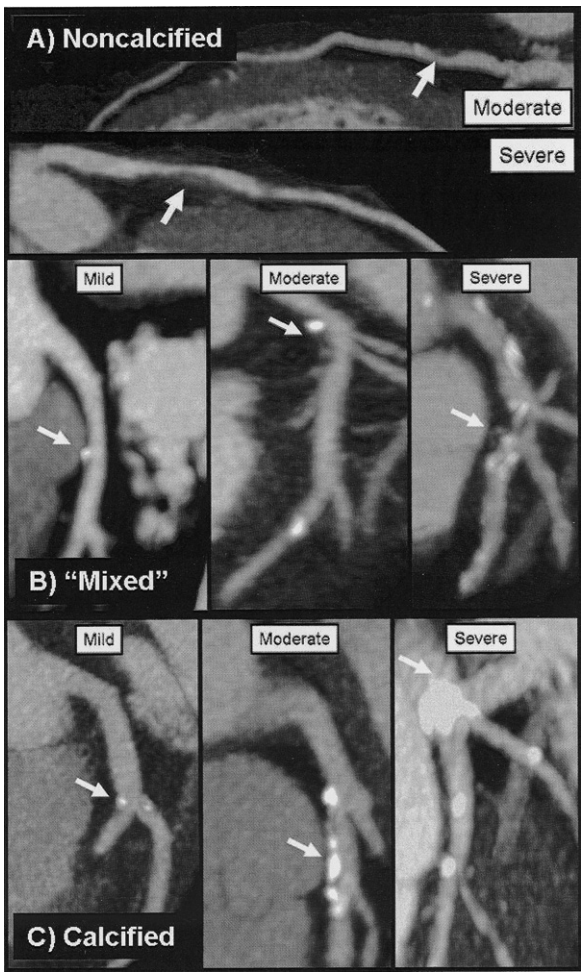

Figure 1 Grading of Plaque Severity

(A) Examples of moderate and severe extent of noncalcified plaque of the left anterior descending artery. **(B)** Examples of mild, moderate, and severe extent of mixed plaque of the left anterior descending artery. **(C)** Examples of mild, moderate, and severe extent of calcified plaque of the left anterior descending artery. **Arrows** indicate coronary artery plaque.

30% to 49% (including 1 artery with proximal disease (n = 270) or 1 vessel with 50% to 69% stenosis; 3) 2 stenoses 50% to 69% or 1 vessel with ≥70% stenosis (n = 101); 4) 3 stenoses 50% to 69% or 2 vessels with ≥70% stenosis or proximal left anterior descending stenosis ≥70% (n = 145); 5) 3 vessels ≥70% stenoses or 2 vessels ≥70% stenosis with proximal left anterior descending (n = 86); and 6) left main stenosis ≥50% (n = 106). Patients were assigned to the highest disease category.

Third, we constructed three clinical coronary artery plaque scores which are simple and easy to apply: 1) segment-stenosis score; 2) segment-involvement score; and 3) 3-vessel plaque score (Fig. 2). The segment stenosis score was used as a measure of overall coronary artery plaque extent. Each individual coronary segment was graded as having no to severe plaque (i.e., scores from 0 to 3) based on

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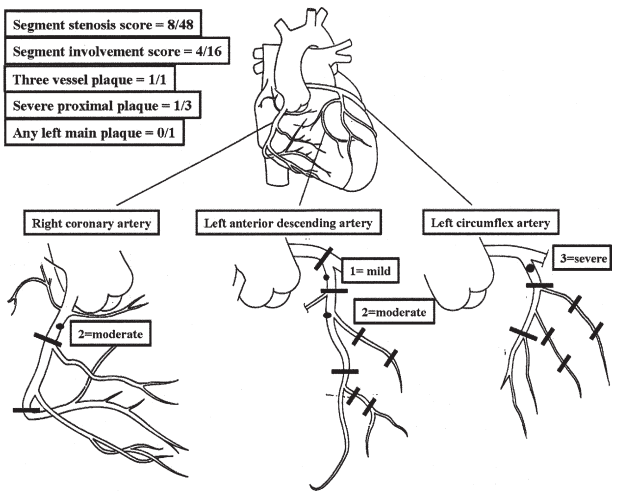

Figure 2 **Coronary Artery Tree Model Depicting Coronary Artery Plaque Scores**

Segment stenosis score was calculated by summation of moderate plaque in the proximal right coronary artery (2) + mild plaque in the proximal left anterior descending artery (1) + moderate plaque in the mid left anterior descending artery (2) + severe plaque in the proximal right coronary artery (3). In this example, the segment stenosis score is 8 out of a possible 48. Segment involvement score was calculated by summation of the absolute number of coronary segments exhibiting plaque, i.e., the proximal right coronary artery (1) + proximal left anterior descending artery (1) + mid left anterior descending artery (1) + proximal right coronary artery (1). In this example, the segment involvement score is 4 out of a possible 16. Three-vessel plaque score was calculated as a binary variable to indicate the presence or absence of 3-vessel coronary artery plaque. Three-vessel plaque score was considered positive if there was concurrent presence of plaque in the left anterior descending artery, left circumflex artery, and right coronary artery. In this example, the 3-vessel plaque score is 1 out of a possible 1. Severe proximal plaque score was measured by presence of severe plaque in the proximal portion of the left anterior descending artery, left circumflex artery, or right coronary artery. In this example, the severe proximal plaque score is 1 out of a possible 3. Left main plaque is measured by any plaque within the left main artery. In this example, the left main plaque score is 0 out of a possible 1.

extent of obstruction of coronary luminal diameter. Then the extent scores of all 16 individual segments were summed to yield a total score ranging from 0 to 48. As a measure of overall coronary artery plaque distribution, a segment involvement score was calculated. The segment involvement score was calculated as the total number of coronary artery segments exhibiting plaque, irrespective of the degree of luminal stenosis within each segment (minimum = 0; maximum = 16). Finally, a 3-vessel plaque score was calculated as 0 or 1 based on the coexisting presence of any plaque in the left anterior descending, left circumflex, and right coronary arteries, irrespective of severity.

Follow-up. The primary end point was time to death from all causes. All patients provided informed consent for follow-up. Follow-up procedures were approved by our center's institutional review board. Death status was ascertained by querying the Social Security Death Index. Death status was ascertained in all patients (i.e., 100% follow-up).

Statistical analysis. We used SPSS version 12.0 (SPSS Inc., Chicago, Illinois) for all statistical analyses. Categoric variables are presented as frequencies and continuous variables as mean ± 1 SD. Variables were compared with chi-square statistic for categoric variables and by Student unpaired *t* test for continuous variables. Time to death from all causes (n = 39) was calculated using univariable Cox proportional hazards models. Risk-adjusted models were also devised including multivariable stepwise models adjusting for baseline cardiac risk factors. Multivariable models were limited to no more than 4 variables to avoid model overfitting. Relative risk ratios were calculated with 95% confidence intervals (CIs) based on binomial distributions. A 2-tailed p value of <0.05 was considered to be statistically significant. In each case, the proportional hazards assumption was met. Finally, we also evaluated effect modification using interaction terms in our Cox models. In particular, we examined the predictive value of CCTA measures by age.

We performed a post hoc power calculation to compare survival in patients with no to mild plaque versus those with 3-vessel or left main disease ($\beta \geq 0.80$; $\alpha = 0.05$), with our current sample yielding sufficient statistical power to detect differences in mortality between these groups or any 2 groups with change in survival rates of 5% or greater.

Results

Clinical characteristics of the CCTA cohort. Of the 1,127 patients, 57% were women with an average age of 61.7 ± 10 years (range 45 to 89 years) (Table 1). Patient characteristics are categorized according to coronary artery plaque score by the Duke prognostic CAD index. Based upon gradations of CAD as defined by the Duke prognostic CAD index, patients exhibiting increasing levels of coronary artery plaque tended to be older ($p < 0.0001$), male ($p < 0.0001$), diabetic ($p < 0.0001$), hyperlipidemic ($p < 0.0001$), and hypertensive ($p < 0.0001$) and had a higher prevalence of known coronary artery disease ($p < 0.0001$). Patients with higher levels of coronary plaque exhibited higher rates of typical angina but lower rates of dyspnea/fatigue ($p < 0.0001$). Individuals exhibiting more coronary plaque had higher pretest likelihood of significant coronary artery disease ($p < 0.0001$).

Clinical characteristics predicting near-term mortality. Survival was evaluated after a mean follow-up period of 15.3 ± 3.9 months (Table 2). At the completion of follow-up, a total of 39 (3.5%) deaths were reported. In univariable Cox models, older age, lack of treatment for dyslipidemia, and no family history of coronary heart disease were associated with mortality. Cumulative survival by pretest likelihood of CAD was 99.2% for low, 96.7% for intermediate (relative risk 3.78 [95% CI 1.1 to 12.8]; p = 0.033), and 91.5% for high likelihood patients (relative risk 8.0 [95% CI 2.4 to 27.2]; p = 0.001).

Univariable CCTA models estimating death from all causes. Patients who died had significantly higher visual estimates of coronary stenosis in the left main coronary artery and the proximal portions of the left anterior de-

Table 1 Clinical Characteristics of the 1,127 Patients in the Study Registry of CCTA Findings by the Duke Prognostic CAD Index for No to Minimal (<30%), Mild (30% to 49%), Moderate (50% to 69%), and Severe (≥70%) Coronary Stenosis

	<50% Stenosis	≥2 Mild Stenoses With Proximal CAD in 1 Artery or 1 Moderate Stenosis	2 Moderate Stenoses or 1 Severe Stenosis	3 Moderate Stenoses, 2 Severe Stenoses, or Severe Stenosis in Proximal LAD	3 Severe Stenoses or 2 Severe Stenoses in Proximal LAD	≥50% Left Main Stenosis	p Value
n	430	270	101	145	86	106	
Age (yrs)	56 ± 8	57 ± 9	59 ± 10	60 ± 10	64 ± 10	67 ± 10	<0.0001
Female gender	73%	69%	54%	39%	30%	47%	<0.0001
Diabetes	10%	17%	18%	22%	27%	30%	<0.0001
Family history of CAD	65%	60%	68%	63%	63%	69%	0.82
Hyperlipidemia	44%	52%	53%	55%	71%	69%	<0.0001
Hypertension	49%	64%	68%	59%	62%	68%	<0.0001
Current smoker	24%	36%	30%	32%	27%	26%	0.32
History of PAD/CVD	2%	2%	2%	2%	2%	4%	0.41
Known CAD	4%	16%	18%	24%	30%	20%	<0.0001
Cardiac arrhythmia	4%	7%	7%	3%	2%	6%	0.54
Positive stress test	2%	9%	5%	2%	1%	6%	0.015
Chest pain							<0.0001
Typical angina	2%	4%	5%	4%	2%	4%	
Atypical angina	66%	51%	52%	36%	33%	35%	
Asymptomatic	28%	40%	39%	50%	54%	48%	
Dyspnea/fatigue	5%	5%	5%	10%	12%	13%	
Pretest likelihood*							<0.0001
Low	40%	38%	31%	20%	19%	20%	
Intermediate	51%	55%	48%	53%	41%	41%	
High	9%	5%	22%	28%	39%	39%	

*Pretest likelihood is defined by age, gender, and anginal symptoms based on American College of Cardiology/American Heart Association Stable Angina Guidelines. Patients with known CAD were categorized as high likelihood.

CAD = coronary artery diesease; CCTA = coronary computed tomography angiography; CVD = cardiovascular disease; LAD = left anterior descending artery; PAD = peripheral artery disease.

scending, diagonal, circumflex, first marginal, and right coronary arteries (all $p < 0.001$) (Tables 3 and 4). All-cause death was predicted by moderate (Fig. 3) or severe (Fig. 4) coronary obstruction of luminal diameter in any coronary artery ($p = 0.007$ and $p < 0.001$, respectively), any severe proximal stenosis ($p = 0.001$), and any left main or left anterior descending artery stenosis ($p = 0.001$) (Fig. 5).

Table 2 Clinical Characteristics of the Study Cohort by Survival Status

	Alive (n = 1,088)	Dead (n = 39)	p Value
Age (yrs)	59.1 ± 10	71.5 ± 11	<0.001
Male gender	42.6%	48.7%	0.45
Diabetes	16.7%	17.9%	0.84
Hypertension	56.6%	53.8%	0.73
Dyslipidemia	52.9%	35.9%	0.04
Smoking history	26.7%	33.3%	0.37
Family history of CAD	66.3%	46.2%	<0.01
Pretest likelihood			0.001
Low	30.7%	7.7%	
Intermediate	47.6%	46.2%	
High	21.7%	46.2%	

Abbreviations as in Table 1.

The Duke prognostic CAD index was a significant predictor of all-cause mortality (Fig. 6). Also, clinical coronary artery plaque scores—segment stenosis score (Fig. 7) and segment involvement score (Fig. 8)—were significant predictors of all-cause death ($p < 0.001$ and $p < 0.001$, respectively).

Multivariable CCTA models estimating death from all causes. First, in multivariable Cox regression analysis, considering age, family history, and dyslipidemia, the presence of plaque in increasing numbers of coronary arteries, moderate (50% to 69% obstruction of coronary luminal diameter) and severe (≥70% obstruction of coronary luminal diameter) plaque, and plaque in the left main artery were independent predictors of all-cause mortality ($p < 0.001$ for both moderate and severe) (Figs. 3 and 4). Also, in multivariable risk-adjusted Cox proportional hazards models, subsets of patients with increasing plaque severity in the proximal left anterior descending artery exhibited higher rates of all-cause death ($p < 0.001$) (Fig. 5).

Second, in parallel multivariable Cox proportional hazards analysis adjusted for the same covariates, the Duke prognostic CAD index was a significant predictor of all-cause mortality (Fig. 6). In particular, subsets of patients exhibiting high risk of all-cause death (listed in increasing

Table 3 Presence and Severity of Plaque by CCTA in Different Coronary Arterial Segments

	Alive (n = 1,088)			Dead (n = 39)			
	n	%	Stenosis Score	n	%	Stenosis Score	p Value
Left main artery	158	14.5%	0.26 ± 0.70	18	46.2%	0.92 ± 1.13	<0.001
Left anterior descending artery							
Proximal	546	50.2%	1.15 ± 1.3	30	76.9%	1.97 ± 1.3	<0.001
Mid	359	33.0%	0.70 ± 1.1	17	43.6%	0.97 ± 1.3	0.12
Distal	55	5.1	0.10 ± 0.5	4	10.3%	0.21 ± 0.7	0.20
Diagonal artery							
Proximal	218	20.0%	0.44 ± 1.0	19	48.7%	1.18 ± 1.4	<0.001
Mid	57	5.2%	0.09 ± 0.4	5	12.8%	0.26 ± 0.75	0.03
Distal	18	1.7%	0.03 ± 0.2	2	5.1%	0.10 ± 0.5	0.08
Left circumflex artery							
Proximal	368	33.8%	0.72 ± 1.1	24	61.5%	1.51 ± 1.4	<0.001
Mid	154	14.2%	0.26 ± 0.7	8	20.5%	0.49 ± 1.0	0.04
Distal	23	2.1%	0.04 ± 0.3	3	7.7%	0.18 ± 0.6	0.008
Obtuse marginal artery							
Proximal	176	16.2%	0.34 ± 0.8	19	48.7%	1.18 ± 1.4	<0.001
Mid	50	4.6%	0.07 ± 0.3	5	12.8%	0.36 ± 1.0	<0.001
Distal	16	1.5%	0.02 ± 0.2	2	5.1%	0.10 ± 0.5	0.02
Right coronary artery							
Proximal	380	34.9%	0.74 ± 1.1	25	64.1%	1.59 ± 1.4	<0.001
Mid	229	21.0%	0.40 ± 0.8	11	28.2%	0.49 ± 0.9	0.50
Distal	75	6.9%	0.14 ± 0.6	4	10.3%	0.21 ± 0.7	0.50
Total			5.5			11.7	

Abbreviations as in Table 1.

risk) include: 1) individuals with 2 segments exhibiting moderate plaque or 1 segment exhibiting severe plaque ($p = 0.013$); 2) individuals with 3 segments exhibiting moderate plaque, 2 segments exhibiting severe plaque, or severe plaque in the proximal left anterior descending artery ($p = 0.002$); 3) individuals with 3 segments exhibiting severe plaque or 2 segments exhibiting severe plaque that includes the proximal left anterior descending artery ($p = 0.001$); and 4) moderate or severe plaque of the left main artery ($p < 0.0001$) (Fig. 6).

Finally, in multivariable Cox regression analyses, adjusting for age, family history, and dyslipidemia, clinical coronary artery plaque scores were independent predictors of all-cause death: segment stenosis score ($p = 0.01$), segment involvement score ($p < 0.01$), and triple-vessel plaque score ($p = 0.05$). When individuals were partitioned into groups with a segment stenosis score or segment involvement score of ≤5 versus >5, those with higher scores had greater all-cause mortality (Figs. 7 and 8). At the mean follow-up interval of 15 months for this study population, the absolute difference in mortality rate for individuals with scores of >5 versus ≤5 was 6.6% versus 1.6%, respectively, for the segment severity score (absolute difference 5.0%; $p = 0.05$) and 8.4% versus 2.5%, respectively, for the segment involvement score (absolute difference 5.9%; $p = 0.05$).

To examine effect modification, interaction terms were used for variables that showed significant main effects. Although most CCTA variables demonstrated the same pattern of relationship in all age groups, there was significant positive interaction with increasing age and the seg-

Table 4 Univariable and Multivariable Cox Models of CCTA Results for All-Cause Mortality*

CCTA Result	Univariable Hazard Ratio (95% CI)	p Value	Risk-Adjusted Hazard Ratio (95% CI)	p Value
Any moderate stenosis	2.89 (1.32–6.27)	0.007	1.37 (0.60–3.11)	NS
Any severe stenosis	4.31 (1.98–9.37)	<0.001	2.14 (0.95–4.81)	0.07
Moderate or severe coronary stenosis (per segment)	1.07 (1.04–1.10)	<0.001	1.05 (1.02–1.09)	<0.01
Any severe proximal stenosis	3.04 (1.62–5.71)	0.001	1.44 (0.74–2.81)	NS
Any left main stenosis	5.03 (2.68–9.43)	0.001	2.65 (1.37–5.12)	<0.01
Segment stenosis score (per segment severity)	1.99 (1.48–2.67)	<0.0001	1.52 (1.09–2.14)	0.01
Segment involvement score (per segments involved)	1.23 (1.13–1.34)	<0.0001	1.16 (1.05–1.28)	0.004
Three-vessel coronary plaque, any severity	4.15 (2.10–8.20)	<0.001	2.04 (0.99–4.20)	0.05

*Multivariable model adjusted for age, dyslipidemia, and family history.
CI = confidence interval; other abbreviations as in Table 1.

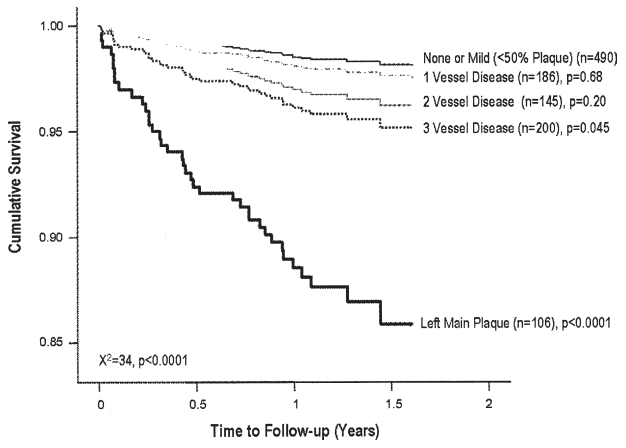

Figure 3 **Cumulative Survival in Patients With Moderate (>50%) Plaque by CCTA**

Risk-adjusted p < 0.001 (controlling for age, family history, and dyslipidemia). CCTA = coronary computed tomographic angiography

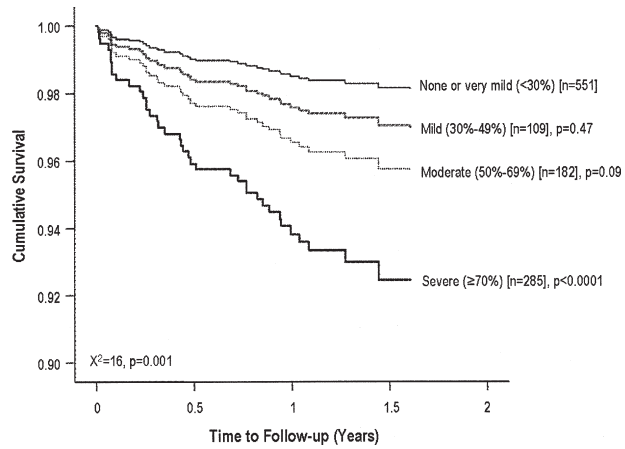

Figure 5 **Cumulative Survival in Patients With Proximal Left Anterior Descending Artery Plaque by CCTA**

Risk-adjusted p < 0.001 (controlling for age, family history, and dyslipidemia). CCTA = coronary computed tomographic angiography.

ment stenosis score (p = 0.01) and the segment involvement score (p = 0.01). Accounting for the significant interaction with increasing age rendered the triple-vessel plaque score nonsignificant as a predictor of death (p = 0.07). In multivariable analysis, when a partition cutoff age of 61 years was used, segment stenosis score and segment involvement score remained independent predictors of all-cause mortality and no longer significantly interacted with age.

Patient subset analyses. We examined the predictive value of CCTA findings in several other patient subgroups. These included patients without any coronary artery plaque, patients without left main plaque, and patients without proximal left anterior descending artery plaque (Table 5). Individuals without evident left main plaque, and individuals who exhibited no coronary plaque in the proximal left anterior descending artery exhibited minimally lower rates of all-cause mortality (1.6% to 2.2%) than the entire population (3.5%). Of note, the 333 patients with no detectable coronary plaque by CCTA had a much lower rate of death than the remainder of the population: 0.3% versus 4.8%, respectively (hazard ratio 0.12, 95% CI 0.02 to 0.89; p = 0.04) (Table 5). Patients without any left main coronary artery plaque exhibited much lower rates of mortality than those with left main coronary plaque (p < 0.001). The negative predictive values for all-cause mortality of the absence of any plaque, absence of left main plaque, or absence of plaque in the proximal left anterior descending artery were 99.7%, 97.8%, 98.4%, respectively.

In the present study, follow-up was available in 10 of 39 individuals who died. Invasive coronary angiography was performed in 2 of these 10 individuals, with 1 undergoing percutaneous intervention and the other undergoing coronary artery bypass surgery. The deaths of these individuals occurred 93 days and 269 days, respectively, after their procedures. In the remaining 8 individuals, no coronary angiography or coronary artery bypass surgery was performed in the follow-up period.

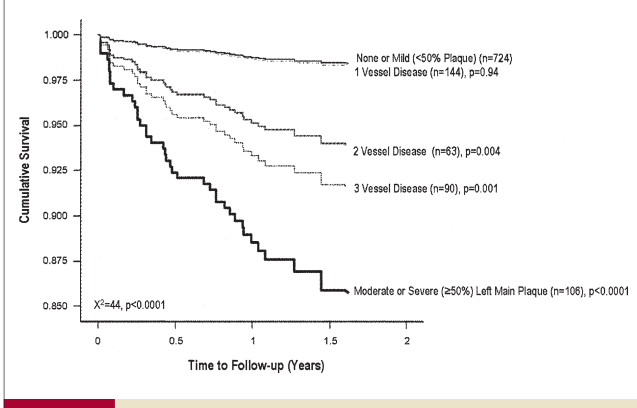

Figure 4 **Cumulative Survival in Patients With Severe Plaque or Moderate/Severe Left Main Plaque by CCTA**

Risk-adjusted p < 0.001 (controlling for age, family history, and dyslipidemia). CCTA = coronary computed tomographic angiography.

Discussion

The primary results from our registry reveal that measures of angiographic disease extent, location, and distribution detected by 3 distinct CCTA grading systems significantly predicted the risk of all-cause death in individuals presenting with chest symptoms. Numerous prognostically valuable CCTA indices were identified. These results extend previous results reported with invasive X-ray angiography.

First, visual estimates of moderate to severe coronary stenosis by CCTA were associated with a higher mortality risk compared with less extensive lesions, and the risk of death increased proportionally with increasing number of

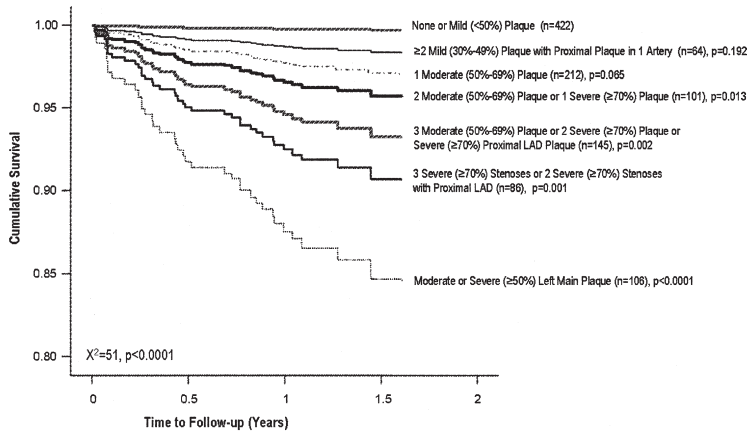

Figure 6 **Cumulative Survival in Patients Exhibiting Plaque by the Duke Prognostic Coronary Artery Disease Index**

Risk-adjusted p < 0.001 (controlling for age, family history, and dyslipidemia). LAD = left anterior descending artery.

major epicardial vessels involved. Higher risk was also associated with proximal disease, especially when identified in the left anterior descending coronary artery. Patients with a visual estimate of ≥50% stenosis had the worst survival (85%) at 1.5 years, compared with a mortality rate of 0.3% for patients with <50% stenosis.

Second, using a modified Duke prognostic coronary artery score, incrementally higher overall risk of death was identified in individuals with 2 moderate or 1 severe stenosis, 3 moderate or 2 severe stenoses, or 3 severe or 2 severe stenoses with proximal left anterior descending artery involvement. Patients exhibiting moderate or severe left main coronary plaque by CCTA fared the worst.

Finally, clinical coronary artery plaque scores—namely, segment stenosis score, segment involvement score, and 3-vessel plaque score assessing overall coronary artery plaque extent, distribution, and number of coronary vessels involved—were all predictive of greater rates of all-cause death.

Each of these high-risk markers significantly predicted overall mortality independently of other traditional clinical cardiovascular risk factors, underscoring the incremental value of CCTA examination of coronary artery anatomy to assess future risk of symptomatic individuals without active acute coronary syndromes.

Although the identification of a positive CCTA conferring increased risk is of great significance, whether a negative CCTA coronary angiogram can safely "rule out" future risk in symptomatic individuals is of equal, or perhaps greater, import. In the present study, we found that the absence of any coronary artery plaque, of any left main artery plaque, or of any proximal left anterior descending artery

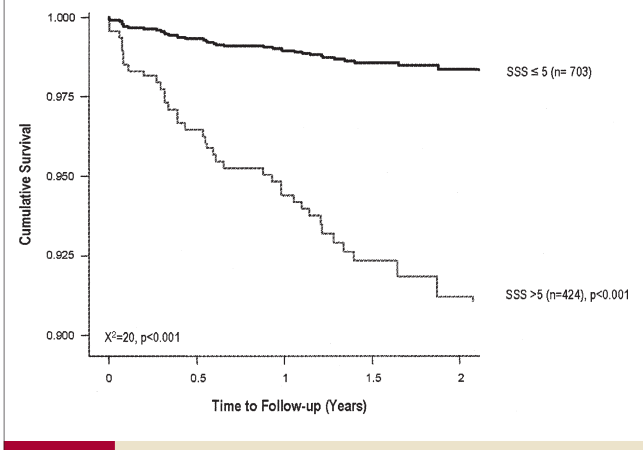

Figure 7 **Cumulative Survival in Patients With or Without SSS of >5**

Risk-adjusted p < 0.001 (controlling for age, family history, and dyslipidemia). SSS = segment stenosis score.

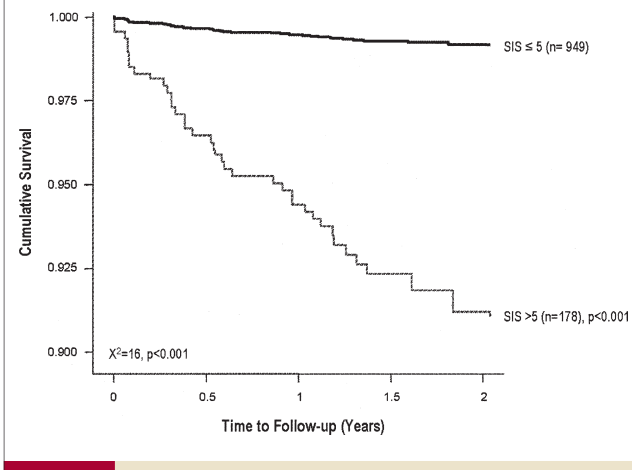

Figure 8 **Cumulative Survival in Patients With or Without SIS of >5**

Risk-adjusted p < 0.001 (controlling for age, family history, and dyslipidemia). SIS = segment involvement score.

Table 5 Prognostic Value of CCTA Results in Subsets of Population

Risk Factor	Patients (n)	Deaths (n)	%
Coronary artery plaque score = 0	333	1	0.3%
No left main plaque	951	20	2.1%
No proximal LAD plaque	551	9	1.6%

Abbreviations as in Table 1.

plaque was associated with high negative predictive values (97.8% to 99.7%) for near-term all-cause death.

The prognostic utility of CCTA in evaluation of patients presenting with chest symptoms documented by the present study should be placed in the context of previously reported results from nuclear and echocardiographic stress imaging (11,12). Several indices from these imaging modalities have been identified as markers of high risk, traditionally defined as a >3% annual mortality rate. These include severe resting left ventricular systolic dysfunction (left ventricular ejection fraction <35%), segmental wall motion abnormalities, and severe perfusion abnormalities. The absolute all-cause mortality rate at the end of 15 months of follow-up was about 5% higher with a segment stenosis score >5 versus ≤5, with an even larger 6% absolute difference associated with higher segment involvement scores (Figs. 7 and 8). These rates correspond to 12-month increments of 4.4% and 4.7%, respectively, indicating that these CCTA indices equal or exceed the present conventional definitions of "high risk."

The prognostic value of CCTA should also be placed in the context of earlier investigations examining coronary artery stenosis and adverse cardiovascular outcomes. Earlier studies have demonstrated that myocardial infarctions most often occur at lesion sites that have no significant stenosis (i.e., luminal stenosis <50%); in contrast, significant stenoses (i.e., luminal stenosis >70%) comprise only a minority of myocardial infarctions (13). Indeed, this is likely due to the increased prevalence of nonobstructive coronary artery lesions over obstructive coronary artery lesions. The present investigation supports these earlier data. In multivariate analysis, the segment involvement score, a measure of the overall number of coronary segments exhibiting plaque regardless of stenosis severity, was significantly predictive of all-cause mortality.

Recent data are emerging that support the notion of the prognostic value of CCTA. In a study of 100 patients, Pundziute et al. (14) examined the prognostic value of CCTA coronary plaque assessment for the combined end point of cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, and revascularization. Similar to the results in the present study, obstructive plaque, particularly in the left main or left anterior descending arteries, conferred the highest risk. Conversely, a normal CCTA was associated with a 0% event rate. These findings are in keeping with the present data and reinforce the value of coronary plaque identification by CCTA.

Because the spatial resolution of the CT scanner utilized in the current study was limited to 0.625 mm, the ability to identify atherosclerotic plaques causing minimal stenosis (e.g., <5%) was difficult. However, the detection of minimal stenosis appears to possess limited clinical relevance. When individual coronary artery plaque is considered, increasing luminal stenosis severity predicts higher event rates. In a 5-year follow-up of the CASS (Coronary Artery Surgery Study), comparison of coronary segments exhibiting minimal (<5% stenosis), mild (5% to 49% stenosis), moderate (50% to 80%) and severe plaque (81% to 95% stenosis) revealed 0.7%, 2.3%, 10.1%, and 23.6% of respective segments progressing to total occlusion (15). These findings confirm the notion that initially identified lesion severity is vital for predicting progression of coronary artery disease. Our clinical outcomes corroborate these angiographic findings, because increasing numbers of segments exhibiting moderate and severe stenosis were more predictive of death than minimal or mild stenosis.

Study limitations. The present study is retrospective and was performed at a single center, which makes it uncertain whether the results will be equally applicable to other populations. The clinical demographic information, cardiac risk profile, and symptom complex were procured prospectively for each individual, and the end point was all-cause death, which disencumbers the current investigation from information bias relating to confounders or ascertainment.

The major outcome of the present analysis was all-cause mortality, with the etiology of death being of uncertain cause. Extensive literature is available as to death misclassification (16). However, cardiovascular disease remains the leading cause of death in this type of patient cohort and, as such, our results will have similarities to cardiac-specific models. Whether CCTA is prognostically valuable for the prediction of cardiac death, ST-segment elevation myocardial infarction, or other less stringent end points, such as non–ST-segment elevation myocardial infarction or urgent target vessel revascularization, will require larger multicenter studies.

The prevalence of individuals exhibiting 3-vessel, left main, and proximal left anterior descending artery plaque is high in the current study. Which of these individuals received specific therapies is not fully known. These data represent actual clinical practice patterns from numerous physicians referring patients for CCTA at a single center. As such, the reasons a particular individual may or may not have undergone a specific treatment, or whether survivors fared better because of more optimal treatment and nonsurvivors fared poorly because of inadequate treatment, are not known.

In the present study, follow-up was available in 10 of 39 individuals who died. Invasive coronary angiography was performed in 2 of these 10 individuals, with deaths of these individuals occurring 93 and 269 days after their procedures. In the remaining 8 individuals, no coronary angiography or coronary artery bypass surgery was performed in the follow-up period. These partial results support the notion that increased death did not occur as a complication of cardiac procedures but from other causes.

The present study does not measure overall plaque volumes. Current-generation CCTA scanners are limited to

a 0.5- to 0.8-mm isotropic voxel spatial resolution, which permits partial volume averaging artifact from calcified plaque. As such, calcified plaque is often overestimated, and earlier data suggest that noncalcified plaque may be consistently underestimated (17). Recent data indicate that current-generation 64-detector row CT scanners are less prone to the over- and underestimation of coronary plaque volumes. Although a few studies to date have attempted to measure coronary plaque volumes, no accurate software currently exists for the automated quantification of noncalcified and mixed plaque volumes in large-scale populations.

Conclusions and Clinical Implications

Multidetector CCTA performed in a large group of patients presenting with chest symptoms successfully identified patients at 5% to 6% higher 15-month absolute risk of all-cause death. Our sample is sufficiently powered ($\beta \geq 0.80$; $\alpha = 0.05$) to detect differences in mortality between patients with no to mild plaque compared with those with 3-vessel or left main disease. The CCTA scores measuring coronary plaque severity, global coronary artery plaque extent, coronary artery plaque distribution, presence of left main or left anterior descending artery plaque, and 3-vessel coronary artery plaque were all predictive of death. Patients with normal coronary artery plaque scores, absence of left main plaque, or absence of proximal left anterior descending artery plaque have a low risk of death during short- to intermediate-term follow-up. These results, taken in combination, suggest that CCTA coronary angiography may be a prognostically useful noninvasive imaging modality for the evaluation of patients with chest symptoms. The present results reveal the prognostic value of CCTA findings and provide the first mortality data which may be used to guide clinical application of this new technology.

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