

Prognostic Value of 64-Slice Cardiac Computed Tomography

Severity of Coronary Artery Disease, Coronary Atherosclerosis, and Left Ventricular Ejection Fraction

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- Objectives** We sought to determine the prognostic and incremental value of coronary artery disease (CAD) severity, coronary atherosclerosis, and left ventricular ejection fraction (LVEF) measured with cardiac computed tomography angiography (CTA).
- Background** CTA is an emerging tool used for the detection of obstructive CAD. However, there are limited data supporting the prognostic value of 64-slice CTA and its ability to predict all-cause mortality and major adverse cardiac events such as cardiac death and nonfatal myocardial infarction.
- Methods** Consecutive patients (without history of revascularization, heart transplantation, and congenital heart disease) were prospectively enrolled. Each CTA was evaluated for CAD severity, total plaque score, and LVEF. Patients were followed, and all events were confirmed with death certificates or hospital or physician records and reviewed by a clinical events committee.
- Results** Between February 2006 and February 2008, 2,076 consecutive patients were prospectively enrolled and followed for a mean of 16 ± 8 months. At follow-up, a total of 31 (1.5%) patients had cardiac death or nonfatal myocardial infarction and 47 (2.3%) had all-cause mortality or nonfatal myocardial infarction. Multivariate analysis showed that CAD severity (hazard ratio [HR]: 3.02; 95% confidence interval [CI]: 1.89 to 4.83) was a predictor of major adverse cardiac events and that LVEF (HR: 1.47; 95% CI: 1.17 to 1.86) had incremental value over CAD severity. Total plaque score had incremental value over CAD severity and LVEF for all-cause mortality and nonfatal myocardial infarction (HR: 1.17; 95% CI: 1.06 to 1.29).
- Conclusions** Using CTA, CAD severity, LVEF, and total plaque score seems to have prognostic and incremental value over routine clinical predictors. Cardiac CTA seems to be a promising noninvasive modality with prognostic value. (J Am Coll Cardiol 2010;55:1017–28) © 2010 by the American College of Cardiology Foundation

Cardiac computed tomography angiography (CTA) is a rapidly emerging noninvasive diagnostic tool for the detection of obstructive coronary artery disease (CAD). Studies

have demonstrated that CTA has good operating characteristics for the diagnosis of CAD and may reduce referrals for invasive coronary angiography (1–5).

CTA seems to be a promising modality, but there are limited data supporting the prognostic value of 64-slice CTA. Early studies demonstrated that CTA is a predictor of all-cause mortality (6,7), and smaller studies demonstrated that CTA is an independent predictor of cardiac events (8–10). To further

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support the clinical acceptance of CTA, larger cohort studies are needed to understand the prognostic value of 64-slice CTA on major adverse cardiac events (MACE) such as cardiac death and nonfatal myocardial infarction (MI).

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**Abbreviations
and Acronyms**

| | |
|-------------|---|
| CAD | = coronary artery disease |
| CI | = confidence interval |
| CT | = computed tomography |
| CTA | = cardiac computed tomography angiography |
| ECG | = electrocardiogram |
| HR | = hazard ratio |
| LV | = left ventricular |
| LVEF | = left ventricular ejection fraction |
| MACE | = major adverse cardiac events |
| MI | = myocardial infarction |
| NRI | = net reclassification improvement |
| TPS | = total plaque score |
| VD | = vessel disease |

patients undergoing CTA were prospectively enrolled in a cardiac computed tomography (CT) registry (5) and were followed for all-cause mortality and MACE (cardiac death and nonfatal MI). Patients with a history of coronary revascularization, heart transplantation, and congenital heart disease were excluded. The study was approved by the University of Ottawa Heart Institute Human Research Ethics Board, and all patients provided written informed consent.

Clinical predictors. At the time of CTA, a medical history and laboratory test results were recorded for all patients. Pre-test probability for obstructive CAD was calculated for individual patients using age, sex, and symptoms (14–16). Based on the National Cholesterol Education Program/Adult Treatment Panel III Guidelines, cardiac risk factors (smoking, hypertension [blood pressure $\geq 140/90$ mm Hg on antihypertensive medication], family history of premature CAD [first-degree family member (men younger than 55 years of age and women younger than 65 years of age) with a history of MI or revascularization], dyslipidemia [based on a fasting lipid profile or treatment for hyperlipidemia], and diabetes) were used to estimate each patient's risk of a future cardiac event (17).

CTA. Before image acquisition, metoprolol or diltiazem (oral and/or intravenous) was administered, targeting a heart rate of ≤ 65 beats/min. Patients without contraindications received nitroglycerin (0.8 mg) sublingually (18,19).

A biphasic timing bolus (15 to 25 ml of contrast; 40 ml of saline solution; 5 to 9 ml/s) was used to measure transit time (interval between intravenous contrast [Visipaque 320 or Omnipaque 350, GE Healthcare, Milwaukee, Wisconsin] infusion and peak aorta opacification) (5).

Other diagnostic modalities have shown that severity of CAD, left ventricular ejection fraction (LVEF), and coronary atherosclerosis all have prognostic value and predict MACE (11–13). However CTA is a unique noninvasive modality with the ability to obtain all 3 measures (CAD severity, LVEF, and coronary atherosclerosis) with a single image acquisition.

The objective of this large prospective cohort study is to understand the potential prognostic and incremental value of 64-slice CTA using measures of CAD severity, coronary atherosclerosis, plaque characteristics, and LVEF.

Methods

Between February 2006 and February 2008, consecutive pa-

CTA image acquisition, using a triphasic intravenous contrast administration protocol (100% contrast, 40%/60% contrast/saline solution [50 ml], and saline solution [40 ml]), was initiated 2 seconds after the calculated transit time. The volume of the second phase (contrast/saline solution) was increased if assessment of right-sided structures was indicated. The volume and rate (5 to 9 ml/s) of contrast were individualized according to scan time and patient body habitus (5,18). Flow rates of ≥ 8 ml/s were reserved for patients with a very high body mass index and/or significant chest wall attenuation.

Retrospective electrocardiogram (ECG)-gated datasets were acquired with the GE Volume CT (GE Healthcare) with 64×0.625 -mm slice collimation and a gantry rotation of 350 ms (mA = 400 to 800, kV = 120) using ECG-gated X-ray tube modulation (200 to 275 mA) with the peak milliamperes between 70% and 80% phases. Pitch (0.16 to 0.24) was individualized according to heart rate. The CTA datasets were reconstructed, at the 70%, 75%, and 80% phases using a slice thickness of 0.625 mm with an increment of 0.4 mm (5). If significant cardiac motion was present, additional phases were reconstructed. An additional 10 phases (5% to 95%) were reconstructed with 1.25-mm slice collimation with an increment of 0.625 mm and were used to measure left ventricular (LV) volumes.

CTA image analysis. ECG-gated CT images were post-processed using the GE Advantage Volume Share Workstation (GE Healthcare) and interpreted by expert observers (≥ 2 years of experience) blinded to all clinical data. To emulate clinical practice, the blinded interpretation of the observer who would eventually be clinically responsible for the interpretation was used for analysis. Coronary artery lumen and plaque were assessed using axial images, oblique multiplanar reformations, and window levels and widths optimized for each study to enable the identification of coronary atherosclerotic plaque (20).

A 17-segment model of the coronary arteries and 4-point grading score (normal, mild [$<50\%$], moderate [50% to 69%], severe [$\geq 70\%$]) was used for the evaluation of coronary diameter stenosis (21). In segments that were unevaluable, forced reading was performed and readers provided their best educated guess. Patients were categorized into 3 broad categories (normal, nonobstructive CAD, obstructive CAD). Patients with obstructive CAD were further categorized as having high-risk CAD (defined as having a left main stenosis [$\geq 50\%$], 3-vessel disease [VD] [$\geq 70\%$], or 2-VD [$\geq 70\%$] involving the proximal left anterior descending artery) or non-high-risk CAD (CAD model 1) (22,23). In addition, patients with obstructive CAD ($\geq 50\%$ diameter stenosis) were categorized as 1-, 2-, or 3-VD (CAD model 2) (7).

The same 17-segment model of the coronary arteries (2,21) was used for the evaluation and visual semiquantification of coronary artery calcific, noncalcific, and mixed plaque. The total plaque score (TPS) was determined by summing the number of assessable coronary segments with

calcific, noncalcific, or mixed plaque (maximum score = 17). The same method was used to sum segments according to plaque composition (isolated calcific, isolated noncalcific plaque, and mixed plaque).

Using a semiautomated volumetric algorithm (Advantage Workstation, Ejection Fraction, GE Healthcare), LV volumes were measured at end diastole and end systole, and the LVEF was calculated (24).

Patient follow-up. Patient follow-up was performed (6-month intervals) by telephone interview by trained research staff blinded to all clinical data. All events were confirmed with death records, hospital records, or correspondence with treating physicians. All events were reviewed by a blinded clinical events committee composed of 2 clinical cardiologists and a nurse.

Outcome measures. The primary outcome measure was a composite of all MACE (cardiac death and nonfatal MI). All deaths were reviewed and classified as cardiac or noncardiac. Nonfatal MI was defined as myocardial ischemia resulting in abnormal cardiac biomarkers (>99th percentile of the upper limits of normal) (25). A secondary composite outcome (all-cause mortality and nonfatal MI) and all-cause mortality were also assessed. Revascularized patients were not excluded from analysis.

Statistical analysis. Statistical analyses were performed (G.W. and L.C.) using SAS (version 9.1.3, SAS Institute Inc., Cary, North Carolina), and statistical significance was defined as $p < 0.05$. Continuous variables are presented as means and SDs, and categorical variables are presented as frequencies with percentages. To compare patient characteristics and CTA imaging parameters, Wilcoxon rank sum test was used to compare continuous variables, and the Fisher exact test was used for categorical variables.

The prognostic value of CAD severity for unadjusted and adjusted outcomes and cardiac events was assessed for the study population. All unadjusted comparisons of cardiac events were performed with survival analysis log-rank tests. Annual event rates were calculated by dividing the Kaplan-Meier event rates by mean number of years of follow-up.

For the risk-adjusted analysis, Cox proportional hazard models were used to assess the independent prognostic value of CAD severity (controlling for baseline patient characteristics) and create adjusted survival curves. The Cox models with and without CAD severity, LVEF, and TPS measures were compared to determine their incremental values. The incremental prognostic values of these measures were defined by a statistically significant increase in the global chi-square value of the models with CAD severity, LVEF, and TPS. The incremental values of plaque characteristics over CAD severity and LVEF were also evaluated using the Cox models. Receiver-operator characteristic curves were constructed for clinical predictors and for a model of clinical predictors and CAD severity. Area under the curves was compared to evaluate each model's ability to predict MACE (26). The improvement of reclassification using the models (CAD severity, LVEF, and TPS) was also assessed by

calculating the net reclassification improvement (NRI) (27) for 10-year categories of risk (<10%, 10% to 20%, >20% risk) (17).

Results

Over an enrollment period of 25 months, 2,609 consecutive patients underwent CTA with a total of 2,584 (99.0%) patients prospectively enrolled in the University of Ottawa Heart Institute Cardiac CT Registry. Of these, 412 patients with a history of coronary revascularization, heart transplantation, and congenital heart disease were excluded. The remaining 2,172 patients (mean age 57.6 ± 11.8 years, 52.6% men; mean pre-test probability for obstructive CAD $33.4 \pm 34.4\%$) met the inclusion criteria for this study. Primary indications for CTA were chest pain (58.1%), and dyspnea (16.0%) (Table 1). Of asymptomatic patients, 241 (11.1%) had multiple cardiac risk factors and CT was requested to rule out CAD, 139 (6.4%) had an equivocal or abnormal stress test, and 84 (3.9%) had CTA performed before noncoronary cardiac surgery. Follow-up was obtained for 2,076 (95.6%) patients, with only 96 patients lost to follow-up. Compared with patients with follow-up, patients lost to follow-up were younger, had less hypertension, but were more likely to have a family history of premature CAD (Table 1). Statistically significant differences in imaging parameters were detected but were unlikely clinically significant (Table 2).

Cardiac events. At follow-up, 31 patients had 34 MACE with 11 cardiac deaths and 23 nonfatal MIs (Table 3). All-cause mortality was observed in 27 patients, with 41% attributed to cardiac causes. Causes of the 16 noncardiac deaths were malignancy (6 deaths), vascular event (3 deaths), sepsis (2 deaths), post-operative noncardiac complication (2 deaths), and other (3 deaths). A total of 243 patients underwent revascularization (157 percutaneous coronary interventions and 86 bypass surgeries).

Univariate analysis. Clinical parameters (age, smoking history, National Cholesterol Education Program/Adult Treatment Panel III risk, pre-test likelihood of CAD) and CT parameters (severity of CAD, TPS, LVEF) were all significant predictors of MACE and all-cause mortality and nonfatal MI (Table 4).

CAD severity and MACE. Patients without visible coronary atherosclerosis had excellent prognoses, with only 1 patient dying of a nonischemic cardiac cause (metastatic cardiac angiosarcoma). MACE were observed in 7 (0.8%) of the 866 patients with nonobstructive CAD (Table 3).

Using a patient-based analysis, MACE occurred in 23 (3.7%) of 619 patients with obstructive CAD (coronary diameter stenoses $\geq 50\%$). Using CAD model 1, 4 (4.1%) of the 97 patients with high-risk CAD experienced MACE compared with 19 (3.6%) of 522 patients with non-high-risk CAD. Using CAD model 2, MACE were observed in

Table 1 Patient Characteristics: All Patients and Patients With and Without Follow-Up

| | All Patients (n = 2,172) | Follow-Up Patients (n = 2,076) | Patients Lost to Follow-Up (n = 96) | p Value* |
|--------------------------------------|-----------------------------|-----------------------------------|--|----------|
| Mean follow-up (months) | — | 16.8 ± 8.3 | — | — |
| Age (yrs) | 57.6 ± 11.8 | 58.0 ± 11.7 | 50.6 ± 11.8 | <0.001 |
| Men | 1,142 (52.6%) | 1,087 (52.4%) | 55 (57.3%) | 0.200 |
| Body mass index (kg/m ²) | 29.1 ± 6.3 | 29.1 ± 6.3 | 28.7 ± 5.9 | 0.685 |
| Pre-test likelihood for CAD (%) | 33.4 ± 34.4 | 33.4 ± 34.3 | 32.1 ± 35.7 | 0.193 |
| Cardiac risk factors | | | | |
| Smoker/ex-smoker | 1,184 (54.5%) | 1,129 (54.5%) | 55 (57.3%) | 0.326 |
| Hypertension | 1,112 (51.2%) | 1,076 (51.8%) | 36 (37.5%) | 0.004 |
| Dyslipidemia | 1,151 (53.0%) | 1,103 (53.1%) | 48 (50.0%) | 0.309 |
| Treated with lipid-lowering agent | 977 (45.0%) | 940 (45.3%) | 37 (38.5%) | 0.209 |
| Diabetes | 309 (14.2%) | 300 (14.5%) | 9 (9.4%) | 0.103 |
| Family history of CAD | 922 (42.4%) | 869 (41.9%) | 53 (55.2%) | 0.007 |
| Indications for study | | | | |
| Chest pain | 1,262 (58.1%) | 1,204 (58.0%) | 58 (60.4%) | 0.463 |
| Nonanginal chest pain | 607 (27.9%) | 577 (27.8%) | 30 (31.3%) | 0.485 |
| Atypical angina | 317 (14.6%) | 302 (14.5%) | 15 (15.6%) | 0.767 |
| Typical angina | 338 (15.6%) | 325 (15.7%) | 13 (13.5%) | 0.667 |
| Dyspnea | 347 (16.0%) | 331 (15.9%) | 16 (16.7%) | 0.887 |
| History of chest pain (resolved) | 6 (0.3%) | 5 (0.2%) | 1 (1.0%) | 0.641 |
| Palpitations | 23 (1.1%) | 20 (1.0%) | 3 (3.1%) | 0.121 |
| Syncope | 19 (0.9%) | 19 (0.9%) | 0 (0.0%) | 0.715 |
| Asymptomatic | | | | |
| Rule out CAD/cardiac risk factors | 241 (11.1%) | 231 (11.1%) | 10 (10.4%) | 0.890 |
| Equivocal/abnormal stress test | 139 (6.4%) | 133 (6.4%) | 6 (6.3%) | 0.893 |
| Pre-cardiac surgery | 84 (3.9%) | 82 (3.9%) | 2 (2.1%) | 0.501 |
| LV dysfunction | 13 (0.6%) | 13 (0.6%) | 0 (0.0%) | 0.946 |
| Other | 38 (1.7%) | 38 (1.8%) | 0 (0.0%) | 0.359 |

Values given are mean ± SD or n (%). *Comparison of the patients with and without follow-up.
CAD = coronary artery disease; LV = left ventricular.

0.2%, 0.8%, 1.6%, 5.3%, and 7.0% of patients with no CAD, nonobstructive CAD, and 1-, 2-, and 3-VD, respectively.

Cox models of risk-adjusted outcomes. Clinical predictors were identified and used to determine the incremental value of CTA measures (Table 4). A risk-adjusted model of CAD severity (model 1) was tested, and CAD severity (model 1) remained an independent predictor of MACE after adjusting for clinical characteristics (Table 5). Patients with high risk and non-high-risk obstructive CAD had adjusted hazard ratios (HRs) of 7.08 (95% confidence interval [CI]: 2.02 to 24.79) and 4.14 (95% CI: 1.70 to 10.05) (p = 0.002).

A receiver-operator characteristic curve was created for clinical predictors versus clinical predictors plus CAD severity (Fig. 1). The area under the curve for clinical predictors plus CAD severity (model 1) (HR: 0.81; 95% CI: 0.74 to 0.87) was significantly higher than those of the clinical predictors (HR: 0.72; 95% CI: 0.63 to 0.82; p = 0.010) (Fig. 1) and was confirmed with reclassification calibration (NRI: 22.4%, p = 0.011).

Incremental prognostic value of CAD severity and LVEF. The incremental value of CAD severity and LVEF was assessed for MACE. A statistically significant

increase in global chi-square values confirmed that CAD severity has the incremental value (43.81 vs. 24.97, p < 0.001) over clinical predictors and that LVEF has incremental value (54.48 vs. 43.81, p = 0.001) over CAD severity and clinical predictors (Table 5, Fig. 2). The discrimination of the CT model (clinical predictors, CAD severity, and LVEF) was significantly better than that of the clinical model (clinical predictors alone) (NRI: 19.5%, p = 0.007). To ensure that model overfitting did not bias results, a sensitivity analysis was performed to confirm the incremental value of LVEF over CAD severity and the remaining clinical predictor (pre-test likelihood of CAD) after excluding the clinical variable National Cholesterol Education Program.

Annual MACE. In our study population, the annualized rate of MACE was 1.1%. The absence of obstructive CAD conferred an excellent prognosis. Patients without visible coronary atherosclerosis had a very low (0.1%) annual rate of MACE, with slightly higher rates in patients with nonobstructive CAD (0.5%). Patients with obstructive CAD (coronary diameter stenoses ≥50%) had an annual MACE rate of 2.7%. Using CAD model 1, patients with high-risk CAD had an annual rate of 5.8% compared with 3.3% in patients with non-high-risk CAD (Table 3). Using CAD

| | All Patients (n = 2,172) | Follow-Up Patients (n = 2,076) | Patients Lost to Follow-Up (n = 96) | p Value* |
|--------------------------------|-----------------------------|-----------------------------------|--|----------|
| CTA imaging parameters | | | | |
| Imaging heart rate (beats/min) | 57.2 ± 7.5 | 57.1 ± 7.5 | 57.9 ± 7.5 | 0.223 |
| Contrast infusion rate (ml/s) | 6.2 ± 0.9 | 6.2 ± 0.9 | 6.5 ± 0.8 | 0.001 |
| Timing bolus (ml) | | | | |
| Contrast | 19.2 ± 5.0 | 19.1 ± 5.0 | 20.8 ± 4.6 | <0.001 |
| Saline | 40.0 ± 0.0 | 40.0 ± 0.0 | 40.0 ± 0.0 | 1.000 |
| Triphasic protocol (ml) | | | | |
| Phase I | | | | |
| Contrast | 60.7 ± 12.0 | 60.6 ± 12.1 | 62.9 ± 8.3 | 0.001 |
| Phase II | | | | |
| Contrast | 20.0 ± 1.9 | 20.0 ± 1.9 | 20.0 ± 0.4 | 0.767 |
| Saline | 29.8 ± 2.3 | 29.8 ± 2.4 | 29.9 ± 0.6 | 0.606 |
| Total | 49.9 ± 3.5 | 49.9 ± 3.5 | 49.9 ± 1.0 | 0.892 |
| Phase III | | | | |
| Saline | 40.3 ± 3.1 | 40.3 ± 3.2 | 40.2 ± 1.4 | 0.878 |
| Total contrast volume (ml) | 99.9 ± 15.2 | 99.7 ± 15.3 | 103.7 ± 11.7 | <0.001 |
| Effective dose (mSv)† | 14.9 ± 3.8 | 14.9 ± 3.8 | 15.1 ± 2.9 | 0.266 |
| CTA results | | | | |
| Normal coronaries | 623 (28.7%) | 591 (28.5%) | 32 (33.3%) | 0.179 |
| Nonobstructive CAD | 908 (41.8%) | 866 (41.7%) | 42 (43.8%) | 0.384 |
| Obstructive CAD (≥50%) | 641 (29.5%) | 619 (29.8%) | 22 (22.9%) | 0.089 |
| Obstructive CAD (≥70%) | 446 (20.5%) | 427 (20.6%) | 19 (19.8%) | 0.487 |
| High-risk CAD | 100 (4.6%) | 97 (4.7%) | 3 (3.1%) | 0.623 |
| Non-high-risk CAD | 541 (24.9%) | 522 (25.1%) | 19 (19.8%) | 0.278 |
| LV ejection fraction (%) | 64.1 ± 10.5 | 64.2 ± 10.5 | 63.1 ± 10.8 | 0.276 |
| LV end-diastolic volume (ml) | 134.7 ± 41.3 | 134.4 ± 41.0 | 142.9 ± 47.4 | 0.048 |
| LV end-systolic volume (ml) | 50.3 ± 32.5 | 50.1 ± 32.3 | 55.4 ± 37.0 | 0.083 |
| ≥1 unassessable segment | 217 (10.0%) | 205 (9.9%) | 12 (12.5%) | 0.402 |

Values given are mean ± SD or n (%). *Comparison of the patients with and without follow-up. †Effective dose (mSv) = dose length product × 0.014. CTA = cardiac computed tomography angiography; other abbreviations as in Table 1.

model 2, rates of MACE increased with the severity of CAD. Patients with 1-, 2-, and 3-VD had annual rates of 1.4%, 4.3%, and 9.8%, respectively (Table 3).

Incremental prognostic value of CAD severity, TPS, and LVEF. To prevent overfitting for the model, the incremental value of CAD severity (model 1), LVEF, and TPS over

| | n | All Death | Cardiac Death | Nonfatal MI | MACE (Cardiac Death, Nonfatal MI) | Annual Event Rate | All Death, Nonfatal MI | Annual Event Rate |
|-------------------------------|-----|-----------|---------------|-------------|--------------------------------------|----------------------|---------------------------|----------------------|
| CAD severity: model 1 | | | | | | | | |
| No CAD | 591 | 2 (0.3%) | 1 (0.2%) | 0 (0%) | 1 (0.2%) | 0.13% | 2 (0.3%) | 0.26% |
| Nonobstructive CAD | 866 | 8 (0.9%) | 3 (0.4%) | 5 (0.6%) | 7 (0.8%) | 0.52% | 12 (1.4%) | 0.87% |
| Non-high-risk obstructive CAD | 522 | 15 (2.9%) | 6 (1.2%) | 15 (2.9%) | 19 (3.6%) | 3.25% | 28 (5.4%) | 4.61% |
| High-risk obstructive CAD | 97 | 2 (2.1%) | 1 (1.0%) | 3 (3.1%) | 4 (4.1%) | 5.79% | 5 (5.2%) | 8.31% |
| Log-rank p value | | <0.001 | 0.015 | <0.001 | <0.001 | | <0.001 | |
| CAD severity: model 2 | | | | | | | | |
| No CAD | 591 | 2 (0.3%) | 1 (0.2%) | 0 (0%) | 1 (0.2%) | 0.13% | 2 (0.3%) | 0.26% |
| Nonobstructive CAD (<50%) | 866 | 8 (0.9%) | 3 (0.4%) | 5 (0.6%) | 7 (0.8%) | 0.52% | 12 (1.4%) | 0.87% |
| 1-Vessel disease (≥50%) | 321 | 9 (2.8%) | 3 (0.9%) | 4 (1.3%) | 5 (1.6%) | 1.44% | 11 (3.4%) | 2.76% |
| 2-Vessel disease (≥50%) | 170 | 6 (3.5%) | 3 (1.8%) | 6 (3.5%) | 9 (5.3%) | 4.30% | 12 (7.1%) | 6.41% |
| 3-Vessel disease (≥50%) | 128 | 2 (1.6%) | 1 (0.8%) | 8 (6.3%) | 9 (7.0%) | 9.79% | 10 (7.8%) | 10.52% |
| Log-rank p value | | <0.001 | 0.012 | <0.001 | <0.001 | | <0.001 | |

Coronary artery disease (CAD) model 1: patients were categorized into normal coronaries, nonobstructive CAD (<50%), high-risk CAD (left main stenosis [≥50%], or 3-vessel disease [≥70%] or 2-vessel disease [≥70%] involving the proximal left anterior descending artery) or non-high-risk CAD. CAD model 2: patients were categorized into normal coronaries, nonobstructive CAD (<50%), 1-, 2-, or 3-vessel disease (≥50% diameter stenosis).

MACE = major adverse cardiac events; MI = myocardial infarction.

Table 4 **Univariate Analysis of Clinical Characteristics for MACE**

| | MACE (n = 31) | No MACE (n = 2,045) | Hazard Ratio (95% CI) | p Value | Nonfatal MI | | | |
|--------------------------------------|------------------|------------------------|--------------------------|---------|------------------------------------|--|--------------------------|---------|
| | | | | | All-Cause Mortality (n = 47) | No All-Cause Mortality (n = 2,029) | Hazard Ratio (95% CI) | p Value |
| Age (yrs) | 62.8 ± 11.2 | 57.9 ± 11.7 | 1.04 (1.01-1.07) | 0.015 | 65.5 ± 11.2 | 57.8 ± 11.7 | 1.06 (1.04-1.09) | <0.001 |
| Male | 21 (67.7%) | 1,066 (52.1%) | 1.97 (0.93-4.17) | 0.079 | 27 (57.5%) | 1,060 (52.2%) | 1.27 (0.71-2.27) | 0.414 |
| Body mass index (kg/m ²) | 29.1 ± 5.6 | 29.1 ± 6.3 | 1.00 (0.94-1.05) | 0.898 | 28.1 ± 5.6 | 29.2 ± 6.3 | 0.97 (0.92-1.02) | 0.247 |
| Pre-test likelihood for CAD (%) | | | | | | | | |
| Low | 3 (9.7%) | 680 (33.3%) | 3.75 (2.13-6.60) | <0.001 | 8 (17.0%) | 675 (33.3%) | 2.71 (1.73-4.23) | <0.001 |
| Intermediate | 15 (48.4%) | 1,091 (53.4%) | | | 22 (46.8%) | 1,084 (53.4%) | | |
| High | 13 (41.9%) | 274 (13.4%) | | | 17 (36.2%) | 270 (13.3%) | | |
| Cardiac risk factors | | | | | | | | |
| Diabetes | 5 (16.1%) | 295 (14.4%) | 1.18 (0.45-3.07) | 0.736 | 10 (21.3%) | 290 (14.3%) | 1.66 (0.83-3.35) | 0.153 |
| Dyslipidemia | 20 (64.5%) | 1,083 (53.0%) | 1.59 (0.78-3.25) | 0.207 | 24 (51.1%) | 1,079 (53.2%) | 0.93 (0.53-1.64) | 0.811 |
| Hypertension | 19 (61.3%) | 1,057 (51.7%) | 1.49 (0.73-3.04) | 0.277 | 29 (61.7%) | 1,047 (51.6%) | 1.53 (0.85-2.73) | 0.154 |
| Family history of CAD | 13 (41.9%) | 856 (41.9%) | 0.87 (0.45-1.70) | 0.689 | 19 (40.4%) | 850 (41.9%) | 0.83 (0.48-1.44) | 0.508 |
| Smoker/ex-smoker | 25 (80.7%) | 1,104 (54.0%) | 3.58 (1.47-8.72) | 0.005 | 36 (76.6%) | 1,093 (53.9%) | 2.84 (1.44-5.58) | 0.003 |
| NCEP/ATPIII risk | | | | | | | | |
| Low | 1 (3.2%) | 159 (7.8%) | 3.32 (1.70-6.46) | <0.001 | 1 (2.1%) | 159 (7.8%) | 3.96 (2.27-6.90) | <0.001 |
| Intermediate | 12 (38.7%) | 1,323 (64.7%) | | | 17 (36.2%) | 1,318 (65.0%) | | |
| High | 18 (58.1%) | 563 (27.5%) | | | 29 (61.7%) | 552 (27.2%) | | |
| Total plaque burden | 8.74 ± 3.89 | 3.89 ± 3.98 | 1.33 (1.23-1.45) | <0.001 | 7.94 ± 3.91 | 3.87 ± 3.98 | 1.28 (1.20-1.37) | <0.001 |
| LVEF (%)* | 57.5 ± 16.0 | 64.3 ± 10.4 | 1.57 (1.24-1.99) | <0.001 | 56.8 ± 17.9 | 64.3 ± 10.2 | 1.61 (1.34-1.94) | <0.001 |

*Left ventricular volumes could not be accurately measured in 53 patients (due to severe misregistration artifact or poor signal-to-noise ratio at end systole); therefore, LVEF in the remaining 2,023 (97.4%) patients was used for analysis.

CI = confidence interval; LVEF = left ventricular ejection fraction; NCEP/ATPIII = National Cholesterol Education Program/Adult Treatment Panel III; other abbreviations as in Tables 1 and 3.

clinical predictors was evaluated using the secondary outcome measure (all-cause mortality and nonfatal MI), which had 47 events. All 3 variables were independent predictors of all-cause mortality and nonfatal MI. A statistically significant increase in global chi-square values confirmed

that CAD severity (model 1) had incremental value over clinical predictors (58.61 vs. 31.38, p < 0.001), LVEF has incremental value over CAD severity + clinical (78.88 vs. 58.61, p < 0.001), and TPS had incremental value over LVEF + CAD + clinical (87.27 vs. 78.88, p = 0.004)

Table 5 **Cox Models of CTA Measures (CAD Model 1) and MACE**

| Models | Hazard Ratio (95% CI) | p Value | Global Chi-Square Value | Model Comparisons p Value |
|-----------------------------------|--------------------------|---------|----------------------------|------------------------------|
| Clinical variables | | | | |
| NCEP/ATPIII risk | 2.01 (0.97-4.17) | 0.062 | 24.97 | |
| Pre-test likelihood for CAD | 2.86 (1.55-5.25) | <0.001 | | |
| Clinical + CAD | | | | |
| NCEP/ATPIII risk | 1.78 (0.86-3.66) | 0.119 | 43.81 | <0.001 |
| Pre-test likelihood for CAD | 2.10 (1.16-3.79) | 0.014 | | |
| CAD severity | | | | |
| No CAD | 0.25 (0.03-2.03) | 0.194 | 7.08 (2.02-24.79) | 0.002 |
| Nonobstructive CAD (<50%) | 1.0 | — | | |
| Obstructive (≥50%), not high risk | 4.14 (1.70-10.05) | 0.002 | | |
| Obstructive, high risk | 7.08 (2.02-24.79) | 0.002 | | |
| Clinical + CAD + LVEF | | | | |
| NCEP/ATPIII risk | 1.67 (0.80-3.45) | 0.170 | 54.48 | 0.001 |
| Pre-test likelihood for CAD | 2.10 (1.18-3.74) | 0.012 | | |
| CAD severity | | | | |
| No CAD | 0.25 (0.03-2.07) | 0.201 | 8.10 (2.33-28.19) | 0.001 |
| Nonobstructive CAD (<50%) | 1.0 | — | | |
| Obstructive (≥50%), not high risk | 4.18 (1.72-10.18) | 0.002 | | |
| Obstructive, high risk | 8.10 (2.33-28.19) | 0.001 | | |
| LVEF (10% reduction) | 1.47 (1.17-1.86) | 0.001 | | |

Abbreviations as in Tables 1 and 4.

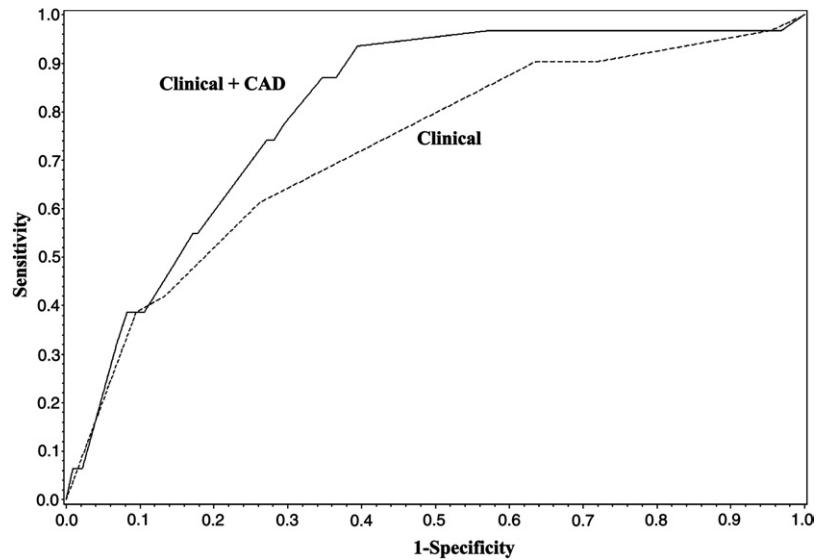


Figure 1 Receiver-Operator Characteristic Curves of CAD Severity (Model 1) and Clinical Predictors

Receiver-operator characteristic curves showing the incremental value of the coronary artery disease (CAD) severity. Model 1 (solid line) (area under the curve [AUC]: 0.81; 95% confidence interval [CI]: 0.74 to 0.87) over clinical predictors (dashed line) (AUC: 0.72; 95% CI: 0.63 to 0.82, $p = 0.010$).

(Table 6). When CAD severity was added to the model for all-cause mortality and nonfatal MI, the NRI was 15.9% ($p = 0.010$), and further improved to 27.1% ($p < 0.001$) with the addition of LVEF and TPS. When CAD severity was added to the model for all-cause mortality, the NRI was 19.6% ($p = 0.010$) (Table 7, Fig. 3).

Plaque characteristics. Using a scoring system similar to TPS, segments with visible noncalcific and calcific plaque were summed. Summed isolated noncalcific plaque scores did not seem to have incremental value over CAD severity and LVEF; however, summed segments with isolated calcific plaque and summed segments with calcific plaque or mixed plaque seemed to have similar incremental value as TPS (Table 8).

Discussion

Our study demonstrates that severity of CAD as measured by 64-slice CTA has prognostic value and extends the findings of previously performed studies. We confirm that the absence of obstructive CAD confers an excellent prognosis with an annual event rate $<0.4\%$ and that CAD severity (HR: 3.02; 95% CI: 1.89 to 4.83) and every 10% reduction in LVEF (HR: 1.47; 95% CI: 1.17 to 1.86) were independent predictors of MACE. We also demonstrate that TPS was an independent predictor (HR: 1.17; 95% CI: 1.06 to 1.29) and had incremental value for all-cause mortality and nonfatal MI.

An understanding of a new modality's diagnostic and prognostic value is required before adopting it into clinical practice. Numerous studies demonstrated that CTA has very good operating characteristics, but data supporting its prognostic value are limited. The results of our study

support previous studies that demonstrated the prognostic value of CTA (6,7,28). However, our study expands on previous literature by further investigating the prognosis of 64-slice CTA, in a large patient population using "hard" major adverse events (cardiac death, nonfatal MI, and all-cause mortality) using LVEF and plaque burden.

Prognostic value of CTA. Several groups examined the prognostic value of CTA and showed that normal CTA findings confer an excellent prognosis and abnormal CTA findings are associated with adverse events (6–10). Using a U.S. national death registry, Min et al. (6) examined the prognostic value of 16-slice CTA and Ostrom et al. (7) studied the prognostic value of electron beam CTA. In both studies, CAD severity and coronary atherosclerosis predicted all-cause mortality. However, their studies were not able to stratify according to cause of death nor did they track other MACE such as cardiac death and nonfatal MI. Several other CTA prognosis studies collected MACE as end points but have been small (8–10,28) with short follow-up (8,9), and some have been driven by early revascularization (9,10). Our results expand on previous literature by using 64-slice CTA, capturing MACE, but also highlighting the incremental value of LVEF and plaque burden.

Prognostic value of LVEF. The prognostic value of LVEF has been well established and is used routinely in clinical practice. Because many centers perform CTA with a retrospective ECG-gated acquisition protocol, LV volumes are routinely available. Because LVEF measured by CTA seems to be accurate and similar to measurements using magnetic resonance imaging (29,30), it may be used as an independent predictor of patient outcomes. The results of

| Table 6 Cox Models of CTA Measures (CAD Model 1) and All-Cause Mortality and Nonfatal MI | | | | |
|---|-----------------------|---------|-------------------------|---------------------------|
| Models | Hazard Ratio (95% CI) | p Value | Global Chi-Square Value | Model Comparisons p Value |
| Clinical variables | | | | |
| NCEP/ATPIII risk | 2.98 (1.64–5.43) | <0.001 | 31.38 | |
| Pre-test likelihood for CAD | 1.85 (1.17–2.94) | 0.009 | | |
| Clinical + CAD | | | | |
| NCEP/ATPIII risk | 2.56 (1.41–4.64) | 0.002 | 58.61 | <0.001 |
| Pre-test likelihood for CAD | 1.44 (0.92–2.25) | 0.111 | | |
| CAD severity | 2.82 (1.95–4.09) | <0.001 | | |
| No CAD | 0.27 (0.06–1.22) | 0.090 | | |
| Nonobstructive CAD (<50%) | 1.0 | — | | |
| Obstructive (≥50%), not high risk | 3.79 (1.89–7.57) | <0.001 | | |
| Obstructive, high risk | 5.61 (1.94–16.20) | 0.001 | | |
| Clinical + CAD + LVEF | | | | |
| NCEP/ATPIII risk | 2.41 (1.32–4.39) | 0.004 | 78.88 | <0.001 |
| Pre-test likelihood for CAD | 1.44 (0.93–2.23) | 0.102 | | |
| CAD severity | 2.91 (2.00–4.24) | <0.001 | | |
| No CAD | 0.28 (0.06–1.26) | 0.097 | | |
| Nonobstructive CAD (<50%) | 1.0 | — | | |
| Obstructive (≥50%), not high risk | 3.93 (1.96–7.88) | <0.001 | | |
| Obstructive, high risk | 6.15 (2.13–17.74) | <0.001 | | |
| LVEF (10% reduction) | 1.50 (1.25–1.81) | <0.001 | | |
| Clinical + CAD + LVEF + TPS | | | | |
| NCEP/ATPIII risk | 2.30 (1.26–4.21) | 0.007 | 87.27 | 0.004 |
| Pre-test likelihood for CAD | 1.31 (0.85–2.03) | 0.200 | | |
| CAD severity | 1.66 (0.98–2.80) | 0.058 | | |
| No CAD | 0.53 (0.11–2.54) | 0.424 | | |
| Nonobstructive CAD (<50%) | 1.0 | — | | |
| Obstructive (≥50%), not high risk | 2.24 (1.02–4.92) | 0.046 | | |
| Obstructive, high risk | 2.21 (0.64–7.67) | 0.212 | | |
| LVEF (10% reduction) | 1.51 (1.26–1.82) | <0.001 | | |
| TPS | 1.17 (1.06–1.29) | 0.002 | | |

TPS = total plaque score; other abbreviations as in Tables 1 to 4.

our study support the findings of previous studies and the incremental value of LVEF for MACE (12). We propose that LVEF be measured and reported whenever possible.

Prognostic value of CT plaque imaging. CTA is a noninvasive modality capable of detecting obstructive and nonobstructive CAD (2,3) and compares well with intra-

vascular ultrasonography for the detection and/or exclusion of atherosclerotic plaque (20,31–33). The identification of subclinical calcific and noncalcific atherosclerosis may be important because 1) the extent of plaque has been shown to predict myocardial ischemia (34); and 2) nonobstructive lesions are frequently the culprits in acute coronary syn-

| Table 7 Cox Models of CTA Measures (CAD Model 1) and All-Cause Mortality | | | | |
|---|-----------------------|---------|-------------------------|---------------------------|
| Models | Hazard Ratio (95% CI) | p Value | Global Chi-Square Value | Model Comparisons p Value |
| Clinical variables | | | | |
| NCEP/ATP III risk | 3.85 (1.78–8.33) | <0.001 | 13.58 | |
| Pre-test likelihood for CAD | 1.06 (0.60–1.90) | 0.835 | | |
| Clinical + CAD | | | | |
| NCEP/ATP III risk | 3.23 (1.49–7.01) | 0.003 | 27.92 | <0.001 |
| Pre-test likelihood for CAD | 0.88 (0.50–1.54) | 0.648 | | |
| CAD severity | 2.50 (1.55–4.04) | <0.001 | | |
| No CAD | 0.25 (0.03–2.03) | 0.194 | | |
| Nonobstructive CAD (<50%) | 1.0 | — | | |
| Obstructive (≥50%), not high risk | 4.14 (1.70–10.05) | 0.002 | | |
| Obstructive, high risk | 7.08 (2.02–24.79) | 0.002 | | |

Abbreviations as in Tables 1 and 4.

| Table 8 Incremental Values of Plaque Characteristics Over CTA Measures (CAD Model 1) for MACE | | | | |
|---|-----------------------|---------|-------------------------|----------------------------|
| Models | Hazard Ratio (95% CI) | p Value | Global Chi-Square Value | Model Comparisons p Value* |
| CAD + LVEF | | | | |
| CAD severity | 3.67 (2.36–5.70) | <0.001 | 48.50 | |
| LVEF (10% reduction) | 1.49 (1.18–1.89) | <0.001 | | |
| CAD + LVEF + isolated noncalcific plaque | | | | |
| CAD severity | 3.48 (2.20–5.51) | <0.001 | 48.65 | 0.699 |
| LVEF (10% reduction) | 1.52 (1.20–1.93) | <0.001 | | |
| Only soft plaque score | 1.11 (0.93–1.33) | 0.262 | | |
| CAD + LVEF + isolated calcific plaque | | | | |
| CAD severity | 3.32 (2.09–5.27) | <0.001 | 52.77 | 0.039 |
| LVEF (10% reduction) | 1.50 (1.19–1.89) | <0.001 | | |
| Isolated calcific plaque | 1.15 (1.01–1.31) | 0.036 | | |
| CAD + LVEF + noncalcific and mixed plaque | | | | |
| CAD severity | 2.34 (1.30–4.23) | 0.005 | 53.56 | 0.024 |
| LVEF (10% reduction) | 1.52 (1.20–1.93) | <0.001 | | |
| Noncalcific and mixed plaque | 1.15 (1.02–1.29) | 0.018 | | |
| CAD + LVEF + mixed plaque | | | | |
| CAD severity | 2.64 (1.51–4.62) | <0.001 | 53.89 | 0.020 |
| LVEF (10% reduction) | 1.49 (1.18–1.88) | <0.001 | | |
| Mixed plaque | 1.13 (1.00–1.27) | 0.053 | | |
| CAD + LVEF + calcific and mixed plaque | | | | |
| CAD severity | 2.10 (1.18–3.75) | 0.012 | 57.45 | 0.003 |
| LVEF (10% reduction) | 1.48 (1.18–1.87) | <0.001 | | |
| Calcific and mixed plaque | 1.18 (1.06–1.32) | 0.002 | | |
| CAD + LVEF + TPS | | | | |
| CAD severity | 1.55 (0.83–2.90) | 0.166 | 58.02 | 0.002 |
| LVEF (10% reduction) | 1.53 (1.21–1.93) | <0.001 | | |
| TPS | 1.27 (1.13–1.43) | <0.001 | | |

*Compared with the model CAD + LVEF.
 Abbreviations as in Tables 1 to 4 and 6.

dromes and sudden cardiac death (35,36). Matsumoto et al. (37) showed that patients with mild and moderate coronary stenoses (25% to 75% stenosis) had annual death and acute coronary syndrome event rates of 0.25% and 0.93%, respectively. Motoyama et al. (38) demonstrated that coronary segments with positive remodeling and low attenuation plaques were predictors of acute coronary syndromes. Although investigators are beginning to focus on specific plaque characteristics that hold promise, we sought a simple measure that can be easily performed and incorporated into clinical practice. Interobserver variability was assessed in a subgroup of 828 patients and demonstrated very good correlation between readers ($r = 0.92$, $p < 0.001$). The results of our study demonstrate that a simple measure of plaque (TPS) was a predictor of all-cause mortality and nonfatal MI and had incremental value over CAD and LVEF. Due to potential model overfitting error, the incremental value of TPS could not be assessed using our primary outcome of MACE but should be a focus of future studies.

Acknowledging the potential value of plaque composition, we also examined plaque characteristics. Although isolated noncalcific plaque did not seem to have incremental value over CAD severity and LVEF, summed segments with calcific and/or mixed plaque and TPS seemed to have

the greatest incremental value. Plaque with calcific components may be an important feature in predicting adverse events; however, further research is needed.

Nonfatal MI. Recognizing that MI post-percutaneous intervention (type IV MI) could increase event rates, all MI records were reviewed. One patient had a type IV MI, but excluding this patient from analysis did not change study results.

All-cause mortality. We observed a lower rate of all-cause mortality in patients with high-risk CAD than non-high-risk CAD. Although these results were unexpected, 2 reasons may be offered. 1) It is possible that, due to the small population of patients with high-risk CAD, these observations occurred by chance. 2) One may also speculate that there may have been fewer noncardiac deaths in revascularized patients because they may have been better able to tolerate noncardiac illnesses such as sepsis.

Study limitations. This was a single-center, prospective study, and the results of our study may not necessarily reflect the patient population or physician practice at other centers. Given the limited number of events, we recognize that our analysis is subject to overfitting; however, a recent article (39) suggests that current rules may be too conservative. Additionally, our sensitivity analysis suggests that this is

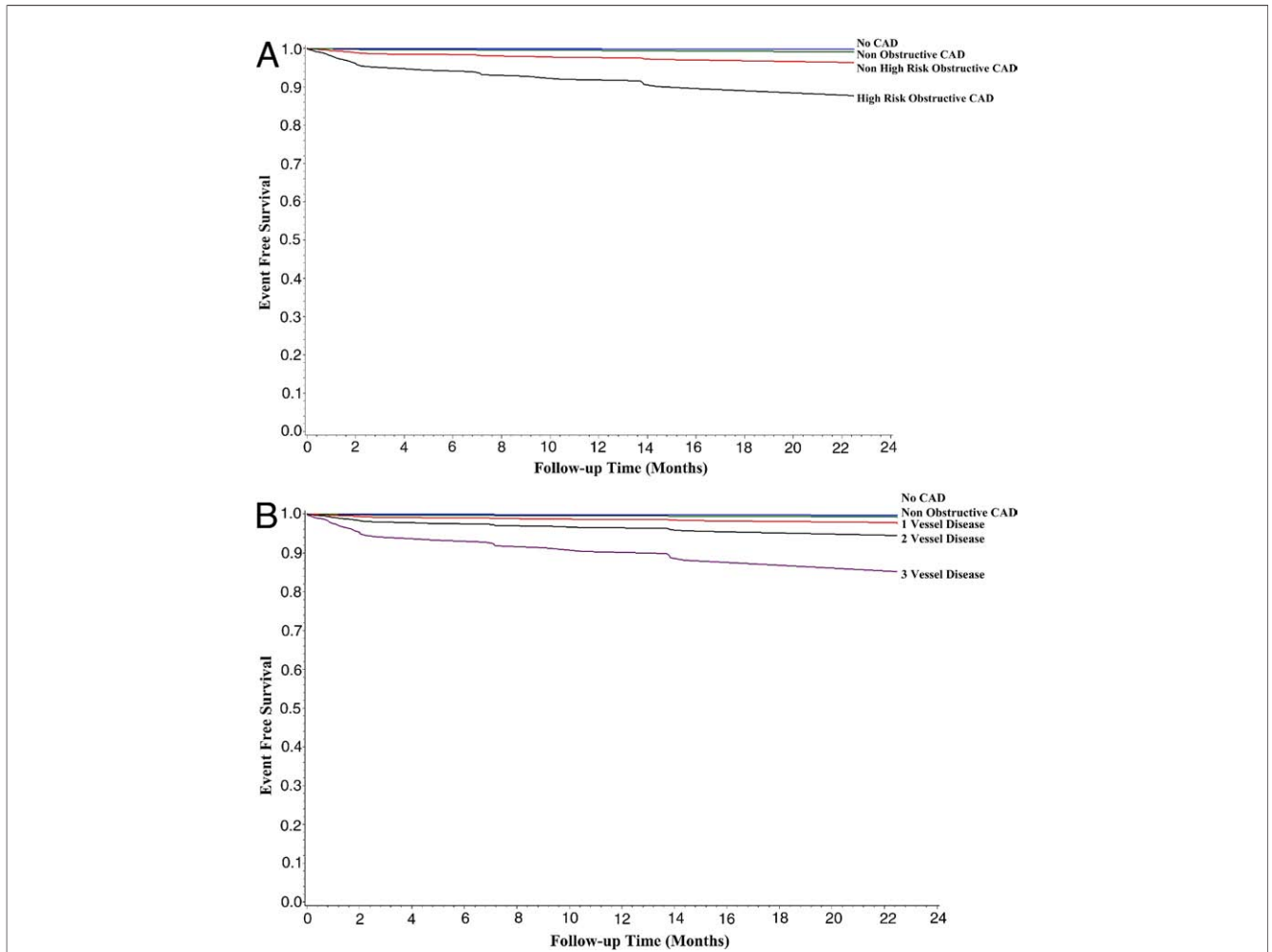


Figure 2 Risk-Adjusted MACE-Free Survival as a Function of CAD Severity: Models 1 and 2

(A) Risk-adjusted major adverse coronary event (MACE)-free survival as a function of coronary artery disease (CAD) severity (model 1) for patients without coronary atherosclerosis (**blue line**), nonobstructive CAD (**green line**), non-high-risk CAD (**red line**), and high-risk CAD (**black line**); log rank $p < 0.001$. **(B)** Risk-adjusted MACE-free survival as a function of CAD severity (model 2) for patients without coronary atherosclerosis (**blue line**), nonobstructive CAD (**green line**), single-vessel disease (**red line**), double-vessel disease (**black line**), and triple-vessel disease (**purple line**); log rank $p < 0.001$.

unlikely. Our results are similar to those of previous prognostic studies and thus lend further evidence to the prognostic value of CTA. Large multicenter cohort studies with extended follow-up are still required to fully comprehend the prognostic value of CTA.

We also recognize that incomplete follow-up may result in underreporting of MACE. However, the follow-up in our study was excellent (95.6%) and similar to that of previous prognostic studies (40). Because the 96 patients lost to follow-up were younger (Table 1), we do not believe that there is significant bias introduced by the lost to follow-up group. In addition, because cardiac catheterization services and cardiac surgery are centralized to our tertiary-care center (servicing a population of 1.5 million to 1.8 million), the majority of cardiac events and revascularization procedures would have been performed locally and thus captured in our database.

It is accepted that coronary calcium scores have prognostic value in the asymptomatic population (13). Because our population was primarily symptomatic, coronary calcium scores were not routinely performed. Although the incremental value of the Agatston score over CTA and LVEF could not be assessed, summed segments with isolated calcific plaque did not seem to have incremental value over TPS, but summed segments with calcific and/or mixed plaque had similar value as TPS.

We recognize that contrast administration and image acquisition protocols vary among physicians and centers. In our study, contrast flow rates were left to the discretion of the physician, which may lead to protocol inconsistencies; however, we believe that these effects are minimal because the local practice of physicians is similar.

Future directions. The results of our study and those of others have demonstrated the potential prognostic value of

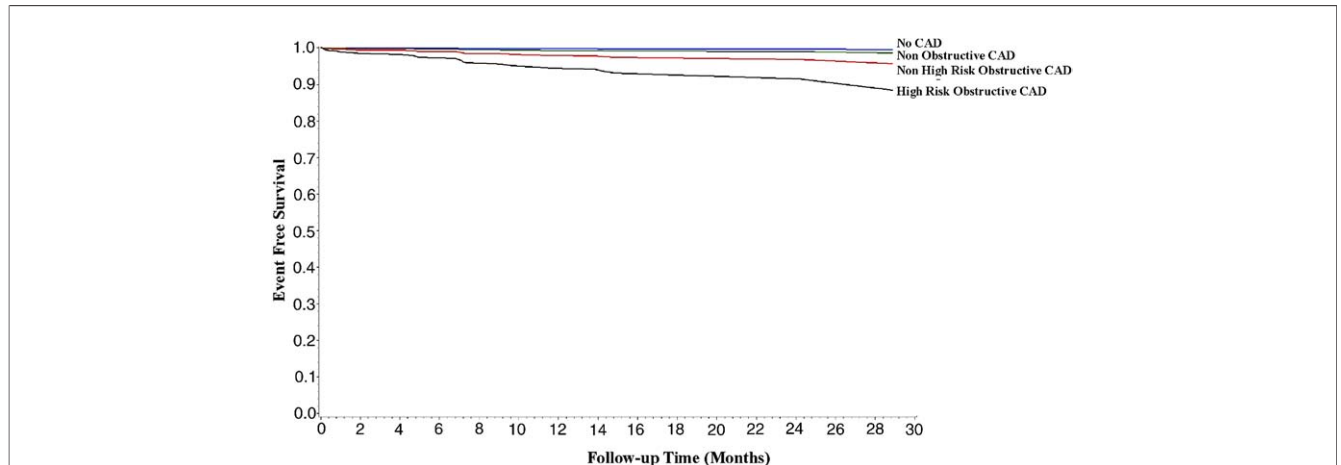


Figure 3 Risk-Adjusted All-Cause Mortality-Free Survival as a Function of CAD Severity (Model 1)

Risk-adjusted all-cause mortality-free survival as a function of coronary artery disease (CAD) severity (model 1) for patients without coronary atherosclerosis (blue line), nonobstructive CAD (green line), non-high-risk CAD (red line), and high-risk CAD (black line); log rank $p < 0.001$.

CTA; however, further studies are needed. Other measures of CAD severity, such as the Duke CAD index, may prove to have value in CTA, but require further investigation (23).

The functional assessment of CAD has incremental prognostic value (41). Whether functional assessment with CTA (42) or other noninvasive modalities has incremental value over the severity of CAD, TPS, and LVEF requires further investigation. In addition, of great interest would be the direct comparison of the prognostic value of CTA with other accepted noninvasive modalities.

Although earlier identification of nonobstructive CAD seems desirable, enthusiasm must be tempered by the fact that the treatment of nonobstructive CAD has not been shown to reduce cardiac morbidity and mortality in a cost-effective manner. Studies examining the beneficial impact of early coronary atherosclerosis detection, plaque characterization, and therapy are also required.

Conclusions

Assessment of CAD severity, TPS, and LVEF with CTA has prognostic value and has incremental value over routine clinical predictors. Although CAD severity is the strongest predictor of adverse events, LVEF and TPS seem to have incremental value. Plaque with calcific components seems to be associated with MACE, but further studies are required. CTA seems to be a promising noninvasive modality with prognostic value.

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