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Authors

Ostrom, Matthew P
Gopal, Ambarish
Ahmadi, Naser
et al.

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Mortality Incidence and the Severity of Coronary Atherosclerosis Assessed by Computed Tomography Angiography

Matthew P. Ostrom, MD, Ambarish Gopal, MD, Naser Ahmadi, MD, Khurram Nasir, MD, MPH, Eric Yang, MD, Ioannis Kakadiaris, PHD, Ferdinand Flores, BS, Song S. Mao, MD, Matthew J. Budoff, MD

Torrance, California

Objectives This study investigated whether cardiac computed tomography angiography (CTA) can predict all-cause mortality in symptomatic patients.

Background Noninvasive coronary angiography is being increasingly performed by CTA to assess for obstructive coronary artery disease (CAD), and minimal outcome data exist for coronary CTA. We have utilized a cohort of symptomatic patients who underwent electron beam tomography to allow for longer follow-up (up to 12 years) than currently available with newer 64-slice multidetector-row computed tomography studies.

Methods In all, 2,538 consecutive patients who underwent CTA by electron beam tomography (age 59 ± 14 years, 70% males) without known CAD were studied. Computed tomographic angiography results were categorized as significant CAD (≥50% luminal narrowing), mild CAD (<50% stenosis), and normal coronary arteries. Multivariable Cox proportional hazards models were developed to predict all-cause mortality. Risk-adjusted models incorporated traditional risk factors for coronary disease and coronary artery calcification (CAC).

Results During a mean follow-up of 78 ± 12 months, the death rate was 3.4% (86 deaths). The CTA-diagnosed CAD was an independent predictor of mortality in a multivariable model adjusted for age, gender, cardiac risk factors, and CAC ($p < 0.0001$). The addition of CAC to CTA-diagnosed CAD increased the concordance index significantly (0.69 for risk factors, 0.83 for the CTA-diagnosed CAD, and 0.89 for the addition of CAC to CAD, $p < 0.0001$). Risk-adjusted hazard ratios for CTA-diagnosed CAD were 1.7-, 1.8-, 2.3-, and 2.6-fold for 3-vessel nonobstructive, 1-vessel obstructive, 2-vessel obstructive, and 3-vessel obstructive CAD, respectively ($p < 0.0001$), when compared with the group who did not have CAD.

Conclusions The primary results of our study reveal that the burden of angiographic disease detected by CTA provides both independent and incremental value in predicting all-cause mortality in symptomatic patients independent of age, gender, conventional risk factors, and CAC. (J Am Coll Cardiol 2008;52:1335–43) © 2008 by the American College of Cardiology Foundation

Cardiovascular disease remains the leading cause of death in the U.S. (1). Current guidelines recommend that primary care physicians appropriately screen, identify, and implement various treatment interventions in patients at intermediate and high risk for coronary heart disease (CHD). Standard CHD risk factor assessment in combination with traditional noninvasive stress imaging modalities, and more recently, coronary artery calcium score (CACS), are able to predict those patients who are at risk for coronary atherosclerosis. Invasive coronary angiography remains the gold standard for detection of anatomic coronary disease. Coronary computed tomography angiography (CTA) is an emerging technology that has the potential to become a powerful tool in the gamut of noninvasive modalities to identify and prognosticate those patients with coronary artery disease (CAD).

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Cardiac computed tomography is a robust technology for the noninvasive assessment of a spectrum of cardiovascular disease processes. Considerable advances have been made in the field of cardiac imaging, particularly in the ability to

From the Division of Cardiology, Department of Medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California. Dr. Budoff is on the Speakers' Bureau for General Electric. This study complies with current ethical considerations and was approved by the Institutional Review Board.

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Abbreviations and Acronyms

AUC = area under the curve
CAC = coronary artery calcification
CACS = coronary artery calcium score
CAD = coronary artery disease
CHD = coronary heart disease
CI = confidence interval
CTA = computed tomography angiography
EBT = electron beam tomography
HR = hazard ratio
MDCT = multidetector-row computed tomography
ROC = receiver-operator characteristic

view the coronary artery lumen with sufficient diagnostic accuracy (2). Traditionally, noninvasive coronary angiography has been an arduous process given the rapid cardiac motion, small size of the vessels, tortuous anatomical patterns, concomitant calcification, and overlying veins. These challenges require imaging modalities used for noninvasive coronary angiography to possess both high temporal and spatial resolution. Cardiac computed tomography has developed rapidly and is now poised to become a noninvasive method to evaluate the lumen of the coronary arteries. Original CTA studies were performed with electron beam tomography (EBT) (3). This current study utilized a cohort of symptomatic patients who underwent EBT to allow for longer follow-up (up to 12 years) than currently available with newer 64-slice multidetector-row computed tomography (MDCT) studies. Computed tomographic angiography, with both EBT and MDCT, has excellent negative predictive value and is an invaluable tool in evaluating symptomatic patients with an intermediate likelihood of CAD. The ability to visualize coronary plaque (using both noncontrast and contrast computed tomography [CT]) is promising, but fraught with some limitations (i.e., limited reproducibility, inability to distinguish between fibrous and lipid laden plaque). Despite very high negative predictive values for both obstructive disease and short-term cardiac events, use of CTA in asymptomatic patients as a screening test is currently not recommended because of its requirements for both significant radiation and contrast administration. The purpose of this study was to evaluate the incremental prognostic value of atherosclerotic burden and degree of stenotic disease on CTA as well as of CAC over traditional risk factors in predicting all-cause mortality in an outpatient setting with long-term follow-up.

Methods

Patient population. This study sample included 2,538 consecutive patients, 1,774 men and 764 women with an average age of 59 years (range 36 to 89 years), who were physician referred for evaluation of suspected CAD. Patients were excluded if found to have an irregular heart rate, allergy to contrast medium, or impaired renal function. Patients referred for CTA evaluation with known prior CAD, including prior myocardial infarction, coronary artery disease on prior catheterization, or prior revascularization, were also excluded. After receiving a full explanation about the procedure, all eligible patients provided signed written informed consent before the CTA.

Subjects were given a risk-factor questionnaire to assess ethnicity and cardiovascular risk factors. The presence and number of risk factors were calculated on the basis of the National Cholesterol Education Program guidelines (4). Risk factors included age (men >45 years, women >55 years), current cigarette smoking, diabetes mellitus, history of premature coronary disease in a first-degree relative (men age <55 years, women age <65 years), hypertension, and hypercholesterolemia. In addition, body mass index data were collected.

CTA protocol. The studies were performed with a C300 EBT Scanner (GE-Imatron, South San Francisco, California). A noncontrast scan acquiring 35 slices was initially performed craniocaudally (3-mm section thickness without gap) to obtain CACS. After this, a flow study was performed (8-mm section thickness with 4-mm intersection gap) to obtain the circulation time (the time from the contrast injection in the vein to the peak visualization of the ascending aorta). The circulation time (average of 19 s in this study) was determined by a time-density curve at the aortic root, using 15 to 20 ml nonionic contrast injection (Iopamidol 370, Bracco Diagnostics, Plainsboro, New Jersey). To facilitate adequate breath hold, the patients were connected to an oxygen mask and asked to hyperventilate before breath hold during scanning. Atropine was used to increase heart rates when heart rates were <55 beats/min, and nitroglycerine (0.4 mg sublingual) was used in all studies unless contraindicated.

All CTA images utilized a 100-ms acquisition per image and were reconstructed with 512 × 512 matrix, 18-cm field of view, yielding a voxel size of 0.34 × 0.34 × 3.0 mm^3. Nonionic contrast was administered through an antecubital vein with an injection rate of 4 ml/s and total volume of 120 to 160 ml. Image acquisition was triggered to the patient's electrocardiogram. Electrocardiogram-triggering corresponding to a fixed point after the R-wave (rate-adjusted trigger) to approximate end systole was done (5). The delay time after the R-wave was varied on the basis of the resting heart rate just before the scan, previously demonstrated to improve both calcium reproducibility and diagnostic accuracy of CTA (6–8). The trigger delay was 350 ms for heart rates <60 beats/min, 320 ms for 61 to 70 beats/min, 300 ms for 71 to 80 beats/min, 280 ms for 81 to 90 beats/min, 260 ms for 91 to 100 beats/min, and 246 ms for heart rates >100 beats/min. The data obtained by the scanner for the analysis were transferred and processed at a dedicated, commercially available image workstation (Insight, Neo Imagery Technology, Industry, California).

CTA study interpretation and reporting. All studies were analyzed by an experienced reader, blinded to all clinical variables, history, and patient demographics. Axial data (Fig. 1), as well as maximum intensity and volume-rendered

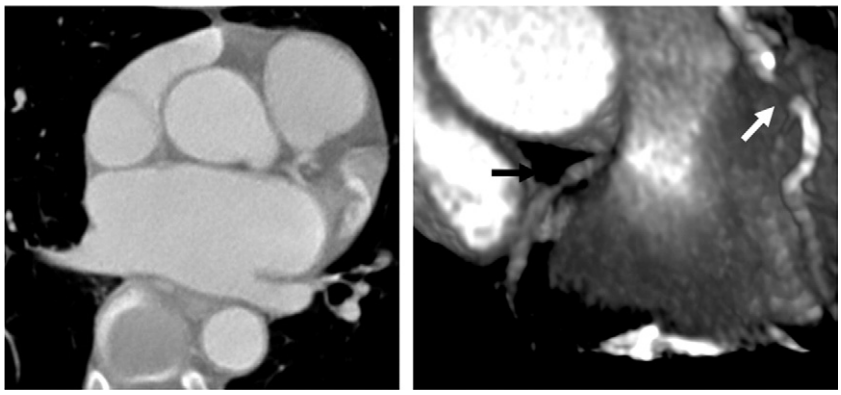

Figure 1 Noninvasive Angiography

Noninvasive angiography shows axial slice **(right)** and volume-rendered images **(left)**. The volume-rendered image demonstrates a high-grade stenosis of both the left anterior descending artery **(white arrow)** and the right coronary artery **(black arrow)**.

subsets were used for analysis (Fig. 2). On the basis of the CTA results, the patients were assigned to 1 of the following groups: normal study (normal coronary arteries), mild nonobstructive coronary artery disease (low-grade atherosclerosis of the coronary artery or arteries and lesions <50%), or significant obstructive coronary artery disease (lesions ≥50%). Because of the higher spatial resolution of EBT, no segments were deemed uninterpretable due to motion. Dense calcifications were treated as nonobstructed segments for the purpose of analysis. Within each of the groups, the patients were further subdivided with respect to the number of vessels diseased: 1-, 2-, or 3-vessel disease. Three-vessel disease was defined as either obstructive CAD in all 3 of the major epicardial vessels (right coronary, left anterior descending, and left circumflex arteries) or right coronary artery and left main artery disease.

CACS. Coronary artery calcium was defined as a plaque of at least 3 contiguous pixels (area = 1.03 mm^2) with attenuation of 130 HU or greater. The quantitative CACS was calculated according to the Agatston method (9,10). The total CACS was calculated from the sum of each of the 4 major epicardial vessels (left main, left anterior descending, circumflex, and right coronary arteries).

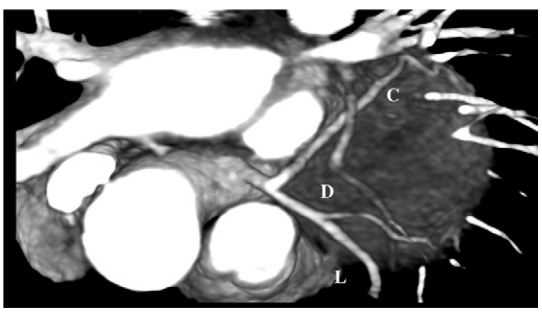

Figure 2 Volume-Rendered CTA Image

A volume-rendered study demonstrating normal left anterior descending artery (L), diagonal (D), and circumflex (C) branches. CTA = computed tomography angiography.

End points and definitions. Epidemiologic methods for follow-up included ascertainment of events blinded to CTA results. The primary end point was occurrence of all-cause mortality, which was verified by querying the Social Security Death Index. Death status was ascertained in all patients (i.e., 100% follow-up). Patients who underwent cardiovascular scanning were followed up for a mean of 6.5 ± 1 years.

Statistical analysis. Analyses were performed with SPSS, version 15 (SPSS Inc., Chicago, Illinois). All continuous data are presented as a mean value ± SD, and all categorical data are reported as a percentage or absolute number. Kruskal-Wallis tests and analysis of variance tests were used to assess differences between groups. Kaplan-Meier survival curves were constructed for CTA-diagnosed CAD and were compared with the log-rank test.

The effect of the CAD diagnosed by cardiac CT angiography on all-cause mortality was determined using Cox regression analysis. After adjustment for age, gender, diabetes mellitus, hypertension, hypercholesterolemia, family history of premature CHD, and coronary artery calcification, the forward stepwise model was used to determine independent predictors for all-cause mortality. Hazard ratios (HRs) and confidence intervals (CIs) were calculated. Receiver-operator characteristic (ROC) curves were constructed for 3 models: model I, a comparative analysis of age and other cardiac risk factors; model II, CTA-diagnosed CAD; and model III, a combination of CTA-diagnosed CAD and CACS. Area under the curve (AUC) was calculated to predict the ability of each model to detect all-cause mortality, with an AUC value of 0.50 indicating no accuracy and a value of 1.00 indicating maximal accuracy.

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Table 1 Association of Cardiovascular Risk Factors and Severity of CAD Diagnosed by CTA

Variable	No CAD (n = 1,085)	CTA-Diagnosed CAD: 1-Vessel Nonobstructive (n = 750)	2-Vessel Nonobstructive (n = 238)	3-Vessel Nonobstructive (n = 72)	1-Vessel Obstructive (n = 310)	2-Vessel Obstructive (n = 68)	3-Vessel Obstructive (n = 15)	p Value
Age (yrs)	54 ± 15	61 ± 11	61 ± 10	65 ± 12	64 ± 11	62 ± 11	64 ± 9	0.0001
Gender (male)	61% (662)	73% (547)	77% (183)	78% (56)	81% (251)	82% (56)	87% (13)	0.0001
Hypertension	35% (380)	44% (330)	47% (111)	43% (31)	50% (155)	54% (37)	67% (10)	0.0001
Diabetes mellitus	11% (119)	14% (105)	13% (31)	13% (9)	19% (59)	26% (18)	17% (3)	0.001
Hypercholesterolemia	38% (412)	54% (405)	68% (162)	46% (33)	60% (186)	56% (38)	58% (9)	0.0001
History of smoking	5% (54)	7% (52)	8% (19)	7% (5)	8% (25)	4% (3)	20% (3)	0.12
Family history of CHD	35% (380)	47% (325)	53% (126)	46% (33)	42% (130)	51% (35)	67% (10)	0.0001
BMI (kg/m^2)	28.1 ± 2.3	32.4 ± 2.5	27.9 ± 3.4	27.6 ± 3.4	28.4 ± 3.2	28.6 ± 2.5	29 ± 3.1	0.9
CACS	—	343 ± 40	466 ± 34	738 ± 70	590 ± 35	748 ± 78	1,030 ± 97	0.0001
All-cause mortality	18	20	11	5	22	7	3	0.0001
Survival rate	98.3%	97.3%	95.4%	93.1%	92.9%	89.7%	80%	0.0001

BMI = body mass index; CACS = coronary artery calcium score; CAD = coronary artery disease; CHD = coronary heart disease; CTA = computed tomography angiography.

Results

Clinical characteristics. Overall, the study population consisted of 2,538 patients; 70% were men and the mean age was 59 ± 14 years (range 36 to 89 years). The majority of the patients were Caucasian (n = 1,893, 75.4%); 10.2% (n = 259) were African American; 9.5% (n = 241) Asian; 3.3% (n = 84) Hispanic; and 2.4% (n = 61) other. Of the studied patients, 1,085 (43%) had no CTA evidence of disease, 1,060 (42%) had nonobstructive CAD (<50% stenosis severity), and 393 (15%) had obstructive CAD. Patients with increasing severity of CAD tended to be older, male, hypertensive, hypercholesterolemic, and have a family history of premature CHD ($p < 0.0001$) and diabetes ($p < 0.001$). The CACS also increased with severity of CTA-diagnosed CAD ($p < 0.0001$) (Table 1).

Survival by absence or presence of CAD. In the 15-year follow-up period, 86 all-cause deaths were observed, with an event rate of 3.4% (86 of 2,538). Overall survival was 98.3% and 95.3% among the cohort when grouped according to the absence or presence of CAD, respectively ($p = 0.0001$) (Fig. 3). The unadjusted and adjusted HRs for mortality are shown in Table 2. After adjustment for age, gender, hypertension, diabetes mellitus, hypercholesterolemia, history of smoking, family history of CHD, and baseline CAC, the stepwise multivariable model showed that the presence of coronary atherosclerosis was an independent predictor of mortality and had

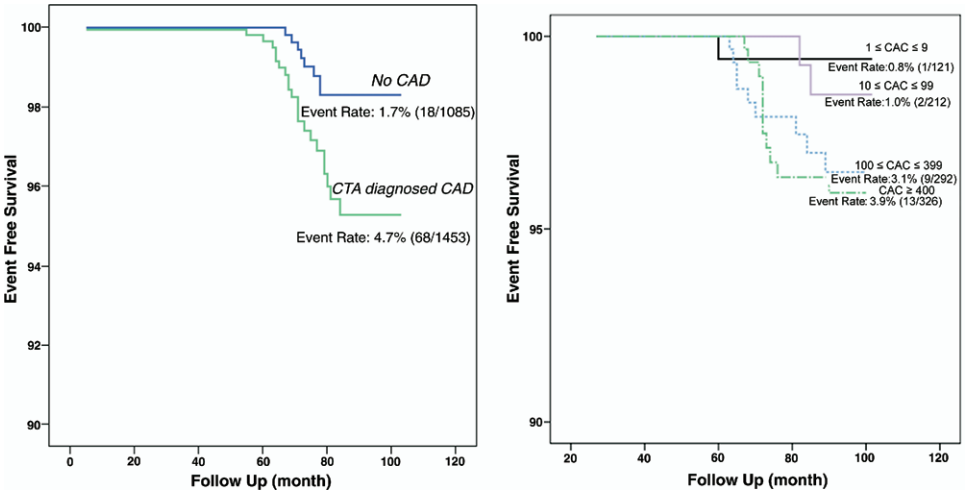

Figure 3 Event-Free Survival by CTA

Risk-adjusted event-free survival by computed tomography angiography (CTA)-diagnosed coronary artery disease (CAD) **(left)**, and coronary artery calcium score (CACS) in the group with CTA-diagnosed nonobstructive CAD **(right)**. Risk adjustment included the following variables: age, gender, hypertension, hypercholesterolemia, diabetes mellitus, smoking, family history of premature coronary heart disease **(right)**, and CACS **(left)**. The presence of CTA-diagnosed CAD increased the risk of all-cause mortality. In patients with CTA-diagnosed nonobstructive CAD, increasing CACS was associated with decreased survival.

Table 2 Hazard Ratios of Death and 95% Confidence Interval (in Parentheses) According to CAD Status

Models	Unadjusted Model	Risk Factors Adjusted Model	Risk Factors and CACS Adjusted Model
With CTA-diagnosed any CAD	2.98 (1.78–5.01), p = 0.0001	2.69 (1.59–4.53), p = 0.0001	2.51 (1.47–4.25), p = 0.0001
Without CTA-diagnosed CAD	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
1-vessel nonobstructive disease	1.13 (0.56–2.28), p = 0.73	1.03 (0.30–1.75), p = 0.69	0.97 (0.47–1.94), p = 0.94
2-vessel nonobstructive disease	1.19 (0.72–1.95), p = 0.49	1.02 (0.68–1.9), p = 0.52	0.98 (0.58–1.66), p = 0.96
3-vessel nonobstructive disease	1.82 (1.37–2.40), p = 0.0001	1.77 (1.34–2.34), p = 0.0001	1.74 (1.49–2.05), p = 0.0001
1-vessel obstructive disease	1.89 (1.51–2.38), p = 0.0001	1.87 (1.4–2.51), p = 0.0001	1.82 (1.45–2.3), p = 0.0001
2-vessel obstructive disease	2.44 (1.96–3.03), p = 0.0001	2.37 (1.91–2.93), p = 0.0001	2.31 (1.86–2.89), p = 0.0001
3-vessel obstructive disease	2.63 (2.01–3.39), p = 0.0001	2.61 (2–3.37), p = 0.0001	2.59 (1.99–3.68), p = 0.0001

Relative risk adjustment included age, gender, hypertension, hyperlipidemia, diabetes mellitus, family history of premature coronary heart disease, and smoking. Abbreviations as in Table 1.

significant incremental value over clinical risk factors and CAC (HR: 2.51, 95% CI: 1.47 to 4.25, p = 0.0001).

Survival by severity of CAD. Patients with CAD detected by CTA were further partitioned into subgroups of obstructive (≥50% stenosis by CTA) and nonobstructive (<50% stenosis by CTA) disease and quantified as to number of epicardial vessels involved. Survival rates were 97.3%, 95.4%, and 93.1% for patients with 1-, 2-, and 3-vessel nonobstructive CAD, respectively. Survival rates were 92.9%, 89.7%, and 80% for patients with 1-, 2-, and 3-vessel obstructive CAD, respectively (Fig. 4). Unadjusted and adjusted HRs for mortality are shown in Table 2. The classification of CAD severity by 3-vessel nonobstructive CAD and 1-, 2-, and 3-vessel obstructive CAD had corresponding HRs of 1.74, 1.82, 2.31, and 2.59 (p = 0.0001), demonstrating the additional prognostic predictive power of severity of CAD.

Survival by CACS in patients with nonobstructive CAD. Among the 1,060 patients with CTA-diagnosed nonobstructive CAD, coronary artery calcium was found to be an independent predictor of all-cause mortality. Six percent of patients had scores of zero with nonobstructive disease present on contrast-enhanced EBT. Patients with nonobstructive CAD were divided into 4 groups according to CACS: 1 to 9 (n = 121), 10 to 99 (n = 212), 100 to 399 (n = 292), and ≥400 (n = 326); the corresponding survival rates were 99.2%, 99%, 96.9%, and 96.1% (Fig. 3). After adjustment for age, gender, hypertension, diabetes mellitus, hypercholesterolemia, history of smoking, and family history of CHD, the stepwise multivariable model (Cox regression) showed that a CACS 100 to 399 and ≥400 were independent predictors of mortality in patients with nonobstructive CAD and had significant incremental value (HR: 5.1, 95% CI: 1.6 to 14.56, p = 0.003; HR: 6.2, 95%

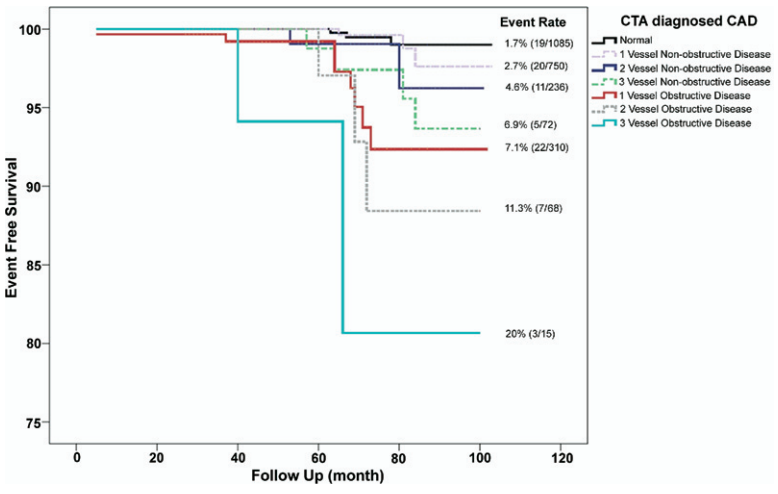

Figure 4 CTA Event-Free Survival

Risk-adjusted event-free survival by computed tomographic angiography (CTA)-diagnosed coronary artery disease (CAD) stratified by severity of disease and number of diseased coronary arteries. Risk adjustment included the following variables: age, gender, hypercholesterolemia, diabetes mellitus, smoking, hypertension, family history of premature coronary heart disease, and coronary artery calcium score. All-cause mortality increased significantly by increasing severity of CTA-diagnosed CAD and number of diseased coronary arteries.

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Table 3 Hazard Ratios of Death and 95% Confidence Interval (in Parentheses) Across Groups of Patients With Increasing CACS Among Those With CTA-Diagnosed Nonobstructive CAD (n = 1,060)

Models	Unadjusted Model	Risk Factors Adjusted RR
CACS 1–9	1.0 (Reference)	1.0 (Reference)
CACS 10–99	2.6 (0.17–17.84), p = 0.46	1.7 (0.21–12.84), p = 0.39
CACS 100–399	5.4 (1.8–15.4), p = 0.002	5.1 (1.6–14.56), p = 0.003
CACS ≥400	6.4 (1.6–12.3), p = 0.001	6.2 (1.5–10.5), p = 0.001

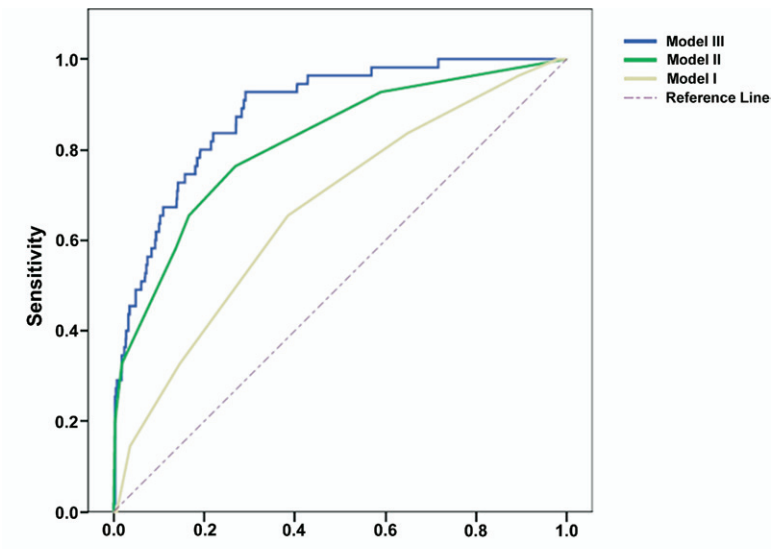
Risk factors adjusted were age, gender, hypertension, hyperlipidemia, diabetes mellitus, family history of premature coronary heart disease, and smoking.
RR = relative risk; other abbreviations as in Table 1.

CI: 1.5 to 10.5, p = 0.001, respectively) (Table 3). In comparison, the patients with nonobstructive CAD and CACS of 1 to 9 had a 99.2% survival rate, with only 1 event among 121 patients.

Incremental value of burden of CAD on CTA in predicting survival. Receiver-operator characteristic curves were generated to determine the predictive value of traditional risk factor assessment, extent of CAD as determined by CTA, and CACS in combination with CTA disease burden with respect to mortality. The AUC was calculated for each model (Fig. 5). In our cohort of patients, we found that the angiographically significant CAD characteristics as detected by CTA (model II) more accurately predicted mortality than did traditional risk factor assessment (model I [AUC 0.83, 95% CI: 0.77 to 0.88, p = 0.0001 vs. AUC 0.69, 95% CI: 0.61 to 0.77, p = 0.0001]). When CACS was combined with significant CAD detected on CTA (model III), the AUC demonstrated even greater predictive power than presence of significant CAD alone (AUC 0.89, 95% CI: 0.86 to 0.93, p = 0.0001).

Discussion

The primary results of our study reveal that the burden of angiographic disease detected by CTA positively correlates with the incidence of all-cause mortality among patients with suspected CAD referred for evaluation in an outpatient setting. Furthermore, this is the first study to demonstrate that CTA is incremental to traditional risk factors plus coronary calcium in predicting all-cause mortality. Given the recent emergence of CTA as an evaluation tool for CAD, very few prognostic data exist. To our knowledge, this cohort represents the largest and longest follow-up after CTA in such a population, and is one of few studies demonstrating the prognostic value of this technology. The end point, all-cause mortality, with 86 events, provides this investigation with significant statistical power to evaluate the prognostic significance of CTA using EBT.



Model	AUC(±S.D.)	95% Confidence Interval	P
Model I	0.69 (0.04)	0.61-0.77	.0001
Model II	0.83 (0.03)	0.77-0.88	.0001
Model III	0.89 (0.01)	0.86-0.93	.0001

Model I: diabetes, hypertension, hypercholesterolemia, family history of premature CHD, smoking
Model II: CTA diagnosed CAD
Model III: CTA diagnosed CAD and CACS
*P<0.0001 in model II and III compared to model I

Figure 5 Receiver-Operator Characteristic Curves

Receiver-operator characteristic curves for 3 models created to assess the ability of a combination of clinical variables to predict all-cause mortality among symptomatic patients. CACS = coronary artery calcium score; CAD = coronary artery disease; CHD = coronary heart disease; CTA = computed tomography angiography.

We utilized EBT to allow for longer follow-up. Clearly, improved spatial resolution is available now with MDCT. At the time of the EBT studies, adequate MDCT angiography was not yet available because of lower rotation speeds and fewer detectors. One of the most important advances for coronary imaging has been faster gantry rotation speed, resulting in better temporal resolution and improved *z*-axis spatial resolution made possible by thin collimations with extensive volumetric acquisition (11). The new 64-slice MDCT scanners provide fast scan times, improved cardiac gating options, and isotropic resolution (which provides 3-dimensional information free of superimposed tissues or interference, resulting in uniform resolution throughout). The 64-slice detectors yield a 3-dimensional data set: for example, near isotropic voxels of $0.35 \times 0.35 \times 0.5$ mm^3 that could be rotated in any given plane without loss of resolution (12).

Our results suggest that CTA is a noninvasive modality that incrementally predicts all-cause mortality over traditional risk factor assessment. Computed tomographic angiography is a noninvasive method able to accurately quantify anatomic epicardial coronary disease and differs from other noninvasive methods that rely on functional measurements and surrogates of CAD. In our study, we have shown that the presence and extent of coronary atherosclerosis as detected by contrast-enhanced EBT adds incremental prognostic value over traditional risk factor assessment and the CACS alone. There is a clear difference with respect to survival among patients with normal CT angiograms and those with detected atherosclerosis. Among the patients with nonobstructive CAD by CTA, the CACS has further predictive power as patients with CACS >100 had a significantly lower survival rate than patients with CACS 1 to 9. Patients with nonobstructive CAD and CACS 1 to 9 had a survival rate of 99.2%, with only 1 event occurring in the group of 121 patients. Patients with a normal CTA and CACS of 0 had a survival rate of 99.8%, with only 1 event occurring in the group of 403 patients. This event rate is similar to a recent analysis of 25,257 patients in which the 10-year adjusted survival rate was 99.4% for patients with a calcium score of 0 (13). A normal CTA with a CACS of 0 conveyed an excellent prognosis in this study population.

In the patients with CTA-detected disease, survival is significantly negatively correlated with burden of angiographic obstructive CAD, as well as 3-vessel nonobstructive CAD. In the patients with 1- and 2-vessel nonobstructive CAD, there was a trend toward increased mortality; however, the p value did not meet significance. Patients with the highest degree of CAD, 3-vessel obstructive disease, had the lowest survival rates (80%), and the survival rates improved as the severity of CAD decreased. The results remain evident even when adjusting for risk factors and CACS. We know from previous studies using conventional invasive coronary angiography that higher angiographic disease burden conveys a worse prognosis. The 6-year follow-up of the medical treatment arm in the CASS (Coronary Artery Surgery Study) trial (7) demonstrated a higher incidence of mortality associated with higher angiographic burden of disease. At 6 years, the survival rates were as follows: no obstructive disease, 92%; 1-vessel disease, 87%; 2-vessel disease, 74%; and 3-vessel disease, 56% (7). Although our results show a similar trend, the overall survival among our cohort is improved, likely reflecting the myriad advancements in medical, interventional, and surgical therapies for the treatment of CAD in the last 3 decades, including revascularization and other antiatherosclerotic therapies.

In our last analysis, we demonstrate the incremental power of CTA for detection and prognostication of all-cause mortality over traditional risk factor assessment alone. When combined with CACS, CTA becomes even more robust in predicting all-cause mortality, with an AUC of 0.89.

It must be stressed that this CTA study was performed with EBT, not the more current 64- to 320-slice detector systems available. It is more difficult to detect noncalcified, nonstenotic plaque by EBT compared with newer scanners, and it is possible that a lot of the plaque that is now seen in 64-slice MDCT was missed by EBT scans. However, clinical diagnostic results from EBT parallel those of MDCT scanners. Several papers have compared calcium scores, demonstrating almost identical results (8,14). Outcome studies of calcium scores have yielded similar prediction of events using both MDCT and EBT (15). Similarly, we have published results on the diagnostic accuracy of CT angiography using EBT compared with angiography that parallel closely the diagnostic results of MDCT and coronary angiography (16,17). We have published intravascular ultrasound comparison data comparing electron beam computed tomography-detected plaque and intravascular ultrasound, and the results parallel those in papers using MDCT angiography (1). Overall accuracy for electron beam computed tomography angiography to determine plaque morphology was 92% (54 of 59), demonstrating excellent detection of underlying plaque type (calcified vs. noncalcified) (18). The higher spatial resolution of MDCT should improve the diagnostic accuracy and the visualization of noncalcified (nonobstructive) disease.

It has been suggested that CTA may be helpful to rule out the presence of significant CAD and avoid invasive coronary angiography in patients with a low to intermediate clinical likelihood of significant CAD. Multiple studies have demonstrated CTA accuracies over 90%, with negative predictive values of 96% and 98% for the presence of obstructive CAD (19,20). Outcome data with CTA are just developing. Lesser et al. (21) evaluated the accuracy of CTA with 16-slice MDCT for determining significant CAD and a 6-month prognosis and clinical outcome in a "real world" clinical setting. The 6-month follow-up of the 834 patients originally not referred for cardiac catheterization showed 2 patients (0.2%) who subsequently had significant CAD. There were no cardiovas-

cular deaths (21). Pundziute et al. (22) analyzed the prognostic value of CTA in patients with known or suspected CAD. A total of 100 patients (73 men, age 59 ± 12 years) who were referred for further cardiac evaluation based on suspicion of significant CAD underwent additional CTA to evaluate the presence and severity of CAD. The first-year event rate was 0% for patients with normal coronary arteries on CTA versus 30% for patients with any evidence of CAD on CTA. However, Pundzuite et al. (22) assessed "soft" events (mainly revascularizations that may have been prompted by the CT results). This study and others suggest that a normal CTA provides an excellent prognosis. Min et al. (23) studied the association of all-cause death with the CTA-defined extent and severity of CAD. In a single-center consecutive cohort of 1,127 patients ages ≥45 years with chest symptoms, stenosis by CTA was scored as minimal (<30%), mild (30% to 49%), moderate (50% to 69%), or severe (≥70%) for each coronary artery. In patients with chest pain, CTA identified increased risk for all-cause death. Importantly, in both the study by Min et al. (23) and the present study, a negative CTA portends an extremely low risk for death.

Gilard et al. (24) studied 141 patients whose CTA were considered normal. During the follow-up period (mean 14.7 months), those patients experienced 0% mortality, a 3.5% rate of subsequent invasive angiography, and a 0.7% rate of myocardial infarction (24). The risks of subsequent death, new referral for invasive angiography, and coronary events compare favorably with risks after normal invasive angiography, which were 0.4%, 4.3%, and 0.6%, respectively.

In our study, the majority of the deaths (54 of 86, 63%) occurred among the patients without obstructive CAD by EBT. Patients with minor or intermediate coronary narrowings had an intermediate event rate, higher than that of patients with normal or near normal coronary vessels. Acute coronary events frequently occur after acute or subacute obstruction to coronary blood flow at a site of previously nonobstructive coronary atheroma. Multiple studies over the last decade have demonstrated that the vast majority of myocardial infarctions (60% to 83%) occur at the site of a nonobstructive plaque (25,26). Virmani et al. (27) pointed out that these sites are frequently characterized by plaque with a thin fibrous cap and necrotic core that do not usually show severe narrowing but rather positive arterial remodeling. In addition, our study further adds evidence to the fact that increasing plaque burden as denoted by higher CACS is a significant risk factor for outcomes in these vulnerable patients and should be considered an excellent risk stratification marker in the absence of significant nonstenotic CAD.

Study limitations. This study was a single-center, retrospective, observational analysis of a large cohort of patients referred for CTA. The majority of patients had cardiac risk factors and, therefore, are not representative of the general population. In addition, we had incomplete information with respect to risk factors and the various treatment interventions implemented, as this information was obtained by survey.

Given the design of the study, we were unable to determine the cause of death, and only report on all-cause mortality; thus, our model likely includes events unrelated to atherosclerotic disease. However, the bias resulting from cause of death misclassification does not occur in this model, and for this age group, the prevalence of CHD death has been reported to be approximately one-half of deaths from all causes (28). With our rates of coronary risk factors higher than in the general population, we expect our rates of cardiac death also to be accordingly higher than the general population rate of one-half of all-cause mortality. Patients with active cancer, acquired immune deficiency, congestive heart failure, or advanced lung disease were generally not referred for CTA evaluation and were excluded from this study.

There could also exist a treatment bias, whereby patients with higher CAD burdens are more likely to be treated aggressively, improving outcomes. We have previously demonstrated that patients with higher calcium burdens are more likely to be placed on a regimen of statin therapy and more likely to maintain statin therapy (improved adherence) over the subsequent 3 to 5 years (29). Thus, higher calcium scores (and presumably CTA burdens) are confounded by improved antiatherosclerotic therapies that would possibly lower cardiovascular mortality. However, this confounder would weaken the predictive value of cardiac CT.

We utilized a cutpoint of 50% luminal severity due to the inexactness of measuring stenosis on CTA. Symptomatic lesions with ≥50% to 75% diameter stenosis are generally considered significant, and stenotic lesions >70% often result in revascularization procedures when evidence of viable, ischemic myocardium is present in that vascular distribution. Patients with lesser degrees of coronary arterial stenosis may be managed with medical therapies. We utilized a lesser cutpoint (≥50% stenosis present by CTA) to be more conservative, given the intertest variability between CTA and cardiac catheterization (8,14–16,30). A CTA cutpoint of ≥70% luminal irregularity would have led to fewer patients classified as having significant CAD, and thus likely to decreased sensitivity for detection of obstructive disease.

Given the early experience of our center with CTA, all data included in this study were obtained using contrast-enhanced EBT with electrocardiographic triggering as opposed to newer MDCT scanner technology that is currently available. The ability to discern mixed plaque and noncalcific plaque has been demonstrated to be superior using the newer technology (7), and better risk stratification may now be obtainable.

Conclusions

Aside from several small studies with short-term follow-up, there is a paucity of outcome data for the emerging technology of CTA, a modality that is currently being utilized with increasing frequency. These results offer further validation of CTA and its clinical role in CAD evaluation and help to fill the outcome data void that exists for this promising technology. Our results show that CTA demonstrating the presence of luminal obstruction or nonobstructive, noncalcified plaque in contrast-enhanced EBT coronary angiography is a powerful noninvasive modality that accurately predicts all-cause mortality as correlated with severity of CAD, with incremental benefit over traditional risk factor assessment and CACS. Moreover, CAC scoring, performed concurrently with CTA at our institution, provides further prognostic information about patients with normal CT angiograms, and also imparts additional predictive power when combined with CTA for patients with atherosclerosis.

Reprint requests and correspondence: Dr. Matthew J. Budoff, Harbor-UCLA Medical Center, 1124 W. Carson Street, RB2, Torrance, California 90502. E-mail: mbudoff@labiomed.org.

REFERENCES

1. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006;113:e85–151.
2. Schussler JM, Grayburn PA. CT imaging of the coronary arteries. Heart 2007;93:290–7.
3. Budoff MJ, Achenbach S, Duerinckx A. Clinical utility of computed tomography and magnetic resonance techniques for noninvasive coronary angiography. J Am Coll Cardiol 2003;42;1867–78.
4. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel On Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
5. Lu B, Mao SS, Zhuang N, Bakhsheshi H, et al. Coronary artery motion during the cardiac cycle and optimal ECG triggering for coronary artery imaging. Invest Radiol 2001;36:250–6.
6. Mao SS, Budoff MJ, Bakhsheshi H, Liu SCK. Improved reproducibility of coronary artery calcium scoring by electron beam tomography with a new ECG trigger method. Invest Radiol 2001;36:363–7.
7. Ringqvist I, Fisher LD, Mock M, et al. Prognostic value of angiographic indicies of coronary artery disease from the Coronary Artery Surgery Study (CASS). J Clin Invest 1983;71:1854–66.
8. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation 2006;114:1761–91.
9. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
10. Nasir K, Shaw LJ, Liu ST, et al. Ethnic differences in the prognostic value of coronary calcification for all-cause mortality. J Am Coll Cardiol 2007;10:953–60.
11. Cademartiri F, Runza G, Belgrano M, et al. Introduction to coronary imaging with 64-slice computed tomography. Radiol Med (Torino) 2005;110:16–41.
12. Budoff MJ, Gopal A, Gopalakrishnan D. Cardiac computed tomography: diagnostic utility and integration in clinical practice. Clin Cardiol 2006;29 Suppl 1:4–14.
13. Budoff MJ, Shaw LJ, Lui ST, et al. Long-term prognosis associated with coronary calcification: observation from a registry of 25,253 patients. J Am Coll Cardiol 2007;49:1860–70.
14. Mao SS, Pal RS, McKay CR, et al. Comparison of coronary artery calcium scores between electron beam computed tomography and 64 multidetector computed tomographic scanner. J Comput Assist Tomogr 2008. In press.
15. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–45.
16. Budoff MJ, Lu B, Shinbane JS, et al. Methodology for improved detection of coronary stenoses with computed tomographic angiography. Am Heart J 2004;148:1085–90.
17. Lu B, Shavelle DM, Mao S, et al. Improved accuracy of noninvasive electron beam coronary angiography. Invest Radiol 2004;39:73–9.
18. Rasouli ML, Shavelle DM, French WJ, McKay CR, Budoff MJ. Assessment of coronary plaque morphology by contrast-enhanced computed tomographic angiography: comparison with intravascular ultrasound. Cor Artery Dis 2006;17:359–64.
19. Budoff MJ, Lu B, Shinbane JS, et al. Methodology for improved detection of coronary stenoses with computed tomographic angiography. Am Heart J 2004;148:1085–90.
20. Lu B, Shavelle DM, Mao S, et al. Improved accuracy of noninvasive electron beam coronary angiography. Invest Radiol 2004;39:73–9.
21. Lesser JR, Flygenring B, Knickelbine T, et al. Clinical utility of coronary CT angiography: coronary stenosis detection and prognosis in ambulatory patients. Catheter Cardiovasc Interv 2007;69:64–72.
22. Pundziute G, Schuijf JD, Jukema JW, et al. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. J Am Coll Cardiol 2007;49:62–70.
23. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol 2007;50:1161–70.
24. Gilard M, Le Gal G, Cornily JC, et al. Midterm prognosis of patients with suspected coronary artery disease and normal multislice computed tomographic findings: a prospective management outcome study. Arch Intern Med 2007;167:1686–9.
25. Giroud D, Li JM, Urban P, et al. Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography Am J Cardiol 1992;69:729–32.
26. Budoff MJ. Prognostic value of coronary artery calcification. Vasc Dis Prev 2005;2:2–10.
27. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. J Am Coll Cardiol 2006;47 Suppl:C13–8.
28. The burden of chronic diseases as causes of death, United States. Available at: http://www.cdc.gov/nccdphp/burdenbook2004/Section01/tables.htm. Accessed July 31, 2005.
29. Kalia NK, Miller LG, Nasir K, Blumenthal RS, Agrawal N, Budoff MJ. Visualizing coronary calcium is associated with improvements in adherence to statin therapy. Atherosclerosis 2006;185:394–9.
30. Maruyama T, Yoshizumi T, Tamura R, et al. Comparison of visibility and diagnostic capability of noninvasive coronary angiography by eight-slice multidetector-row computed tomography versus conventional coronary angiography. Am J Cardiol 2004;93:537–42.

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