Coronary Artery Disease Detected by Coronary Computed Tomographic Angiography Is Associated With Intensification of Preventive Medical Therapy and Lower Low-Density Lipoprotein Cholesterol

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**Background**—Coronary computed tomographic angiography (CCTA) is an accurate test for the identification of coronary artery disease (CAD), yet the impact of CCTA results on subsequent medical therapy and risk factors has not been widely reported.

**Methods and Results**—We identified consecutive patients aged >18 years without prior CAD who underwent CCTA from 2004 to 2011 and had complete data on medications before and after CCTA. CCTA results were categorized as no CAD, <50% stenosis, and ≥50% stenosis. Based on the number of involved segments, extent of disease was categorized as nonextensive (≤4 segments) or extensive CAD (>4 segments). Electronic medical records and patient interviews were reviewed blinded to CCTA findings to assess initiation of aspirin and intensification of lipid-lowering therapies. Survival analysis was performed to evaluate intensification of lipid therapy as a predictor of cardiovascular death or nonfatal myocardial infarction. Among 2839 patients with mean follow-up of 3.6 years, the odds of physician intensification of lipid-lowering therapy significantly increased for those with nonobstructive CAD (odds ratio, 3.6; 95% confidence interval, 2.9–4.9; \( P<0.001 \)) and obstructive CAD (odds ratio, 5.6; 95% confidence interval, 4.3–7.3; \( P<0.001 \)). Low-density lipoprotein cholesterol levels declined significantly in association with intensification of lipid-lowering therapy after CCTA in all patient subgroups. In a hypothesis-generating analysis, among patients with nonobstructive but extensive CAD, statin use after CCTA was associated with a reduction in cardiovascular death or myocardial infarction (hazards ratio, 0.18; 95% confidence interval, 0.05–0.66; \( P=0.01 \)).

**Conclusions**—Abnormal CCTA findings are associated with downstream intensification in statin and aspirin therapy. In particular, CCTA may lead to increased use of prognostically beneficial therapies in patients identified as having extensive, nonobstructive CAD. (Circ Cardiovasc Imaging. 2014;7:629-638.)

**Key Words:** aspirin ■ prevention and control ■ prognosis

Although coronary computed tomographic angiography (CCTA) provides useful diagnostic and prognostic information and can reclassify the risk of future cardiovascular events,\(^1\) the impact of this examination’s results on patient management is not fully understood.\(^1-4\) Some studies have shown that CCTA results may change patient and physician behavior.\(^2,3\) although a multicenter registry\(^5\) concluded that CCTA had only a modest association with post-test changes in medical therapy.

**Clinical Perspective on p 638**

As was underscored in a workshop sponsored by the National Heart, Lung, and Blood Institute,\(^6\) tests do not directly

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affect clinical outcomes. Instead, we must presume that they lead clinicians to modify behavior. Therefore, in order for a diagnostic test such as CCTA to improve patient outcomes, it is essential that the test leads to meaningful changes in therapies and, consequently, risk factors. Only a few prior studies have demonstrated favorable changes in risk factor profile early after CCTA.4–6 However, because the rate of events in stable coronary artery disease is low, for such changes to have a meaningful impact on prognosis, they should persist over a long-term period.9–11

Therefore, our aim was to evaluate the impact of CCTA results on subsequent medical therapies and to determine whether these changes are associated with changes in short- and long-term low-density lipoprotein (LDL) cholesterol levels and cardiovascular outcomes.

Methods

Study Population

Consecutive subjects aged ≥18 years who underwent CCTA at Massachusetts General Hospital or Brigham and Women’s Hospital from 2004 to 2011 who had available data on medications pre- and post-CCTA were included. Scans were conducted using a 64-multi-detector CT or newer technology. We excluded patients with known CAD (defined as clinically manifest by prior myocardial infarction [MI], percutaneous coronary intervention, or coronary artery bypass graft surgery). The study was approved by the Partners’ Healthcare Institutional Review Board.

CCTA Examination and Interpretation

All CCTA exams were performed in accordance with hospital protocol and existing guidelines.12,13 CCTA findings were ordinarily categorized as no CAD (no plaque; 0% stenosis), nonobstructive CAD (<50% stenosis), or obstructive CAD (≥50% stenosis). We categorized the number of vessels with CAD (left anterior descending, left circumflex, and right coronary artery) as 1-vessel, 2-vessel, and 3-vessel/left main disease. We categorized the extent of plaque according to an 18-segment model proposed by the American Heart Association, modified by the Society of Coronary Computed Tomography.13 Based on the number of segments with plaque, the extent of CAD was categorized as nonextensive (≤4 segments) or extensive (>4 segments).14,15

Baseline Cardiovascular Risk Factors

All clinical data prior to the CCTA were used to categorize baseline cardiovascular risk. Age, symptoms, and risk factors were entered into a validated risk score (Morise score) to estimate baseline pretest probability of CAD.16 We defined hypertension as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, or diagnosis/treatment of hypertension. We defined dyslipidemia as total cholesterol >240 mg/dL or high-density lipoprotein cholesterol <40 mg/dL (men) or <50 mg/dL (women) or diagnosis/treatment of dyslipidemia.12 We defined diabetes mellitus as hemoglobin A1C ≥6.5% or diagnosis/treatment of diabetes mellitus.16 We defined smoking as current (tobacco products used within the previous month), former, or never. We defined family history of premature CAD as any first-degree relative with clinical manifest CAD before the age of 60 years.

Changes in Medical Therapy and Laboratory Values

Electronic medical records were reviewed for ≤2 years before the CCTAs for prescription of primary preventive lipid-lowering therapy and aspirin therapy. Post-CCTA medical records were reviewed for ≤1 year for prescription of primary preventive lipid-lowering therapy and aspirin therapy. We categorized whether patients were on pre-CCTA lipid-lowering therapy, post-CCTA lipid-lowering therapy, and whether there was no change in the intensity from pre- to post-CCTA or an intensification of the lipid-lowering therapy post-CCTA. Intensification was defined when new lipid-lowering therapy was prescribed post-CCTA or if there was an increase in the dose of an existing agent or addition of adjunctive agents to a prior lipid-lowering regimen (eg, adding ezetimibe to a pre-CCTA regimen of atorvastatin 80 mg daily) or change from one lipid lowering regimen to a more intensive regimen (eg, change from simvastatin 40 mg to atorvastatin 80 mg daily).

Laboratory values were extracted from the Partners electronic medical record. Pre-CCTA laboratory values were included if they were recorded from a window 365 to 0 days pre-CCTA. Post-CCTA laboratory values were included if recorded 30 days post-CCTA to any time post-CCTA.

Cardiovascular Outcomes

As previously described,14 2 cardiologists blinded to CCTA results reviewed electronic medical records as well as patient questionnaires and phone interview data to adjudicate cardiovascular events. All self-reported events were verified via outside medical records.

The primary end point for clinical outcomes was a composite of cardiovascular mortality and nonfatal MI to avoid inherent bias of softer outcomes (eg, angina, coronary revascularization). All-cause mortality was additionally reported.

Deaths were confirmed by the Social Security Death Index. Cause of death was determined by review of death certificates as well as all available clinical records. We supplemented this information with mortality data from the Massachusetts Department of Vital Statistics. All deaths were adjudicated by 2 cardiologists with cardiovascular mortality defined as a primary cause of acute MI, atherosclerotic coronary vascular disease, congestive heart failure, valvular heart disease, arrhythmia, heart disease, stroke, or other structural or primary cardiac causes of death. Diagnosis of MI was confirmed by 2 of 3 causes: chest pain or equivalent symptom complex, positive cardiac biomarkers, ECG changes typical of MI.19 Coronary revascularizations consisted of coronary artery bypass grafting or percutaneous coronary intervention and were considered early if they occurred <90 days after CCTA.

Statistical Analysis

Continuous variables are reported as mean±SD or medians where appropriate. Categorical variables are reported as counts and proportions. Continuous variables are compared using ANOVA. Categorical variables were compared using χ² or Fisher exact test, where appropriate. Univariable and multivariable logistic regression was used to assess the relationship between covariates and post-CCTA preventive medical therapy.

As a sensitivity analysis, we compared the changes in medical therapy after CTA was observed in the current study (Partners CT registry) with a cohort of patients from the same institutions without CAD who did not undergo CTA, but were enrolled in the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease (SPARC) registry.7

Because of the limited power (see the Data Supplement) to detect differences in hard cardiovascular events in our cohort, we also performed a prespecified subgroup analysis to examine the association of treatment with hard outcomes (ie, cardiovascular death or MI) among patients with nonobstructive CAD.

Kaplan–Meier analysis was used to assess prognosis for event-free survival from adverse clinical outcomes. To evaluate a potential association of CAD by CCTA with changes in post-test medical therapy and prognosis for cardiovascular death and MI, a propensity-weighted Cox proportional hazards analysis20,21 was performed to adjust for baseline differences that affect the decision to treat with statin. The assumption of nonproportional hazards was tested using a significance test base on the unscaled and scaled Schoenfeld residuals and resulted in nonsignificant findings in all analyses. All statistics were performed using Stata version 12.1 (Statacorp, College Station, TX).
Results

Clinical Characteristics
Among 3552 consecutive patients who underwent CCTA, 310 (8%) did not have clinical follow-up and 403 (11%) did not have medication information. Thus, 2839 patients (mean age, 56±13 years; 57% men) who underwent CCTA with a mean follow-up of 3.6±1.8 years were included. CCTA findings included 1147 with no CAD, 1068 with <50% stenosis, and 624 with ≥50% stenosis. The presence and severity of CAD was associated with risk factors for cardiovascular disease, age, and male sex, but not with the symptoms prior to the CCTA (Table 1).

Preventive Medication Use According to CAD Pre- and Post-CCTA
Aspirin prescription increased from 10% to 46% for those with no CAD by CCTA, from 17% to 72% for those with <50% stenosis, and from 25% to 89% for those with ≥50% stenosis (Figure 1; P<0.001 comparing pre- to post-CCTA for all groups).

Lipid-lowering therapy prescriptions pre-CCTA were lower for individuals with no CAD on CCTA (32%) than in those with nonobstructive (57%) or obstructive CAD (71%; Figure 2, upper panel; P<0.001). After CCTA, 36% of patients with no CAD were treated with lipid-lowering therapy (18% on same dose as pre-CCTA and 18% intensified); 72% of those with <50% stenosis were treated with lipid-lowering therapy (25% on same dose as pre-CCTA and 47% intensified); and 90% of those with ≥50% stenosis were treated with lipid-lowering therapy (27% on same dose as pre-CCTA and 63% intensified). The proportion of those on lipid-lowering therapy pre-CCTA, on same dose post-CCTA, and intensified post-CCTA all differed (P<0.001) by no CAD, <50% stenosis, and ≥50% stenosis. When considering the various lipid-lowering therapies used, the vast majority of prescriptions (93%) were for statins, whereas the remainder included fibrates, ezetimibe, or niacin.

Multivariable Analysis to Predict Medication Use After CCTA
Age, sex, dyslipidemia, hypertension, diabetes mellitus, pre-CCTA statin therapy, revascularization early after CCTA (<90 days), and presence of ≥50% stenosis on CCTA were associated with increased use of statins during follow-up (Table 2). Changes in statin therapy did not differ according to year of CCTA. Using multivariable logistic regression, the odds of a post-CCTA aspirin prescription were significantly increased for those with <50% stenosis as well as those with ≥50% stenosis when compared with patients with no CAD (Figure 3; P=0.001). Similarly, the adjusted odds of post-CCTA statin and any lipid-lowering medication prescription were significantly increased among those with <50% and ≥50% stenosis compared with patients with no CAD (Figure 3; P<0.001). The odds of change in prescription of statin versus any lipid-lowering medication were similar (P=0.76 for patients with nonobstructive disease; P=0.92 for those with obstructive disease).

A subgroup of 855 (30%) patients who underwent CAC scoring22 at the time of CCTA was evaluated for the potential of CAC to influence post-test medical therapy. This information has been provided as Figure I in the Data Supplement. When the propensity-adjusted odds ratio (OR) for intensification of statin therapy according to any CAD by CCTA (OR, 4.59±0.5) was compared with the propensity-adjusted OR for CAC >0 (OR, 3.79±0.7), they were not significantly different (P=0.15). Similarly, when the propensity-adjusted odds of post-test aspirin therapy for any CAD by CCTA (OR, 3.10±0.4) was compared with CAC >0 (OR, 2.84±0.6), there was no significant difference (P=0.81).

A sensitivity analysis was performed to evaluate for the effect of patients with missing data on the rates of pre- and post-test medical therapy. Using the most conservative assumption

Table 1. Demographics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=2839)</th>
<th>No CAD (n=1147)</th>
<th>&lt;50% Stenosis (n=1068)</th>
<th>≥50% Stenosis (n=624)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56 (13.3)</td>
<td>48.2 (12.3)</td>
<td>59.5 (11.4)</td>
<td>64.3 (10.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1628 (57.3)</td>
<td>538 (46.9)</td>
<td>636 (59.6)</td>
<td>454 (72.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1390 (54.6)</td>
<td>393 (38.2)</td>
<td>570 (59.8)</td>
<td>427 (76.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>375 (15.1)</td>
<td>98 (9.7)</td>
<td>141 (15.2)</td>
<td>136 (25.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1432 (56.3)</td>
<td>387 (37.6)</td>
<td>583 (61.2)</td>
<td>462 (82.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>255 (10.8)</td>
<td>97 (9.9)</td>
<td>102 (11.7)</td>
<td>56 (11)</td>
<td>0.44</td>
</tr>
<tr>
<td>Family history of premature clinical CAD</td>
<td>841 (49.3)</td>
<td>307 (45.9)</td>
<td>329 (50.3)</td>
<td>205 (53.5)</td>
<td>0.047</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.225</td>
</tr>
<tr>
<td>Unknown</td>
<td>88 (3.1)</td>
<td>38 (3.3)</td>
<td>35 (3.3)</td>
<td>15 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>221 (7.8)</td>
<td>100 (8.7)</td>
<td>83 (7.8)</td>
<td>38 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Nonanginal chest pain</td>
<td>1159 (40.8)</td>
<td>459 (40)</td>
<td>442 (41.4)</td>
<td>258 (41.3)</td>
<td></td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>1147 (40.4)</td>
<td>465 (40.5)</td>
<td>432 (40.4)</td>
<td>250 (40.1)</td>
<td></td>
</tr>
<tr>
<td>Typical chest pain</td>
<td>224 (7.9)</td>
<td>85 (7.4)</td>
<td>76 (7.1)</td>
<td>63 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Pre-test probability of ≥50% stenosis</td>
<td>45.6 (22.4)</td>
<td>34.9 (23.3)</td>
<td>50.8 (19.4)</td>
<td>56.3 (16.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Columns represent n (%) for proportions and mean (SD) for pre-test probability of ≥50% stenosis (as predicted by Morise score). CAD indicates coronary artery disease.
that patients with missing data would have no change in post-test medical therapy, the association of CCTA with changes in medical therapy remained significant but with diminished magnitude of difference in pre- and post-CCTA medication rates, as expected based on this assumption (Figure II in the Data Supplement).

Comparison of baseline characteristics of patients in the Partners CTA registry with patients from Massachusetts General Hospital/Brigham and Women’s Hospital enrolled in SPARC is shown in Table I in the Data Supplement. When compared with the SPARC cohort, patients in the Partners CTA registry were younger and had a lower prevalence of hypertension, diabetes mellitus, and dyslipidemia. Correspondingly, patients in the SPARC cohort who were referred for nuclear myocardial perfusion imaging stress tests were more likely to be treated with both aspirin and statins at baseline.

The proportion of patients receiving post-test treatment in the 2 groups was similar. However, when stratified by the presence of disease (ie, ≥50% stenosis on CTA or abnormal myocardial perfusion imaging), individuals referred for CTA were more likely to be treated with aspirin (89% versus 64%; \( P < 0.001 \)) and lipid-lowering therapies (90% versus 70%; \( P < 0.001 \)). On the contrary, patients with no CAD on coronary CTA, when compared with individuals with normal MPI, were less likely to receive aspirin (36% versus 62%; \( P < 0.001 \)) or lipid-lowering therapy (36% versus 57%; \( P < 0.001 \)). The proportion of patients treated with aspirin and lipid-lowering therapy pre- and post-MPI in the SPARC Massachusetts General Hospital/Brigham and Women’s Hospital cohort is presented in Figure III in the Data Supplement.

**LDL Cholesterol Levels Pre- and Post-CCTA**

Patients who were using statins before the CCTA had lower baseline LDL cholesterol irrespective of the presence or severity of CAD (\( P < 0.001 \)). Among those who were not using statins at baseline, those who were prescribed a statin after CCTA had lower LDL during follow-up. However, those changes were more significant in the subgroups with CAD (Figure 2, lower panel).

When examining all available pre- and post-CCTA LDL values longitudinally, individuals with CAD who had a change in their statin prescription after CCTA (initiation or intensification) had a significant reduction in LDL cholesterol levels, which remained at 4 years post-CCTA follow-up (Figure 4), whereas individuals on no statin therapy had stable but higher level of LDL, and those continued on the same dose of statin had lower baseline LDL cholesterol that remained stable.

When comparing the change in LDL cholesterol from baseline to 2 years post-CCTA among those not treated with statins post-CCTA versus those who had intensification in therapy...
post-CCTA, there was a 9 mg/dL increase versus a 4 mg/dL decrease in the no CAD group (Figure 4; \( P < 0.001 \)), a 9 mg/dL increase versus a 14 mg/dL decrease in the <50% stenosis group \(( P < 0.001)\), and a 5 mg/dL increase versus a 17 mg/dL decrease in the \( \geq 50\% \) stenosis group \(( P < 0.001)\).

### Adverse Cardiovascular Outcomes

The incidence of adverse cardiovascular events differed by the presence and extent of CAD (Table 3). These findings remained significant after adjustment in a multivariable Cox proportional hazards model.

### Propensity-Weighted Survival Analysis

Significant predictors of statin therapy by logistic regression are depicted in Table 2. Dyslipidemia and pre-CCTA statin use were the strongest predictors of statin prescription. The final propensity score included age, male sex, dyslipidemia, hypertension, diabetes mellitus, pre-CCTA statin therapy, revascularization early after CCTA (<90 days), and presence of \( \geq 50\% \) stenosis on CCTA. The final model \( c \) index was 0.92 (logistic regression \( \chi^2 = 1641; P < 0.001 \)).

Univariable and multivariable predictors of cardiovascular death or MI are presented in Table 4. After adjusting for differences in baseline risk factors, prognosis was no longer significantly associated with changes in medical therapy in a multivariable Cox proportional hazards model for prediction of cardiovascular death or MI across all groups (Table 4).

Statin therapy post-CCTA demonstrated a trend toward associated reduction of cardiovascular death or MI (hazards ratio, 0.44; \( P = 0.065 \)) in the fully adjusted multivariable model (Table 4). However, a significant interaction \(( P = 0.003; Table 4)\) was noted between the extent of disease (Segment Involvement Score \( \leq 4 \) or > 4), and the outcome of cardiovascular death or MI. Among subjects with extensive (Segment Involvement Score >4) nonobstructive CAD (<50% stenosis), statin therapy was associated with a reduction in cardiovascular death or MI (hazards ratio, 0.18; \( P = 0.011 \); Table 4). Decreased survival in this subgroup is demonstrated on the Kaplan–Meier curve in Figure 5.

### Discussion

In the largest study to date assessing the impact of CCTA examination results on downstream medical therapies, we have shown that the presence and severity of CAD were associated with intensification of lipid-lowering medications and aspirin. Furthermore, we demonstrated that such therapies are
strongly associated with improvements in LDL cholesterol levels, which persist up to 4 years of follow-up.

Although our study has limited power to detect differences in cardiovascular outcomes, we observed in a hypothesis-generating analysis that among patients with nonobstructive CAD involving >4 segments, use of statin medications post-CCTA was associated with a reduction in cardiovascular death or MI. Notably, this reduction persisted after adjusting for patient characteristics, pre-test probability of disease (ie, Morise score), and coronary revascularization. It is likely that greater power was present in this subgroup because patients with no CAD or nonextensive plaque would be expected to have a much lower event rate (thus limiting the ability to detect differences in outcomes based on treatment), whereas patients

Table 3. Adverse Cardiovascular Events

<table>
<thead>
<tr>
<th>Condition</th>
<th>Nonfatal MI</th>
<th>CV Death</th>
<th>All-Cause Death</th>
<th>CV Death or MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CAD (n=1147)</td>
<td>2 (0.05)</td>
<td>7 (0.14)</td>
<td>15 (0.31)</td>
<td>9 (0.23)</td>
</tr>
<tr>
<td>Lipid Rx not intensified (n=979)</td>
<td>0 (0)</td>
<td>5 (0.13)</td>
<td>11 (0.28)</td>
<td>5 (0.16)</td>
</tr>
<tr>
<td>Lipid Rx intensified (n=168)</td>
<td>2 (0.26)</td>
<td>2 (0.22)</td>
<td>4 (0.43)</td>
<td>4 (0.53)</td>
</tr>
<tr>
<td>&lt;50% stenosis (n=1068)</td>
<td>16 (0.41)</td>
<td>15 (0.32)</td>
<td>41 (0.87)</td>
<td>27 (0.69)</td>
</tr>
<tr>
<td>Lipid Rx not intensified (n=601)</td>
<td>8 (0.4)</td>
<td>10 (0.41)</td>
<td>25 (1.03)</td>
<td>15 (0.75)</td>
</tr>
<tr>
<td>Lipid Rx intensified (n=467)</td>
<td>8 (0.42)</td>
<td>5 (0.22)</td>
<td>16 (0.7)</td>
<td>12 (0.63)</td>
</tr>
<tr>
<td>≥50% stenosis (n=624)</td>
<td>23 (1.03)</td>
<td>13 (0.48)</td>
<td>33 (1.24)</td>
<td>35 (1.57)</td>
</tr>
<tr>
<td>Lipid Rx not intensified (n=248)</td>
<td>6 (0.72)</td>
<td>4 (0.41)</td>
<td>15 (1.53)</td>
<td>10 (1.19)</td>
</tr>
<tr>
<td>Lipid Rx intensified (n=376)</td>
<td>17 (1.22)</td>
<td>9 (0.54)</td>
<td>18 (1.07)</td>
<td>25 (1.79)</td>
</tr>
<tr>
<td>Total (n=2839)</td>
<td>41 (0.41)</td>
<td>35 (0.29)</td>
<td>89 (0.73)</td>
<td>71 (0.7)</td>
</tr>
</tbody>
</table>

Columns represent absolute events and (percent annualized incidence). P value <0.001 comparing coronary computed tomographic angiography subgroups. No CAD vs <50% stenosis vs ≥50% stenosis. CAD indicates coronary artery disease; CV, cardiovascular; MI, myocardial infarction; and Rx, prescription.
with obstructive disease were more likely to be treated with coronary revascularization (which, because of its benefit, could attenuate the impact of statins) and statins, resulting in a relatively small group of untreated patients and thus a limited ability to detect differences in events.

Because of pleiotropic effects, statin therapy does not only reduce LDL levels but has other important clinical benefits, such as reduction of vascular inflammation and endothelial dysfunction. Nevertheless, LDL levels provide a useful surrogate for statin use. Our finding that CCTA scan results have a strong association with post-test changes in medical therapy is consistent with the findings of several single-center studies. The earliest such study by Scridon et al showed that among 114 patients undergoing CCTA, 52% of patients with moderate to severe plaque underwent statin intensification. Consequently, over a mean follow-up of 1.1 years, this group had a reduction in LDL cholesterol of 31 mg/dL. LaBounty et al reported in 2009 that among 208 patients undergoing CCTA, those with CCTA-diagnosed CAD had a 3× greater odds of post-CCTA treatment with statin or aspirin therapies and had lower LDL cholesterol levels. In a study of 184 patients, Blankstein et al demonstrated that the presence of CAD on CCTA resulted in the intensification in medical therapies in 44% of patients. Next, Ovrehus et al demonstrated in a larger cohort (n=1055) with longer follow-up (median, 18 months) that CCTA findings were associated with increased preventive aspirin and statin therapy. Finally, Cheezum et al recently reported an important retrospective analysis of 1125 patients who underwent CCTA. In that study, when compared with those with normal CCTA, those with nonobstructive CAD were 6.9× more likely to receive aspirin therapy, 6.6× more likely to be treated with statin therapy, and 1.6× more likely to receive blood pressure–lowering therapy. Similarly, those with obstructive CAD were 42× more likely to receive aspirin therapy and 30× more likely to be on statin therapy post-CCTA. Subsequently, among patients with <50% stenosis and ≥50% stenosis, LDL cholesterol post-CCTA decreased by 14.1 and 24.6 mg/dL, whereas systolic blood pressure reduced by 1.4 and 4.9 mm Hg, respectively. Because of few adverse events, Cheezum et al’s study was underpowered for assessing the impact of these changes on patient outcomes.

Extending the observations of these single-center studies, the SPARC multicenter registry showed suboptimal changes in preventive medical therapy in 590 patients who underwent CCTA at 90 days’ follow-up. For example, aspirin therapy among those with moderate to severe stenosis on CCTA increased only from 52.9% to 70.6%, compared with 25% to 89% in our cohort. Similarly, for patients with moderate to severe stenosis on CCTA in SPARC, lipid-lowering therapy

Table 4. Propensity-Weighted Cox Proportional Hazards Univariable and Multivariable Models for Cardiovascular Death and Myocardial Infarction

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-test probability (% predicted by Morise score)</td>
<td>1.02 (1.01–1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No CAD</td>
<td>1</td>
<td>Ref.</td>
</tr>
<tr>
<td>&lt;50% stenosis with SIS ≤4</td>
<td>2.71 (1.01–7.23)</td>
<td>0.047</td>
</tr>
<tr>
<td>&lt;50% stenosis with SIS &gt;4</td>
<td>8.57 (3.16–23.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥50% stenosis</td>
<td>9.81 (4.11–23.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Early revascularization</td>
<td>5.59 (3.26–9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin post-CCTA*</td>
<td>1.44 (1–2.09)</td>
<td>0.051</td>
</tr>
<tr>
<td>Statin post-CCTA</td>
<td>2.39 (1–4.41)</td>
<td>0.005</td>
</tr>
<tr>
<td>Propensity</td>
<td>4.7 (2–11.03)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Interactions tested

Aspirin post-CCTA×Extent of CAD by CCTA (SIS) | ... | 0.50 | NA | NA |
Statin post-CCTA×Extent of CAD by CCTA (SIS) | ... | 0.003 | ... | 0.022 |
Statin post-CCTA (SIS ≤4; worst stenosis <50%) | 2.25 (0.49–10.29) | 0.29 | 1.44 (0.27–7.68) | 0.67 |
Statin post-CCTA (SIS >4; worst stenosis <50%) | 0.24 (0.07–0.82) | 0.023 | 0.18 (0.05–0.66) | 0.011 |

Pre-test probability defined continuously per 1 percentage point of pre-test probability as predicted by the Morise score. CAD indicates coronary artery disease; CCTA, coronary computed tomographic angiography; HR, hazards ratio; NA, not applicable; and SIS, Segment Involvement Score.

*Excluded from multivariate model; did not add to global chi-squared and no significant interaction.

Figure 5. Event-free survival from cardiovascular (CV) death or myocardial infarction (MI) according to presence or absence of statin therapy post-CCTA among those with nonobstructive coronary artery disease (CAD), stratified by extent of disease according to Segment Involvement Score (SIS).
increased from 64.7% to 79.4%, compared with 71% to 90% in our cohort. However, some population and study design differences may have contributed to this. First, communication of test results by imagers to referring physicians may have been less consistent in SPARC than in single-center studies. Second, the SPARC results are based on patient self-report of medication changes (as compared with review of records in our cohort), and the follow-up time for SPARC was relatively short (90 days). Also, SPARC primarily evaluated patients who underwent CCTA in 2006, a time of early clinical experience when limited knowledge on how to define interventions based on the CCTA results existed. Our study, in contrast, enrolled patients from 2004 to 2011; the median date of CCTA was 2008. During this time period, data on the prognostic significance of CCTA findings evolved rapidly (the first data on CCTA results and prognosis was published in 2007), and clinicians may have developed a better understanding of CCTA’s clinical relevance over time. However, in our study, post-CCTA changes in statin therapy did not differ according to the year of CCTA.

One remarkably consistent observation from prior studies and ours is that the rates of preventive medical therapy are not closer to 100% after documented CAD by CCTA, not even for those with severe CAD. The intensification of preventive medical therapy is encouraging, but one wonders why the intensification of preventive medical therapy in patients identified to be at risk but not treated. Although the identification of plaque on CCTA may prompt intensification of aspirin and lipid-lowering therapies, it is conceivable that such therapeutic changes could also be made based on the presence and severity of coronary artery calcium (CAC). Although CAC is less frequently used among symptomatic patients, there is considerable data that among asymptomatic patients, the use of CAC is associated with intensification of medical therapies with subsequent beneficial changes in risk factors. Similarly, among symptomatic patients referred for nuclear myocardial perfusion imaging, the presence of CAC is associated with intensification of medical therapies.

Given the sample size and low adverse event rate, our study was underpowered to detect differences in prognosis by therapy among the entire cohort of patients undergoing CCTA. This limitation is expected given the fact that meta-analyses of primary prevention trials required tens of thousands of subjects to reach adequate statistical power to demonstrate the benefit of statin therapy. On the basis of our sample size calculation (see the Data Supplement), the event rates observed for our sample of 2839 subjects has only 9% power to detect a difference in cardiovascular death and 14% power for cardiovascular death or MI. Although statins are known to be beneficial among patients with significant CAD, this association could not be demonstrated for the obstructive CAD group (hazards ratio, 0.81; P=0.75), an analysis of which had limited power because of few patients (10%) not treated with statin. In addition, statin therapy in those with no CAD was not significant (hazards ratio, 1.83; P=0.62), an analysis that had limited power because of only 9 adverse events. Further contributing to the reduced power is the fact that there is widespread use of (pre-CCTA) statin therapy in our cohort, and statin intensification among pretreated patients (with lower absolute risk because of lower LDL) likely results in a lower absolute risk reduction than initiation of new therapy among statin-naive patients (with higher baseline LDL and higher absolute risk). Supporting these points, a pooled analysis of intensive versus moderate statin therapy among primary and secondary prevention patients demonstrated a risk reduction of 0.90 (for cardiovascular death or MI) and 0.82 (for nonfatal MI). Based on the sample size and event rate in our study, a hazard ratio of ≤0.38 (cardiovascular death) or 0.51 (cardiovascular death and MI) in favor of statin intensification would have been required for statistical power. Although a magnitude of this effect would not be expected across the entire cohort, we did observe a much lower hazard ratio among the subgroup of patients with extensive, nonobstructive CAD.

Although prior studies have shown that CCTA is associated with changes in medical therapy and risk factors, our analysis is the first to show a subgroup in whom medical therapy post-CCTA was associated with improved prognosis. Nevertheless, our findings regarding the potential reduction in cardiovascular death or MI among patients who have ≤4 segments of nonobstructive plaque should only be viewed as hypothesis-generating and require confirmation in future prospective trials. However, given that most MI occur because of plaque rupture at sites of nonobstructive CAD, there is biological plausibility for those with more extensive involvement of CAD to have an increased risk of adverse cardiovascular events and that a reduction of events may be achievable through intensification of medical therapy. These results, although subject to inherent limitations from the retrospective nature of our study, suggest that further studies are needed to investigate whether patients with extensive nonobstructive CAD should be treated more aggressively. Studying the potential role of CCTA in identifying and treating such individuals is important, particularly because patients in this subgroup would not be expected to have abnormal stress testing given the absence of flow-limiting CAD.

The results of this study should be considered in the context of its inherent limitations. Importantly, our study is retrospective and observational in design, and allocation to intensification of lipid lowering or aspirin therapy was not randomized or blinded. Although we did take statistical measures to adjust for this, causation should not be inferred from significant associations, and residual confounding may influence the results. Also, we did not collect information regarding time to therapy intensification and, therefore, were unable to analyze differences in statin intensification using therapy as a time-varying covariate in the survival analysis. Additionally, our patients are referred to tertiary medical centers for coronary testing and not representative of a screening population, as evidenced by a slightly higher-than-background rate of adverse outcomes (0.23% annualized) even among those with normal
CCTA. Next, we did not have full laboratory values (ie, both pre- and post-CCTA) on all patients within the registry, and thus we are unable to provide the exact magnitude of LDL reduction for all patients in our cohort. Finally, we are unable to assess for any differences in outcomes between different lipid-lowering agents as well as between patients who were treated with different doses.

In conclusion, in patients without known prior CAD who are clinically referred for CCTA, diagnosis of nonobstructive CAD is strongly associated with intensification of preventive medical therapy prescriptions. Such changes in management are subsequently associated with improvement in cholesterol laboratories that are sustained for 4 years of follow-up and may improve long-term cardiovascular risk. Propensity-weighted analysis of statin therapy post-CCTA in those with extensive, nonobstructive CAD suggests an associated hazard reduction for cardiovascular death or MI, although this analysis is hypothesis-generating and should be validated with prospective randomized trials.

Disclosures

Dr Hoffmann reports research support from Siemens Medical Systems. Dr Bittencourt was supported by the I.P. Lemann Foundation as a Jorge Paulo Lemann Harvard Medical School Cardiovascular Fellow at Brigham and Women’s Hospital. The opinions and assertions contained herein are the authors’ alone and do not represent the views of the Walter Reed National Military Medical Center, the US army, or the Department of Defense. The other authors report no conflicts.

References


CLINICAL PERSPECTIVE

The association of coronary computed tomographic angiography (CCTA) findings with subsequent preventive medical therapy has not been widely studied. We report the largest cohort to date evaluating changes in medical therapy after CCTA (2839 patients) with mean follow-up of 3.6 years. Findings of nonobstructive or obstructive coronary artery disease (CAD) were associated with intensification of lipid-lowering therapy relative to normal CCTA with an odds ratio of 3.6 and 5.6, respectively. Similarly, nonobstructive CAD and obstructive CAD findings were associated with post-CCTA aspirin therapy (adjusted odds ratio 2.5 and 6.3). Abnormal CCTA findings were also associated with post-CCTA reductions in low-density lipoprotein cholesterol that persisted out to 4 years of follow-up. Because patients without CAD have low event rates and do not warrant statin therapy and patients with obstructive CAD tend to receive intensive statin therapy, we also sought to examine the association between intensification of statin therapy and hard cardiovascular events among patients with nonobstructive CAD. Recent studies have demonstrated that patients with nonobstructive but extensive plaque burden (defined as >4 coronary segments) have increased adverse clinical event rates. We found using a propensity-weighted analysis that intensification of statin therapy in this subgroup was associated with a significant reduction in cardiovascular death or myocardial infarction (hazard ratio, 0.18). This hypothesis-generating finding suggests that patients with nonobstructive but extensive CAD warrant closer consideration for preventive pharmacotherapies. A future randomized trial of intensive statin therapy in this subgroup would be of great value.
Coronary Artery Disease Detected by Coronary Computed Tomographic Angiography Is Associated With Intensification of Preventive Medical Therapy and Lower Low-Density Lipoprotein Cholesterol

Edward Hulten, Marcio Sommer Bittencourt, Avinainder Singh, Daniel O'Leary, Mitalee P. Christman, Wafa Osmani, Suhny Abbara, Michael L. Steigner, Quynh A. Truong, Khurram Nasir, Frank F. Rybicki, Josh Klein, Jon Hainer, Thomas J. Brady, Udo Hoffmann, Brian B. Ghoshhajra, Rory Hachamovitch, Marcelo F. Di Carli and Ron Blankstein

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Coronary Artery Disease Detected by Coronary CT Angiography Is Associated with Intensification of Preventive Medical Therapy and Lower LDL Cholesterol

** SUPPLEMENTARY DATA **

Comparison of medical therapy in the Partners CTA Registry with cohort of patients from same institutions included in the SPARC registry

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7. Cleveland Clinic Foundation, Cleveland, Ohio
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**Power calculation**

Realizing the low cardiovascular event rate associated with statin trials, we performed a power analysis to determine whether differences in outcomes can be detected based on patient treatment in our cohort. We calculated based upon the method of Hsieh and Lavori\(^1\), using estimates from the statin primary prevention subgroup of the Cholesterol Treatment Trialists’ (CTT) meta-analysis\(^2\), that for a hazard ratio of 0.84 (95% CI: 0.77 - 0.91) for cardiovascular death a sample size of 44,904 subjects (95% CI: 19,983 – 153,469) with 1033 (95% CI: 460 – 3530) failure events would be required for 80% power with an alpha of 0.05. For CV death or MI, we calculated based also upon the CTT meta-analysis that for a hazard ratio of 0.77 (95% CI: 0.74 – 0.80), a sample size of 7,660 subjects (95% CI: 5772 - 10,509) with 460 (95% CI: 347 – 631) failure events would be required for 80% power with an alpha of 0.05.
Comparison of Partners CT Registry with SPARC Registry - methods and results

METHODS: We sought to compare the results in medical therapy following CTA observed in our study with a cohort of patients in the same institutions without CAD who did not undergo CTA. To accomplish this, we obtained data of all patients without known CAD at either the Massachusetts General Hospital or Brigham and Women’s Hospital (MGH/BWH) who underwent SPECT or PET myocardial perfusions imaging (MPI) and were prospectively enrolled in the SPARC registry, a large prospective multicenter registry which examined changes in medications following cardiac imaging.

RESULTS: Baseline characteristics of the two populations are listed in the Supplementary Table 1. When compared to the SPARC cohort, patients in the Partners CTA registry were younger and had a lower prevalence of hypertension, diabetes, and dyslipidemia. Correspondingly, patients in the SPARC cohort who were referred for nuclear myocardial perfusion imaging stress tests were more likely to be treated with both aspirin and statins at baseline.

The proportion of patients receiving post test treatment in the two groups was similar. However, when stratified by the presence of disease (i.e. ≥50% stenosis on CTA or abnormal MPI), individuals referred for CTA were more likely to be treated with aspirin (89% vs. 64% p<0.001) and lipid lowering therapies (90% vs. 70% p<0.001). On the other hand, patients with no CAD on coronary CTA, when compared to individuals with normal MPI, were less likely to receive aspirin (36% vs. 62%, p<0.001) or lipid lowering therapy (36% vs. 57% p<0.001). The proportion of patients treated with aspirin and lipid lowering therapy pre and post MPI in the SPARC MGH/BWH cohort is presented on Supplemental Figure 3.
**Supplemental Table 1 – Baseline characteristics of the PARTNERS CTA versus SPARC MGH/BWH cohorts.**

<table>
<thead>
<tr>
<th></th>
<th>Partners Coronary CTA</th>
<th>SPARC cohort</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>2839</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56±13.3</td>
<td>61±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>1628 (57%)</td>
<td>106 (54%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Diabetes</td>
<td>375 (15%)</td>
<td>85 (44%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1390 (55%)</td>
<td>148 (76%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1432 (56%)</td>
<td>135 (69%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>255 (11%)</td>
<td>29 (15%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Family History</td>
<td>841 (49%)</td>
<td>79 (41%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Supplementary Figure 1. Changes in medical therapy for a subgroup of patients who underwent coronary artery calcium scoring in addition to coronary CT angiography. Note that changes in medical therapy could not be solely attributed to CAC testing since the results of CCTA were available to patients and treating clinicians. Asa = aspirin; Rx = prescription.
Supplementary Figure 2. Sensitivity analysis (intention to scan) performed using the most conservative assumption that patients with missing data would have no change in post-test medical therapy.
**Supplemental Figure 3.** Changes in aspirin and lipid lowering therapies stratified by MPI results in the SPARC MGH/BWH patients referred for nuclear MPI. MPI = myocardial perfusion imaging.

![Graph showing changes in aspirin and lipid lowering therapies](image)

**References:**
