Coronary Artery Disease

Prognostic Value of Nonobstructive and Obstructive Coronary Artery Disease Detected by Coronary Computed Tomography Angiography to Identify Cardiovascular Events

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Background—The contribution of plaque extent to predict cardiovascular events among patients with nonobstructive and obstructive coronary artery disease (CAD) is not well defined. Our objective was to evaluate the prognostic value of plaque extent detected by coronary computed tomography angiography.

Methods and Results—All consecutive patients without prior CAD referred for coronary computed tomography angiography to evaluate for CAD were included. Examination findings were classified as normal, nonobstructive (<50% stenosis), or obstructive (≥50%). Based on the number of segments with disease, extent of CAD was classified as nonextensive (≤4 segments) or extensive (>4 segments). The cohort included 3242 patients followed for the primary outcome of cardiovascular death or myocardial infarction for a median of 3.6 (2.1–5.0) years. In a multivariable analysis, the presence of extensive nonobstructive CAD (hazard ratio, 3.1; 95% confidence interval, 1.5–6.4), nonextensive obstructive (hazard ratio, 3.0; 95% confidence interval, 1.3–6.9), and extensive obstructive CAD (hazard ratio, 3.9; 95% confidence interval, 2.2–7.2) were associated with an increased rate of events, whereas nonextensive, nonobstructive CAD was not. The addition of plaque extent to a model that included clinical probability as well as the presence and severity of CAD improved risk prediction.

Conclusions—Among patients with nonobstructive CAD, those with extensive plaque experienced a higher rate of cardiovascular death or myocardial infarction, comparable with those who have nonextensive disease. Even among patients with obstructive CAD, greater extent of nonobstructive plaque was associated with higher event rate. Our findings suggest that regardless of whether obstructive or nonobstructive disease is present, the extent of plaque detected by coronary computed tomography angiography enhances risk assessment. (Circ Cardiovasc Imaging. 2014;7:282-291.)

Key Words: coronary artery disease ■ prognosis ■ risk assessment

Coronary computed tomography angiography (CTA) is a noninvasive imaging technique that allows for accurate detection and exclusion of coronary artery disease (CAD) in symptomatic patients. Because of its availability and favorable diagnostic characteristics, coronary CTA was adopted before comprehensive data on its prognostic value became available.

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Several large, recent studies have demonstrated the impact of coronary CTA on prognosis, although the follow-up time has been relatively short.1,2 Only 1 study has evaluated the longer-term follow-up of cardiovascular events among patients referred for coronary CTA.3 Because patients referred for...
coronary CTA have a low short-term event rate, additional long-term follow-up data are needed to better identify patients at risk for future cardiovascular events.

One particular feature of using coronary CTA to evaluate for CAD is that it provides information on the presence and extent of nonobstructive CAD. Although such disease is unlikely to be detected by functional stress imaging techniques, emerging data suggest that nonobstructive plaque may have an important role in the development of acute coronary events\(^5,6\) and is a predictor of all-cause mortality.\(^2,6\) However, limited data exist on whether nonobstructive plaque is independently associated with higher rate of cardiovascular events.

Therefore, the present study evaluates the long-term prognostic value of the presence and extent of both nonobstructive and obstructive CAD to predict cardiovascular death, myocardial infarction (MI), and coronary revascularizations among patients referred for coronary CTA for the evaluation of CAD.

**Methods**

**Study Population**

We included all consecutive subjects \(\geq 18\) years of age who underwent a clinically indicated coronary CTA for the evaluation of the coronary arteries at the Massachusetts General Hospital or Brigham and Women’s Hospital from 2004 to 2011. Both centers are experienced tertiary hospitals with expertise in the interpretation of coronary CTA and were early adopters of this technology. Patients with congenital heart disease, heart transplantation, or prior CAD, defined as prior percutaneous coronary interventions, coronary artery bypass surgery, or MI, were excluded. We also excluded studies performed for research purposes or for evaluation of masses or other noncoronary structures. The study was approved by the Human Research Committee of both institutions.

**CTA Examination Acquisition and Interpretation**

All scans were performed using 64-row CT scanners or newer technologies. The studies were performed according to established guidelines\(^7,8\) and institutional protocols at the time of the scan. After each scan, the images were reconstructed in single- or multiphase data sets, and images were interpreted using axial and multiplanar reformations. All scans were analyzed by level III trained cardiologists or radiologists with extensive experience in coronary CTA analysis. The coronary CTA s were interpreted according to current guidelines\(^4\) using a previously published 18-segment model.\(^1\) Each coronary segment with a \(\geq 2\)-mm diameter was analyzed for the presence of coronary atherosclerosis, and each lesion was quantified by visual estimation into 3 categories: normal, nonobstructive disease (1%–49% stenosis), and obstructive disease (\(\geq 50\)% stenosis). We excluded 55 scans (1.6%) that were considered uninterpretable because of poor image quality. For all other scans, the best estimate of the CAD for each segment was performed, even when images were of limited quality. Using the presence and extent of disease, each patient was categorized as having no disease, nonobstructive disease, 1-vessel obstructive disease, 2-vessel obstructive disease, and 3-vessel obstructive disease or left main obstruction. To further evaluate the impact of the extent of nonobstructive and obstructive CAD, we used the segment involvement score (SIS), which is the sum of the number of segments with plaque irrespective of the degree of luminal stenosis within each segment.\(^5\) Based on prior data that examined the association of all-cause mortality with extent of disease,\(^6\) we defined nonextensive disease as an SIS \(\leq 4\) and extensive disease as an SIS \(>4\). In addition, we tested this cutoff in our data and found that it was the most robust value to discriminate between patients with and without future cardiovascular events.

**Ascertainment of Risk Factors**

Systemic arterial hypertension was defined as a systolic blood pressure \(\geq 140\) mmHg, diastolic blood pressure \(\geq 90\) mmHg, or diagnosis of hypertension. Dyslipidemia was defined as total cholesterol \(>240\) mg/dL or serum triglycerides \(>150\) mg/dL or high-density lipoprotein cholesterol \(<40\) mg/dL (men) or \(<50\) mg/dL (women) or diagnosis/treatment of dyslipidemia. Diabetes mellitus was defined by a hemoglobin A1C \(\geq 6.5\)%,\(^6\) physician-based diagnosis, or use of anti-diabetic medications. Smoking was defined as current (tobacco products used within the last month), former, or never. Family history of premature CAD was defined as any first-degree family member with a history of clinical CAD before 60 years of age. The presence probability of CAD was calculated using the Morise score,\(^11\) which includes age, sex, risk factors, and symptoms to predict the probability of obstructive CAD.

**Cardiovascular Outcomes**

All patient charts were reviewed by 2 cardiologists who were blinded to coronary CTA results for the adjudication of cardiovascular events. To ensure that events outside of our healthcare network were captured, a standardized questionnaire was mailed to each patient. In addition, patients had the option of completing a web-based version of the questionnaire via the Research Electronic Data Capture system,\(^12\) which is encrypted, secure, and Health Insurance Portability and Accountability Act compliant. For patients who did not reply to the questionnaire on repeated mailings, scripted phone interviews were performed based on the questionnaire. All self-reported events were verified via outside medical record review by 2 cardiologists blinded to coronary CTA results, with discordant events adjudicated by consensus.

The primary outcome was a composite end point of cardiovascular death or nonfatal MI. The secondary end point included a composite end point of major cardiovascular events composed of cardiovascular mortality, nonfatal MI, late coronary revascularization (\(>90\) days), and unstable angina requiring hospital admission. In addition, a tertiar y analysis using the outcome of all-cause mortality was performed.

Deaths were confirmed by the Social Security Death Index. For all patients who died, the cause of death was obtained from the National Death Index. When data were not available, records from the Massachusetts Department of Vital Statistics were obtained. In addition, other pertinent clinical records (eg, death notes, autopsy findings, hospice notes) related to the cause of death were reviewed. Using all available data, the cause of death for each patient was adjudicated by 2 cardiologists blinded to the coronary CTA results. The cause of death was considered to be of cardiovascular origin if the primary cause was defined as acute MI, atherosclerotic coronary vascular disease, congestive heart failure, valvular heart disease, arhythmic heart disease, stroke, or other structural or primary cardiac cause of death. MI was defined when \(\geq 2\) of the following 3 criteria were met: chest pain or equivalent symptom complex, positive cardiac biomarkers, or typical ECG changes.\(^13\) For revascularizations, the time to the first coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass surgery) was evaluated. Early revascularizations (\(\leq 90\) days after coronary CTA) were censored in the survival analysis to minimize verification bias\(^14,16\), because patients with \(\geq 50\)% stenosis by coronary CTA may be referred to invasive angiography and revascularization based on the coronary CTA results alone. On the contrary, late revascularizations (\(>90\) days after coronary CTA) are more likely to be associated with CAD progression and were therefore included as part of the secondary composite end point. Unstable angina requiring admission was defined as chest pain or chest pain equivalent with dynamic ECG changes such as ST depression or T-wave inversion but without abnormal cardiac biomarkers and characterized by (1) rest symptoms, (2) new onset angina (\(<2\) months’ duration), or (3) increasing duration or severity of previously stable anginal symptoms.\(^17\)

**Statistical Analysis**

Continuous variables are expressed as mean±SD, except for time of follow-up and SIS, which is expressed as median and quartiles. Categorical variables are presented as frequencies. Differences between groups were tested using \(\chi^2\) or Fisher exact tests for discrete variables and 1-way analysis of variance for continuous variables. To describe the frequency of events according to time since the coronary CTA, we constructed Kaplan–Meier curves, and the results of
the rate of events were analyzed using a log-rank test. Univariable and multivariable Cox proportional hazards models were constructed to compare risk between groups for the primary, secondary, and tertiary outcomes. The assumption of nonproportional hazards model, a required assumption of Cox regression, was tested using a formal significance test base on the unscaled and scaled Schoenfeld residuals and resulted in nonsignificant findings in all analyses.

After estimating the hazards ratios for each of the outcomes, we computed the likelihood ratios for the following models: model 1—clinical pretest probability of CAD; model 2—clinical pretest probability and the presence/severity of CAD; and model 3—clinical pretest probability, presence/severity of CAD, and extent of plaque, as assessed by SIS ≤4 (nonextensive) and SIS >4 (extensive CAD criteria). We computed the receiver operating characteristic curves and compared models using global χ² the Akaike information criterion, and the area under the receiver operating characteristic curve for the 3 models. In addition, we evaluated the goodness-of-fit using the Gronnesby and Borgan test, in which a non-operating characteristic curve for the 3 models.

Statistical analysis was performed using Stata version 12 (Statacorp, College Station, TX), and statistical significance was defined as P<0.05 (2 tailed).

Results

Patient Population and Baseline Characteristics

Complete follow-up for cardiovascular events was available for 91.5% (3242/3544) of patients. These 3242 patients (57% men; mean age, 56±13 years) formed the study cohort (Table 1). Symptoms prompting the coronary CTA are presented in Table 1. Other concomitant indications included preoperative evaluation in 129 patients (4%), dyspnea in 540 (16%), and prior stress tests in 730 patients (22%). The presence of nonobstructive and obstructive CAD was associated with older age, male sex, and a higher proportion of risk factors. Patients lost to follow-up were younger and had a lower burden of CAD, lower prevalence of risk factors, and reduced mortality rate (Table in the Data Supplement).

Cardiovascular Outcomes

During a median follow-up time of 3.6 (2.1–5.0) years, 144 (4.4%) deaths, 56 (1.7%) cardiovascular deaths, 45 (1.4%) MIs, 56 (1.7%) unstable angina requiring hospitalization events, and 87 (2.7%) late revascularizations occurred. Overall, 92 patients (2.8%) experienced the primary outcome of cardiovascular death or MI, whereas 195 patients (6.0%) experienced the secondary outcome of major cardiovascular events.

Patients who experienced cardiovascular death or MI were older and had a higher prevalence of hypertension, diabetes mellitus, and history of smoking. However, sex, family history of CAD, and presenting symptoms were not associated with cardiovascular death or MI (Table 2).

Coronary CTA and Cardiovascular Outcomes

When considering the coronary CTA examination results, 1301 (40%) had normal coronary CTA, 1224 (38%) had nonobstructive CAD, and 717 (22%) had obstructive CAD. Among the patients with nonobstructive CAD, the median number of segments with disease was 2, with 271 (22%) having >4 segments with disease. Among these patients, the subgroup with nonextensive disease (≤4 segments) had a median SIS of 2 (quartiles, 1–3), whereas those with extensive disease (>4 segments) had a median SIS of 6 (quartiles, 5–7). Among those with obstructive CAD, the median number of segments with plaque was 6, with 538 (75%) patients having >4 segments with disease. Among these patients, the subgroup with nonextensive disease (≤4 segments) had a median SIS of 3 (quartiles, 2–4), whereas those with extensive disease (>4 segments) had a median SIS of 7 (quartiles, 6–9). Among patients with obstructive CAD, 392 (55%) had 1-vessel, 180 (25%) had 2-vessel, and 145 (20%) had 3-vessel or left main obstructive CAD.

Table 1. Baseline Demographic Characteristics According to the Presence and Severity of CAD

<table>
<thead>
<tr>
<th></th>
<th>No CAD</th>
<th>&lt;50% Stenosis</th>
<th>&gt;50% Stenosis</th>
<th>Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects (%)</td>
<td>1301 (40)</td>
<td>1224 (38)</td>
<td>717 (22)</td>
<td>3242</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>48.4±12.2</td>
<td>59.5±11.4</td>
<td>64.1±10.8</td>
<td>56.0±13.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>619 (48)</td>
<td>724 (59)</td>
<td>515 (72)</td>
<td>1858 (57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>437 (38)</td>
<td>633 (60)</td>
<td>490 (78)</td>
<td>1560 (55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>113 (10)</td>
<td>165 (16)</td>
<td>157 (26)</td>
<td>435 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>439 (38)</td>
<td>645 (61)</td>
<td>512 (81)</td>
<td>1596 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior smoking</td>
<td>220 (17)</td>
<td>289 (24)</td>
<td>216 (30)</td>
<td>725 (22)</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>109 (8)</td>
<td>119 (10)</td>
<td>71 (10)</td>
<td>299 (9)</td>
<td></td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>336 (26)</td>
<td>352 (29)</td>
<td>217 (24)</td>
<td>905 (28)</td>
<td>0.11</td>
</tr>
<tr>
<td>Symptoms (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Nonanginal CP</td>
<td>513 (39)</td>
<td>511 (42)</td>
<td>300 (42)</td>
<td>1324 (41)</td>
<td></td>
</tr>
<tr>
<td>Atypical CP</td>
<td>528 (41)</td>
<td>488 (40)</td>
<td>289 (40)</td>
<td>1305 (40)</td>
<td></td>
</tr>
<tr>
<td>Typical CP</td>
<td>95 (7)</td>
<td>87 (7)</td>
<td>68 (9)</td>
<td>250 (8)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>105 (8)</td>
<td>86 (7)</td>
<td>41 (6)</td>
<td>232 (7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>60 (5)</td>
<td>52 (4)</td>
<td>19 (3)</td>
<td>131 (4)</td>
<td></td>
</tr>
<tr>
<td>Pretest probability of &gt;50% CAD</td>
<td>35±23</td>
<td>50±19</td>
<td>55±17</td>
<td>45±22</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The pretest probability of >50% stenosis was calculated using the Morise score, which includes age, sex, risk factors, and symptoms. CAD indicates coronary artery disease; and CP, chest pain.
The incidence of cardiovascular death or MI was 3.6 (95% confidence interval, 2.2–5.8) per 1000 patient years in the group with no CAD, 7.4 (5.2–10.3) for patients with nonobstructive CAD, and 17.6 (13.1–23.5) for patients with obstructive CAD (P<0.001). Among patients with either nonobstructive or obstructive CAD, greater extent of disease was associated with a higher event rate across all outcomes considered (Figure 1). Notably, patients with extensive (ie, >4 segments) nonobstructive plaque had a similar event rate as those with obstructive disease but ≤4 segments with CAD (14.5 versus 13.6; P=0.76 for cardiovascular death or MI and 26.6 versus 26.2; P=0.91 for major cardiovascular events).

**Figure 2** shows the unadjusted Kaplan–Meier cumulative event curves for cardiovascular death or MI (Figure 2A) and major cardiovascular events stratified by (Figure 2B) the presence and severity of disease. When patients with nonobstructive and obstructive disease were further stratified by extent of disease (SIS ≤4 versus >4, Figure 3), patients with more extensive disease were found to have lower survival rates across each outcome. Specifically, patients with nonobstructive CAD with an SIS ≤4 had a similar outcome as those with no CAD, whereas patients with nonobstructive CAD with an SIS >4 had a significant increase in adverse events (Figure 4A and Figures in the Data Supplement). Among the 717 patients with obstructive CAD, the presence of SIS >4 was associated with higher event rate for the primary, secondary, and tertiary outcomes (Figures 3 and 4B and Figures in the Data Supplement).

**Multivariable Models for Outcomes**

When compared with patients with no CAD, and after adjusting for pretest probability of obstructive CAD, the risk of cardiovascular death or MI was higher among the 717 patients with obstructive CAD (hazard ratio, 3.7; 95% confidence interval, 2.0–6.6). Among the 1224 patients with nonobstructive CAD, the hazard ratio was 1.6 (95% confidence interval, 0.9–3.0). When each group was further stratified by extent of CAD, the presence of >4 segments with plaque was associated with a higher rate of events for all outcomes (Figure 5 and Figures in the Data Supplement).

The 3 models used to predict cardiovascular death or MI are summarized in Table 3. When adding the presence and severity of CAD (model 2) to a model that included clinical characteristics (model 1), there was improved overall model fit with subsequent increase in the global \( \chi^2 \) from 23.5 to 46.6 (P<0.001). When the extent of nonobstructive and obstructive CAD (defined as an SIS ≤4 or >4) was then added to model 2, there was further improvement in model fit with an increase in the global \( \chi^2 \) to 53.4 (P<0.001 versus model 1 and P=0.03 versus model 2; Figure 6A). Similarly, with each successive model, there was a stepwise increase in model fit (global \( \chi^2 \)) for the prediction of major cardiovascular events as well as all-cause death (Figure 6B and 6C).

**Discussion**

In this study, we have evaluated the long-term prognostic value of coronary CTA findings in a large cohort of patients without
prior history of CAD. Similar to other studies, we found that during a median follow-up of 3.6 years, the presence and severity of CAD was associated with an increase in cardiovascular events. However, a novel finding in our study is that regardless of whether nonobstructive or obstructive disease was identified, data regarding extent of disease provided additional prognostic value. Patients with nonobstructive CAD who had extensive disease (eg, SIS >4) had a similar rate of cardiovascular death or MI as those with obstructive but less extensive disease. On the contrary, among those with nonobstructive plaque who had less extensive disease (eg, SIS ≤4), the rate of cardiovascular death or MI was similar to the rate observed among patients with no CAD. Notably, these findings persisted after adjusting for baseline patient characteristics.

The management of patients with nonobstructive CAD (which represented 38% of our cohort) has been debated because the clinical implications associated with such findings are often unknown. Furthermore, in the absence of quantitative techniques such as measuring coronary flow reserve,18,19 such patients would be expected to have normal functional test results. Although early coronary CTA studies have combined patients with nonobstructive disease with those who have no disease (mainly attributable to small sample size and limited statistical power),20,21 larger studies by Ostrom et al22 as well as Lin et al8 have suggested that the presence of nonobstructive plaque is associated with increased all-cause mortality. Building on prior studies, we were able to demonstrate that nonobstructive CAD is also associated with an increased risk of hard cardiovascular events (eg, cardiovascular death or MI) as well as an increase in the risk of late revascularizations. It is noteworthy that such patients would not be expected to be referred for early invasive evaluation because nonobstructive lesions are unlikely to be flow limiting or benefit from revascularization. Accordingly, we observed that the increased rate of interventions in this group occurs mainly during longer follow-up, possibly when those patients experienced progression of disease or an acute plaque rupture.23

Although patients with nonobstructive CAD are considered to have only mildly increased risk when compared with those who have no disease,2,3 our study demonstrates that incorporating data on extent of disease (as measured by the SIS score) allows the identification of individuals who have higher risk. Specifically, the 22% of patients with nonobstructive CAD with >4 segments with plaque had a similar rate of cardiovascular death or MI as those who had obstructive disease with ≤4 diseased segments.
On the contrary, the 78% of patients with nonobstructive disease with $\leq 4$ segments with plaque had a similar rate of cardiovascular death or MI as patients with no disease. Although it could be argued that many patients with plaque may be identified by virtue of their risk factors, Lin et al. have shown that even among patients with a low Framingham risk score, for which medical therapy would not be indicated, the extent of nonobstructive disease was associated with increased risk. Future studies are needed to evaluate whether treatment of patients with nonobstructive plaque will result in improved outcomes. Many studies on the prognosis of coronary CTA, including the Coronary CT Angiography Evaluation For Clinical Outcomes (CONFIRM) registry, have demonstrated that coronary CTA is a reliable method to predict all-cause mortality. Although the use of all-cause mortality avoids ascertainment bias from adjudicating cause of death or MI, current data suggest that only 1 in every 3 deaths has a cardiovascular cause. Consequently, the use of a nonspecific outcome, such as all-cause death, leads to misclassification that overestimates the annualized event rate in all subgroups. This causes a nondifferential measurement error that biases the estimates of relative hazard toward the null. Our study found that approximately one third of the death events observed were of cardiac cause, a finding that reinforces the potential limitations of extrapolating all-cause death rates to cardiovascular mortality or other cardiovascular events. Various other studies have also evaluated the prognostic value of coronary CTA for identifying a combination of cardiovascular death, MI, and revascularizations across different clinical scenarios. This has the advantage of focusing on outcomes that are associated with the actual disease process detected by coronary CTA. However, findings from these studies may be driven by revascularizations triggered by the coronary CTA findings. Although outcomes of cardiovascular death or MI may be superior in this regard, prior studies were small and underpowered for detecting differences for this harder outcome.

Our results corroborate prior findings on the value of coronary CTA to not only estimate risk of all-cause mortality but also demonstrate that the
absolute event rates continue to diverge during longer term follow-up. The findings of increased cardiovascular death/MI and major cardiovascular events are comparable with those of Andreini et al., which included 1304 patients undergoing coronary CTA. However, their study observed a significantly higher rate of MI or revascularizations, with 46% of those with obstructive disease having an MI or cardiovascular death. The high rate of hard events observed in this study suggests that this may have been a population with a higher risk profile than prior studies using coronary CTA. However, their study observed a significantly lower rate of coronary heart disease (rate, 0.04%/y). The first case was a 48-year-old woman who presented with an MI more than a year after coronary computed tomography angiography. On invasive angiography, who presented with an MI more than a year after coronary computed tomography angiography. Of 1301 patients with normal CTA, only 14 (1.0%) had events in this group during a median follow-up of 16 months. Although their study was underpowered to detect differences in prognosis in a subgroup of patients with nonobstructive CAD, the presence of obstructive disease, particularly high-risk anatomy, was associated with higher risk of events, even after adjustment for baseline risk factors and symptoms. Similar to our findings, the study by Chow et al. has demonstrated that the number of segments with plaque improves the overall prediction of events by coronary CTA.

Although most studies have reported no MI in patients with normal CTA, we found a low risk of coronary heart disease events among patients with normal coronary computed tomography angiography. Of 1301 patients with normal CTA, only 14 (1.0%) had events in this group during a median follow-up of 3.5 years. Among those events, there were 12 cardiovascular deaths (ie, heart failure, stroke, aortic disease) and only 2 MIs (rate, 0.04%/y). The first case was a 48-year-old woman who presented with an MI more than a year after coronary computed tomography angiography. On invasive angiography, she had stenosis of a small distal circumflex after the second obtuse marginal. Because of the small size of the vessel, no intervention was performed, and the patient was treated medically. The second patient was diagnosed with MI attributable to coronary vasospasm of the right coronary artery (with corresponding infarct demonstrated on cardiac MRI), although no coronary atherosclerosis was identified. Collectively, our findings support prior data on the association of a negative mammalian target of rapamycin inhibitor with a higher risk profile than prior studies using coronary CTA. Our data demonstrate a similar event rate as prior studies.

The study by Chow et al. clearly demonstrated the association of obstructive CAD and the combination of cardiovascular death and MI beyond clinical risk factors during a mean follow-up of 16 months. Although their study was underpowered to detect differences in prognosis in a subgroup of patients with nonobstructive CAD, the presence of obstructive disease, particularly high-risk anatomy, was associated with higher risk of events, even after adjustment for baseline risk factors and symptoms. Similar to our findings, the study by Chow et al. has demonstrated that the number of segments with plaque improves the overall prediction of events by coronary CTA.

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### Table 3. Comparison of Cox Models for the Prediction of Cardiovascular Death or Myocardial Infarction

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fit Statistic</td>
<td>P Value</td>
<td>Fit Statistic</td>
<td>P Value</td>
<td>Fit Statistic</td>
</tr>
<tr>
<td>Global $\chi^2$</td>
<td>23.5</td>
<td>&lt;0.001</td>
<td>46.6</td>
<td>&lt;0.001</td>
<td>53.4</td>
</tr>
<tr>
<td>AIC</td>
<td>1427.9</td>
<td>1408.9</td>
<td>1406.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C index</td>
<td>0.646</td>
<td>0.705</td>
<td>0.729</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goodness-of-fit $\chi^2$</td>
<td>4.1</td>
<td>0.52</td>
<td>2.6</td>
<td>0.75</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Covariates

- Clinical probability (per 10%): $1.3 (1.1–1.4)$ <0.001
- CAD presence and severity: $1.2 (1.1–1.3)$ 0.003
- Nonobstructive: $1.6 (0.9–3.0)$ 0.11
- Obstructive: $3.7 (2.0–6.6)$ <0.001

The study by Chow et al. clearly demonstrated the association of obstructive CAD and the combination of cardiovascular death and MI beyond clinical risk factors during a mean follow-up of 16 months. Although their study was underpowered to detect differences in prognosis in a subgroup of patients with nonobstructive CAD, the presence of obstructive disease, particularly high-risk anatomy, was associated with higher risk of events, even after adjustment for baseline risk factors and symptoms. Similar to our findings, the study by Chow et al. has demonstrated that the number of segments with plaque improves the overall prediction of events by coronary CTA.

Although most studies have reported no MI in patients with normal CTA, we found a low risk of coronary heart disease events among patients with normal coronary computed tomography angiography. Of 1301 patients with normal CTA, only 14 (1.0%) had events in this group during a median follow-up of 3.5 years. Among those events, there were 12 cardiovascular deaths (ie, heart failure, stroke, aortic disease) and only 2 MIs (rate, 0.04%/y). The first case was a 48-year-old woman who presented with an MI more than a year after coronary computed tomography angiography. On invasive angiography, she had stenosis of a small distal circumflex after the second obstruse marginal. Because of the small size of the vessel, no intervention was performed, and the patient was treated medically. The second patient was diagnosed with MI attributable to coronary vasospasm of the right coronary artery (with corresponding infarct demonstrated on cardiac MRI), although no coronary atherosclerosis was identified. Collectively, our findings support prior data on the association of a negative mammalian target of rapamycin inhibitor with a higher risk profile than prior studies using coronary CTA. Our data demonstrate a similar event rate as prior studies.

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Our study was conducted in 2 experienced tertiary centers, which might not be representative of the patient profile and clinical use of coronary CTA in other centers. Finally, the current results are limited to patients with a clinically indicated coronary CTA and should not be extrapolated to asymptomatic patients.

Despite these limitations, we present 1 of the largest and longer follow-up cohort of patients followed for cardiovascular-specific outcomes after coronary CTA. Because of the use of electronic medical records across our healthcare network as well as additional patient follow-up mechanisms (eg, questionnaires, phone interviews), we captured excellent long-term follow-up data. In addition to having detailed information regarding all cardiovascular events within our network, medical information on all events outside our system was collected to ensure high-quality event adjudication.

In conclusion, the presence, extent, and severity of non-obstructive and obstructive CAD added incremental value to the long-term prediction of cardiovascular death and MI across a large population of patients without prior history of CAD referred for coronary CTA. In particular, among patients with nonobstructive CAD, those with >4 segments of disease experienced a significantly higher rate of cardiovascular death or MI, comparable with those who have obstructive disease with ≤4 diseased segments. Similarly, among patients with obstructive CAD, greater extent of nonobstructive plaque was associated with higher event rate. These findings suggest that, regardless of whether obstructive or nonobstructive disease is present, the extent of plaque detected by coronary CTA enhances risk assessment. Whether treatment of patients based on these findings leads to improved outcomes remains to be studied.

Figure 6. A, Comparison of the models to predict cardiovascular (CV) death or myocardial infarction (MI). Model 1 includes the clinical probability score (including age, sex, symptoms, and risk factors). Model 2 includes the clinical probability and the information on the presence and severity of coronary artery disease (CAD) in the coronary computed tomography angiography (CTA). Model 3 includes model 1 and the presence, severity, and extent of CAD in the coronary CTA. B, Comparison of the models to predict major cardiovascular events. C, Comparison of the models to predict all-cause death.

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Dr Bittencourt was supported by the J.P. Lemann Foundation as a Jorge Paulo Lemann Harvard Medical School Cardiovascular Fellow at Brigham and Women’s Hospital.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Although it is known that the presence and severity of coronary artery disease (CAD) detected by coronary computed tomography angiography is associated with adverse cardiovascular events, the current study sought to evaluate the prognostic value of plaque extent for identifying hard cardiovascular events. We included 3242 patients without prior CAD who were referred for coronary computed tomography angiography. Patients were followed for a median of 3.6 years for the primary outcome of cardiovascular death and myocardial infarction. Our results demonstrated that, regardless of whether obstructive or nonobstructive disease is present, plaque extent (ie, >4 segments with CAD) has independent and incremental prognostic value beyond clinical risk factors. Importantly, patients with nonobstructive CAD who had plaque that involved >4 segments had a similar rate of cardiovascular death or myocardial infarction as those with obstructive CAD (≥50%) and ≤4 segments with CAD. Our results highlight the need for incorporating data on extent of plaque when reporting computed tomography angiography and suggest that patients with extensive plaque should be considered for more aggressive preventive therapies.
Prognostic Value of Nonobstructive and Obstructive Coronary Artery Disease Detected by Coronary Computed Tomography Angiography to Identify Cardiovascular Events
Marcio Sommer Bittencourt, Edward Hulten, Brian Ghoshhajra, Daniel O'Leary, Mitalee P. Christman, Philip Montana, Quynh A. Truong, Michael Steignier, Venkatesh L. Murthy, Frank J. Rybicki, Khurram Nasir, Luis Henrique W. Gowdak, Jon Hainer, Thomas J. Brady, Marcelo F. Di Carli, Udo Hoffmann, Suhny Abbara and Ron Blankstein

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### Supplemental data

#### Supplemental table 1: Baseline demographic characteristics stratified by complete and incomplete follow up.

<table>
<thead>
<tr>
<th></th>
<th>Complete Follow up</th>
<th>Incomplete follow up</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>3242</td>
<td>310</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>56.0±13.3</td>
<td>50.4±13.4</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Male (%)</strong></td>
<td>1858 (57)</td>
<td>114 (37)</td>
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<td>0.04</td>
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<tr>
<td><strong>Hypertension (%)</strong></td>
<td>1560 (55)</td>
<td>22 (7)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus (%)</strong></td>
<td>435 (16)</td>
<td>15 (5)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Dyslipidemia (%)</strong></td>
<td>1596 (56)</td>
<td>62 (20)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Smoking (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Prior smoking</strong></td>
<td>725 (22)</td>
<td>25 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current smoking</strong></td>
<td>299 (9)</td>
<td>25 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Family history of CAD</strong></td>
<td>905 (28)</td>
<td>29 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Coronary CTA results</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td>1301 (40)</td>
<td>150 (48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-obstructive</strong></td>
<td>1224 (38)</td>
<td>106 (34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Obstructive</strong></td>
<td>717 (22)</td>
<td>54 (7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The pre-test probability of >50% stenosis was calculated using the Morise score, which includes age, gender, risk factors and symptoms.
Supplemental Figure 1: Survival free from all-cause death according to the presence and severity of disease.
Supplemental Figure 2: Adjusted hazard ratios for the incidence of all-cause death. Cox proportional hazard models adjusted for the clinical probability, which includes age, gender, risk factors and symptoms.