Prognostic Value of Non-Obstructive and Obstructive Coronary Artery Disease Detected by Coronary Computed Tomography Angiography To Identify Cardiovascular Events

Bittencourt et al: Prognosis of Non-obstructive and Obstructive CAD

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Abstract

Background—The contribution of plaque extent to predict cardiovascular (CV) events among patients with non-obstructive 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 (CTA).

Methods and Results—All consecutive patients without prior CAD referred for coronary CTA to evaluate for CAD were included. Exam findings were classified as normal, non-obstructive (<50% stenosis) or obstructive (≥50%). Based on the number of segments with disease, extent of CAD was classified as non-extensive (≤4 segments) or extensive (>4 segments). The cohort included 3242 patients followed for the primary outcome of cardiovascular (CV) death or myocardial infarction (MI) for a median of 3.6 (2.1 – 5.0) years. In a multivariable analysis, the presence of extensive non-obstructive CAD (HR 3.1, 95% confidence interval (CI):1.5–6.4); non-extensive obstructive (HR 3.0, 95%CI: 1.3–6.9) and extensive obstructive CAD (HR:3.9, 95%CI:2.2–7.2) were associated with an increased rate of events, while non-extensive non-obstructive 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 non-obstructive CAD, those with extensive plaque experienced a higher rate CV death or MI, comparable to those who have non-extensive obstructive disease. Even among patients with obstructive CAD, greater extent of non-obstructive plaque was associated with higher event rate. Our findings suggest that regardless whether obstructive or non-obstructive disease is present, the extent of plaque detected by coronary CTA enhances risk assessment.

Key Words: computed tomography angiography, prognosis, risk assessment, coronary artery disease
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. Due to its availability and favorable diagnostic characteristics, coronary CTA was adopted before comprehensive data on its prognostic value became available.

Several large, recent studies have demonstrated the impact of coronary CTA on prognosis, although the follow up time has been relatively short.\textsuperscript{1,2} Only one study has evaluated the longer term follow up of cardiovascular (CV) events among patients referred for coronary CTA.\textsuperscript{3} Since patients referred for coronary CTA have a low short-term event rate, additional long-term follow-up data is needed in order 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 non-obstructive CAD. While such disease is unlikely to be detected by functional stress imaging techniques, emerging data suggests that non-obstructive plaque may have an important role in the development of acute coronary events,\textsuperscript{4,5} and is a predictor of all-cause mortality.\textsuperscript{2,6} However, limited data exists on whether non-obstructive plaque is independently associated with higher rate of CV events.

Therefore, the present study evaluates the long-term prognostic value of the presence and extent of both non-obstructive and obstructive CAD to predict CV 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 18 years or older, 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 CTAs and were early adopters of this technology. Patients with congenital heart disease, heart transplant or prior CAD, defined as prior percutaneous coronary interventions (PCI), coronary artery bypass surgery (CABG) or MI, were excluded. We also excluded studies performed for research purposes, or for evaluation of masses or other non-coronary structures. The study was approved by the Human Research Committee of both institutions.

CTA exam acquisition and interpretation

All scans were performed using 64 row computed tomography scanners or newer technologies. The studies were performed according to established guidelines,7, 8 and institutional protocols at the time of the scan. Following each scan, the images were reconstructed in single or multiphase datasets 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 CTAs were interpreted according to current guidelines8 using a previously published 18-segment model.8 Each coronary segment with a greater than 2 mm diameter was analyzed for the presence of coronary atherosclerosis and each lesion was quantified by visual estimation into 3 categories: normal, non-obstructive disease (1 to 49% stenosis) and obstructive disease (≥50% stenosis). We excluded 55 scans (1.6%) which
were considered uninterpretable due to 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, non-obstructive 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 non-obstructive 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. Based on prior data which examines the association of all-cause mortality with extent of disease, we defined non-extensive disease as a SIS ≤4 and extensive disease as an SIS >4. In addition, we tested this cut-off 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 > 140 mmHg, diastolic blood pressure > 90 mmHg, or diagnosis/treatment of hypertension. Dyslipidemia was defined as total cholesterol > 240 mg/dL or serum triglycerides > 150 mg/dL or high density lipoprotein cholesterol (HDL) <40 mg/dL (male) or < 50 mg/dL (women) or diagnosis/treatment of dyslipidemia. Diabetes was defined by a hemoglobin A1C ≥6.5%, 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 prior to age 60. The pretest probability of CAD was calculated using the Morise score, which includes age, gender, risk factors and symptoms to predict the probability of obstructive CAD.
Cardiovascular outcomes

All patient charts were reviewed by two 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. Additionally, patients had the option of completing a web-based version of the questionnaire via the REDCap (Research Electronic Data Capture) system,12 which is encrypted, secure, and HIPAA compliant. For patients who did not reply to the questionnaire upon repeated mailings, scripted phone interviews were performed based on the questionnaire. All self-reported events were verified via outside medical record review by two cardiologists blinded to coronary CTA results with discordant events adjudicated by consensus.

The primary outcome was a composite end-point of CV death or non-fatal MI. The secondary end-point of included a composite end-point of the major adverse cardiovascular events (MACE) composed of CV mortality, non-fatal MI, late coronary revascularization (>90 days) and unstable angina requiring hospital admission. Additionally, a tertiary 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 was not available, records from the Massachusetts Department of Vital Statistics were obtained. In addition, other pertinent clinical records (e.g. 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 two 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,
arrhythmic heart disease, stroke, or other structural or primary cardiac cause of death. MI was defined when at least two of the following three criteria were met: chest pain or equivalent symptom complex; positive cardiac biomarkers; or typical electrocardiogram (ECG) changes.\textsuperscript{13} For revascularizations, the time to the first coronary revascularization procedure (PCI or CABG) was evaluated. Early revascularizations (\(\leq 90\) days post coronary CTA) were censored in the survival analysis to minimize verification bias,\textsuperscript{14-16} as 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 other hand, late revascularizations (>90 days post 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 (less than 2 months duration); or, 3) increasing duration or severity of previously stable anginal symptoms.\textsuperscript{17}

**Statistical analysis**

Continuous variables are expressed as mean \(\pm\) standard deviation, expect 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-square or Fisher’s exact tests for discrete variables and one-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 non-proportional 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 non-significant 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; model 3 - clinical pretest probability, presence/severity of CAD, and extent of plaque, as assessed by SIS \( \leq 4 \) (non-extensive) and SIS > 4 (extensive CAD criteria). We computed the receiver operating characteristics (ROC) curves compared models using global \( \chi^2 \) and Akaike Information Criterion (AIC), the area under the ROC curve for the 3 models. Additionally, we evaluated the goodness-of-fit using the Gronnesby and Borgan test, where a non-significant p value indicates good fit of the model.

Statistical analysis was performed using Stata version 12 (Statacorp, College Station, USA), and statistical significance was defined as \( p < 0.05 \) (two-tailed).

**Results**

**Patient Population and baseline characteristics**

Complete follow up for cardiovascular events was available for 91.5% (3,242/ 3,544) of patients. These 3,242 patients (57% male, 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 pre-operative evaluation in 129 patients (4%), dyspnea in 540 (16%), and prior stress tests in 730 patients (22%). The presence of non-obstructive and obstructive CAD was associated with older age, male gender, 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 (Supplemental Table).
Cardiovascular Outcomes

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

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

Coronary CTA and cardiovascular outcomes

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

The incidence of CV death or MI was 3.6 (95% CI: 2.2 -5.8) per 1000 patient years in the group with no CAD, 7.4 (5.2 – 10.3) for patients with non-obstructive CAD and 17.6 (13.1 – 23.5) for patients with obstructive CAD (p<0.001). Among patients with either non-obstructive
or obstructive CAD, greater extent of disease was associated with a higher event rate across all outcomes considered (Figure 1). Notably, patients with extensive (i.e. >4 segments) non-obstructive plaque, had a similar event rate as those with obstructive disease but ≤4 segments with CAD. (14.5 vs. 13.6, p=0.76 for CV death or MI; and 26.6 vs. 26.2, p=0.91 for MACE).

Figure 2 shows the unadjusted Kaplan-Meier cumulative event curves for CV death or MI (2A) and major cardiovascular events stratified by (2B) the presence and severity of disease. When patients with non-obstructive 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 non-obstructive CAD with a SIS≤4 had a similar outcome as those with no CAD, whereas patients with non-obstructive CAD with a SIS >4 had a significant increase in adverse events (Figure 4A and Supplemental Figures). 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 (Figure 3, 4B and Supplemental Figures).

**Multivariable models for outcomes**

When compared to patients with no CAD, and after adjusting for pre-test probability of obstructive CAD, the risk of CV death or MI was higher among the 717 patients with obstructive CAD (HR: 3.7, 95% CI: 2.0 – 6.6). Among the 1224 patients with non-obstructive CAD, the HR was 1.6 (95% CI: 0.9 – 3.0). When each group was further stratified by extent of CAD, the presence of more than 4 segments with plaque was associated with a higher rate of events for all outcomes (Figure 5 and Supplemental Figures).

The three models used to predict CV death or MI are summarized in Table 3. When adding the presence and severity of CAD (model 2) to a model which 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 non-obstructive and obstructive CAD (defined as a SIS $\leq$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 MACE as well as all cause death (Figures 6B and C).

**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 over a median follow up of 3.6 years, the presence and severity of CAD was associated with an increase in CV events. However, a novel finding in our study is that regardless of whether non-obstructive or obstructive disease was identified, data regarding extent of disease provided additional prognostic value. Patients with non-obstructive CAD who had extensive disease (e.g. SIS$>$4) had a similar rate of CV death or MI as those with obstructive but less extensive disease. On the other hand, among those with non-obstructive plaque who had less extensive disease (e.g. SIS$\leq$4) the rate of CV 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 non-obstructive CAD (which represented 38% of our cohort), has been debated as 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. While early coronary CTA studies have combined patients with non-obstructive disease with those who have no disease (mainly due to small sample size and limited statistical power), $^{20, 21}$ larger
studies by Ostrom et al\textsuperscript{6,22} as well as Lin et al \textsuperscript{6} have suggested that the presence of non-obstructive plaque is associated with increased all-cause mortality. Building on prior studies, we were able to demonstrate that non-obstructive CAD is also associated with an increased risk of hard CV events (e.g. CV 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, as non-obstructive 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.\textsuperscript{23}

While patients with non-obstructive CAD are considered to have only mildly increased risk when compared to those who have no disease,\textsuperscript{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 non-obstructive CAD with \textgreater 4 segments with plaque had a similar rate of CV death or MI as those who had obstructive disease with \leq 4 diseased segments. On the other hand, the 78\% of patients with non-obstructive disease with \leq 4 segments with plaque had a similar rate of CV death or MI as patients with no disease. While 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,\textsuperscript{6} the extent of non-obstructive disease was associated with increased risk. Future studies are needed in order to evaluate whether treatment of patients with non-obstructive plaque will result in improved outcomes.\textsuperscript{24}

Many studies on the prognosis of coronary CTA, including the CONFIRM registry\textsuperscript{2}, have demonstrated that coronary CTA is a reliable method to predict all-cause mortality.\textsuperscript{9,22} While
the use of all-cause mortality avoids ascertainment bias from adjudicating cause of death or MI, current data suggests that only one in every three deaths has a CV 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 non-differential measurement error which biases the estimates of relative hazard towards the null. Our study found that approximately one third of the deaths events observed were of cardiovascular etiology, a finding that reinforces the potential limitations of extrapolating all-cause death rates to CV mortality or other CV events. Various other studies have also evaluated the prognostic value of coronary CTA for identifying a combination of CV 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. While outcomes of CV 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 estimate risk of all-cause mortality as well as CV events, but also demonstrate that the absolute event rates continue to diverge during longer term follow up. The findings of increased CV death / MI and MACE, are comparable to those of Andreini et al, which included 1304 patients undergoing coronary CTA. However, their study observed a significantly higher rate of MI and revascularizations, with 46% of those with obstructive disease suffering a MI or CV 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. Our data demonstrates a similar event rate as prior studies.
The study by Chow, et al clearly demonstrated the association of obstructive CAD and the combination of CV death and MI beyond clinical risk factors during a mean follow up of 16 months.\(^1\) Although their study was underpowered to detect differences in prognosis in subgroup of patients with non-obstructive 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 has demonstrated that the number of segments with plaque improves the overall prediction of events by coronary CTA.

While most studies have reported no MI in patients with normal CTA, we found a very low risk of coronary heart disease events among patients with normal CCTA. Out of 1301 patients with normal CTA, only 14 (1.0%) patients had events in this group over a median follow-up of 3.5 years. Among those events, there were 12 cardiovascular deaths (i.e. heart failure, stroke, aortic disease) and only 2 myocardial infarctions (rate 0.04 % / year). The first case was a 48-year-old woman who presented with an MI more than a year after CCTA. Upon invasive angiography, she had stenosis of a small distal circumflex after the second OM. Due to the small size of the vessel, no intervention was performed and the patient was treated medically. The second patient was diagnosed with MI due to coronary vasospasm of the RCA (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 coronary CTA with an excellent prognosis and an extremely low risk of events during follow up.

Our study should be interpreted in the context of inherent limitations related to the observational retrospective design. First, all patient management decisions such as revascularization and medical therapies were at the discretion of the referring physicians. Since such therapies may improve patient outcomes,\(^34\) and given that more aggressive therapies were
generally used for patients who had more severe disease, we expect that differences between subgroups would be even greater in the absence of such treatments. However, the lack of difference in the event rates between those individuals with extensive non-obstructive and those with non-extensive obstructive disease may have been attenuated as physicians may have treated the latter group more aggressively. Also, we used visual estimation to categorize the severity of stenosis and the number of segments with disease. There is a degree of variability that is inherent in such qualitative techniques, though this method of interpretation is also used in clinical practice and was used in all prior coronary CTA prognosis papers published to date. While we selected a single cut point to define extensive versus non-extensive disease, future studies would be useful for validating this threshold.

Similar to other studies, due to the inherent spatial resolution limitation of CT, we did not evaluate vessels with small diameters. While small vessels are most often found in distal vessels, a recent publication demonstrated that disease in distal segments is less likely to be associated with future events.\(^3^5\) Our study was conducted in two 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 one of the largest and longer follow up cohort of patients followed for CV specific outcomes after coronary CTA. Due to use of electronic medical records across our healthcare network as well as additional patient follow-up mechanisms (e.g. questionnaires; phone interviews) we captured excellent long-term follow-up data. In addition to having detailed information regarding all CV 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 non-obstructive CAD, those with more than 4 segments of disease experienced a significantly higher rate CV death or MI, comparable to those who have obstructive disease with ≤ 4 diseased segments. Similarly, among patients with obstructive CAD, greater extent of non-obstructive plaque was associated with higher event rate. These findings suggest that regardless whether obstructive or non-obstructive 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.

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Disclosures

None.
References


33. Hulten EA, Carbonaro S, Petrillo SP, Mitchell JD, Villines TC. Prognostic value of cardiac computed tomography angiography: A systematic review and meta-analysis. 

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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>
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<tbody>
<tr>
<td>Number of subjects</td>
<td>1301</td>
<td>1224 (38%)</td>
<td>717 (22%)</td>
<td>3242</td>
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<tr>
<td>Age</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>
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<td>Male (%)</td>
<td>619 (48)</td>
<td>724 (59)</td>
<td>515 (72)</td>
<td>1858 (57)</td>
<td>&lt;0.001</td>
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<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>
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<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>512 (81)</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Prior smoking</td>
<td>220 (17)</td>
<td>289 (24)</td>
<td>216 (30)</td>
<td>725 (22)</td>
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<tr>
<td>Current smoking</td>
<td>109 (8)</td>
<td>119 (10)</td>
<td>71 (10)</td>
<td>299 (9)</td>
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<tr>
<td>Family history of CAD</td>
<td>336 (26)</td>
<td>352 (29)</td>
<td>217 (24)</td>
<td>905 (28)</td>
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<td>Symptoms (%)</td>
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<td>Non-anginal CP</td>
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<td>511 (42)</td>
<td>300 (42)</td>
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<td>Atypical CP</td>
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<td>488 (40)</td>
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<td>Typical CP</td>
<td>95 (7)</td>
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<td>68 (9)</td>
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<td>Asymptomatic</td>
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<td>Unknown</td>
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<td>52 (4)</td>
<td>19 (3)</td>
<td>131 (4)</td>
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<tr>
<td>Pre-test 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 pre-test probability of >50% stenosis was calculated using the Morise score, which includes age, gender, risk factors and symptoms.
Table 2. Baseline demographic characteristics according to whether the participants had a subsequent cardiovascular death or myocardial infarction. *: the clinical probability was calculated using the Morise score.

<table>
<thead>
<tr>
<th></th>
<th>No CV death or MI</th>
<th>CV Death or MI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>3148 (97)</td>
<td>92 (3)</td>
<td>3242</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>55.7±13.2</td>
<td>65.3±12.6</td>
<td>56.0±13.3</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>1808 (58)</td>
<td>50 (53)</td>
<td>1858 (57)</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>1489 (47)</td>
<td>71 (75)</td>
<td>1560 (55)</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus (%)</strong></td>
<td>410 (13)</td>
<td>25 (27)</td>
<td>435 (16)</td>
</tr>
<tr>
<td><strong>Dyslipidemia (%)</strong></td>
<td>1539 (49)</td>
<td>57 (61)</td>
<td>1596 (56)</td>
</tr>
<tr>
<td><strong>Smoking (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior smoking</td>
<td>700 (22)</td>
<td>25 (27)</td>
<td>725 (22)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>284 (9)</td>
<td>15 (16)</td>
<td>299 (9)</td>
</tr>
<tr>
<td><strong>Family history of CAD</strong></td>
<td>887 (28)</td>
<td>18 (20)</td>
<td>905 (28)</td>
</tr>
<tr>
<td><strong>Symptoms (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-anginal CP</td>
<td>1272 (40)</td>
<td>52 (55)</td>
<td>1324 (41)</td>
</tr>
<tr>
<td>Atypical CP</td>
<td>1275 (41)</td>
<td>30 (32)</td>
<td>1305 (40)</td>
</tr>
<tr>
<td>Typical CP</td>
<td>245 (8)</td>
<td>5 (5)</td>
<td>250 (8)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>226 (7)</td>
<td>6 (6)</td>
<td>232 (7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>130 (4)</td>
<td>1 (1)</td>
<td>131 (4)</td>
</tr>
<tr>
<td>Pre-test probability of &gt;50% CAD*</td>
<td>45.2±22.3</td>
<td>56.7±19.2</td>
<td>45±22</td>
</tr>
</tbody>
</table>
Table 3. Comparison of Cox models for the prediction of CV death or MI. (Model 1 included the clinical probability only. Model 2 includes the clinical probability and the severity of disease in the CCTA. Model 3 includes the presence, extent and severity of CAD in the CCTA)

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fit Statistic</td>
<td>p</td>
<td>Fit Statistic</td>
<td>p</td>
<td>Fit statistic</td>
<td>p</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>
<td>0.03</td>
</tr>
<tr>
<td>AIC</td>
<td>1427.9</td>
<td></td>
<td>1408.9</td>
<td></td>
<td>1406.0</td>
<td></td>
</tr>
<tr>
<td>C index</td>
<td>0.646</td>
<td></td>
<td>0.705</td>
<td></td>
<td>0.729</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>
<td>0.83</td>
</tr>
</tbody>
</table>

Covariates

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical prob. (per 10%)</td>
<td>1.3 (1.1 – 1.4)</td>
<td>&lt;0.001</td>
<td>1.2 (1.1 – 1.3)</td>
<td>0.001</td>
<td>1.2 (1.1 – 1.3)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

CAD presence and severity

<table>
<thead>
<tr>
<th>CAD presence and severity</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-obstructive</td>
<td>1.6 (0.9 – 3.0)</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive</td>
<td>3.7 (2.0 – 6.6)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAD presence, extent and severity

<table>
<thead>
<tr>
<th>CAD presence, extent and severity</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-obstructive, SIS ≤4</td>
<td>1.2 (0.7 – 2.4)</td>
<td>0.54</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-obstructive SIS &gt;4</td>
<td>3.1 (1.5 – 6.4)</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive, SIS ≤4</td>
<td>3.0 (1.3 – 6.9)</td>
<td>0.009</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive, SIS &gt;4</td>
<td>3.9 (2.2 – 7.2)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Footnote: * For the global $\chi^2$ the p value for model 2 is in comparison to model 1, and the p value for model 3 is compared to model 2. † For the goodness-of-fit, the p value indicates the likelihood-ratio of the observed events when compared to the expected value for the same model.
Figure Legends

Figure 1. A. Rate of cardiovascular (CV) death or myocardial infarction (MI) according to the presence, severity and extent of CAD. There is a significant difference (p<0.01) in rates for all comparisons except non-obstructive CAD with SIS>4 and obstructive CAD with SIS≤4. B: Rate of major cardiovascular events (MACE). C: Rate of all-cause death. Log-rank p<0.01 for all graphs.

Figure 2. A. Survival free from cardiovascular (CV) death or myocardial infarction (MI) according to the presence and severity of CAD. B: Survival free from major cardiovascular events (MACE) according to the presence and severity of CAD.

Figure 3. A. Survival free from cardiovascular (CV) death or myocardial infarction (MI) according to the presence, severity and extent of CAD. B. Survival free from major cardiovascular events (MACE).

Figure 4. A. Survival free from major cardiovascular events (MACE) according to the presence and extent of non-obstructive CAD. B. Survival free from major cardiovascular events (MACE) according to the extent and severity of obstructive CAD.

Figure 5. A. Hazard ratio for the occurrence of cardiovascular (CV) death or myocardial infarction (MI) according to the presence, severity and extent of CAD. The hazard ratios are significantly different (p<0.05) for all pairwise comparisons except no CAD vs. non-obstructive CAD, SIS≤4; and non-obstructive CAD, SIS>4 vs. obstructive CAD, SIS≤4. B. Hazard ratio for the occurrence of major cardiovascular events (MACE). The hazard ratios are significantly different (p<0.05) for all pairwise comparisons except non-obstructive CAD, SIS>4 vs. obstructive CAD, SIS≤4. The 95% confidence intervals for the hazard ratio are presented in parenthesis.

Figure 6. A. Comparison of the models to predict cardiovascular (CV) death or myocardial infarction (MI). The model 1 includes the clinical probability score (including age, gender, symptoms and risk factors). Model 2 includes the clinical probability and the information on the presence and severity of CAD in the coronary 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 (MACE). C. Comparison of the models to predict all-cause death.
Prediction of CV death or MI

- Clinical probability: 23.5
- Model 1 + CAD presence and severity: 46.6
- Model 2 + CAD extent: 53.4

Significance levels:
- P < 0.01
- P = 0.03
Prediction of MACE

- Clinical probability: 41.9
- Model 1 + CAD presence and severity: 127.6
- Model 2 + CAD extent: 140.7

All comparisons are significant at p < 0.01.
Prediction of all-cause Death

- Clinical probability: 24.8
- Model 1 + CAD presence and severity: 40.5
- Model 2 + CAD extent: 49.2

Significance levels:
- $p < 0.01$
- $P = 0.01$
Prognostic Value of Non-Obstructive 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 Steigner, Venkatesh 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>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>1858 (57)</td>
<td>114 (37)</td>
<td></td>
<td>0.04</td>
</tr>
<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>Prior smoking</td>
<td>725 (22)</td>
<td>25 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</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>Coronar CTA results</strong></td>
<td></td>
<td></td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1301 (40)</td>
<td>150 (48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-obstructive</td>
<td>1224 (38)</td>
<td>106 (34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive</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.