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

Hulten et al: Changes in Preventive Medications after CCTA

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Abstract

Background—Coronary Computed Tomography Angiography (CCTA) is an accurate test for the identification of coronary artery disease (CAD), yet the impact of the CCTA results upon subsequent medical therapy and risk factors has not been widely reported.

Methods and Results—We identified consecutive patients >18 years of age without prior CAD who underwent CCTA from 2004 – 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 non-extensive (≤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 (MI). Among 2839 patients with mean follow-up 3.6 years, the odds of physician intensification of lipid lowering therapy significantly increased for those with non-obstructive CAD (OR 3.6, 95% CI 2.9 – 4.9, p < 0.001) and obstructive CAD (OR 5.6, 95% CI 4.3 – 7.3, p<0.001). Low density lipoprotein (LDL) 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 non-obstructive but extensive CAD, statin use after CCTA was associated with a reduction in cardiovascular death or MI (HR 0.18, 95% CI 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, non-obstructive CAD.

Key Words: computed tomography angiography, statin, aspirin, prevention, prognosis
While coronary CT angiography (CCTA) provides useful diagnostic and prognostic information, and can reclassify the risk of future cardiovascular events\(^1\), the impact of this exam’s results on patient management is not fully understood.\(^1-6\) Some studies have shown that CCTA results may change patient and physician behavior,\(^2, 3\) although a multicenter registry\(^7\) concluded that CCTA had only a modest association with post-test changes in medical therapy.

As was underscored in a workgroup sponsored by the NHLBI\(^8\), tests do not directly 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, since the rate of events in stable coronary artery disease is low, in order for such changes to have a meaningful impact on prognosis, they should persist over a long-term period.\(^9 10, 11\)

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 LDL cholesterol levels and cardiovascular outcomes.

**Methods**

**Study population**

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

**CCTA Exam Acquisition and Interpretation**

All CCTA exams were performed in accordance with hospital protocol and existing guidelines.\(^{12}\)\(^{13}\) CCTA findings were ordinally categorized as no CAD (no plaque, 0% stenosis), non-obstructive CAD (<50% stenosis) or obstructive CAD (≥50% stenosis).

We categorized the number of vessels with CAD [left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA)] as 1-vessel, 2-vessel and 3-vessel/left main (LM) disease. We categorized the extent of plaque according to an 18 segment model proposed by the American Heart Association (AHA), modified by the Society of Coronary Computed Tomography (SCCT).\(^{13}\) Based on the number of segments with plaque, the extent of CAD was categorized as non-extensive (≤4 segments) or extensive CAD (>4 segments).\(^{14,15}\)

**Baseline Cardiovascular Risk Factors**

All clinical data prior to the CCTA was used to categorize baseline cardiovascular risk. Age, symptoms, and risk factors were entered into a validated risk score (Morise score) to estimate baseline pre-test probability of CAD.\(^{16}\) We defined hypertension as systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg, or diagnosis/treatment of hypertension. We defined dyslipidemia as total cholesterol > 240 mg/dL or high density lipoprotein cholesterol (HDL) < 40 mg/dL (male) or HDL < 50 (women) or diagnosis/treatment of dyslipidemia.\(^{17}\) We defined diabetes mellitus (DM) as hemoglobin A1C (HbA1c) ≥ 6.5% or diagnosis/treatment of DM.\(^{18}\) 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 clinically manifest CAD prior to age 60.

**Changes in Medical Therapy and Lab Values**

Electronic medical records were reviewed for up to two years prior to the CCTA for prescription of primary preventive lipid lowering therapy and aspirin therapy. Post-CCTA medical records were reviewed for up to one year post-CCTA 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 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 (e.g., adding ezetimibe to a pre-CCTA regimen of atorvastatin 80 mg daily) or change from one lipid lowering regimen to a more intensive regimen (e.g., change from simvastatin 40 mg to atorvastatin 80 mg daily).

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

**Cardiovascular Outcomes**

As previously described\textsuperscript{14}, two cardiologists blinded to CCTA results reviewed electronic medical records as well as patient questionnaires and phone interview data, in order to adjudicate cardiovascular events. All self-reported events were verified via outside medical records.
The primary endpoint for clinical outcomes was a composite of cardiovascular mortality and non-fatal MI to avoid inherent bias of softer outcomes (e.g. 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 two Cardiologists with cardiovascular mortality defined as a primary cause of 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. Diagnosis of MI was confirmed by two of three: chest pain or equivalent symptom complex; positive cardiac biomarkers; ECG changes typical of MI. Coronary revascularizations consisted of CABG or PCI and were considered early if they occurred within 90 days following CCTA.

**Statistical analysis**

Continuous variables are reported as mean +/- standard deviation or medians where appropriate. Categorical variables are reported as counts and proportions. Continuous variables are compared using analysis of variance. Categorical variables were compared using chi-squared or Fisher’s 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 following CTA 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 SPARC registry.
Due to the limited power (Supplemental Data) to detect differences in hard cardiovascular events in our cohort, we also performed a pre-specified sub-group analysis to examine the association of treatment with hard outcomes (i.e. CV death or MI) among patients with non-obstructive 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 CV death and MI, a propensity weighted Cox-proportional hazards analysis\textsuperscript{20, 21} was performed to adjust for baseline differences that affect the decision to treat with statin. The assumption of non-proportional hazards was tested using a significance test base on the unscaled and scaled Schoenfeld residuals and resulted in non-significant 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\% male) who underwent CCTA with 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 gender, 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 non-obstructive CAD (57%) or obstructive CAD (71%) (Figure 2, upper panel, p<0.001). Following 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 the prescriptions (93%) were for statins while the remainder included fibrates, ezetimibe, or niacin.

Multivariable analysis to predict medication use following CCTA

Age, gender, dyslipidemia, hypertension, diabetes, pre-CCTA statin therapy, revascularization early after CCTA (within 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 to 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 when compared to 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 non-obstructive disease and p = 0.92 for those with obstructive disease).

A subgroup of 855 (30%) patients who underwent CACS at time of CCTA was evaluated for the potential of CAC to influence post-test medical therapy. This information has been provided as Supplemental Figure 1. When the propensity adjusted OR for intensification of statin therapy according to any CAD by CCTA (OR 4.59 ± 0.5) was compared to 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 to 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 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 upon this assumption (Supplemental Figure 2).

Comparison of the baseline characteristics of the patients in the Partners CTA registry with patients from MGH/BWH enrolled in SPARC is listed in the Supplemental 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.

**LDL cholesterol levels pre- and post-CCTA**

Patients who were using statins prior to 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 up to 4 years post CCTA (Figure 4), while 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 year post CCTA among those not treated with statins post-CCTA versus those who had intensification in therapy post-CCTA, there was 9 mg/dL increase versus 4 mg/dL decrease in the no CAD group (Figure 4, p<0.001), a 9 mg/dL increase versus 14 mg/dL decrease in the <50% stenosis group (Figure 4, p<0.001), and 5 mg/dL increase versus 17 mg/dL decrease in the ≥50% stenosis group (Figure 4, 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 (below).

**Propensity Weighted Survival Analysis**

Significant predictors of statin therapy by logistic regression are depicted on Table 2. Diagnosis of dyslipidemia and pre-CCTA statin use were the strongest predictors of statin prescription. The final propensity score included age, male gender, dyslipidemia, hypertension, diabetes, pre-CCTA statin therapy, revascularization early after CCTA (within 90 days), and presence of ≥50% stenosis on CCTA. The final model c-index was 0.92 (LR $X^2 = 1641$, p<0.001).

Univariable and multivariable predictors of CV 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 CV death or MI across all groups (Table 4).

Statin therapy post-CCTA demonstrated a trend toward associated reduction of CV death or MI (HR 0.44, p = 0.065) in the fully adjusted multivariable model (Table 4). However, a significant interaction (p = 0.003, Table 4) was noted for extent of disease (SIS ≤4 or > 4), for
the outcome of CV death or MI. Among subjects with extensive (SIS>4) non-obstructive CAD (<50% stenosis), statin therapy was associated with reduction in CV death or MI (HR = 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 exam 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 have demonstrated that such therapies are strongly associated with improvements in LDL cholesterol levels which persist up to 4 years of follow-up.

While our study has limited power to detect differences in cardiovascular outcomes, we observed in a hypothesis generating analysis that among patients with non-obstructive CAD involving more than 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 (i.e. Morise score), and coronary revascularization. It is likely that greater power was present in this subgroup since patients with no CAD or non-extensive plaque would be expected to have a much lower event rate (thus limiting the ability to detect differences in outcomes based on treatment) while patients with obstructive disease were more likely to be treated with coronary revascularization (which due to 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.
Due to pleiotropic effects\textsuperscript{23} statin therapy does not only reduce LDL levels but has other important clinical benefits such as reduction of vascular inflammation and endothelial dysfunction. On the other hand 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.\textsuperscript{1-5} 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.\textsuperscript{1} Labounty et al reported in 2009 that among 208 patients undergoing CCTA, those with CCTA-diagnosed CAD had a 3 times greater odds of post-CCTA treatment with statin or aspirin therapies, and had lower LDL cholesterol levels.\textsuperscript{4} In a study of 184 patients, Blankstein et al demonstrated that the presence of CAD on CCTA resulted in intensification in medical therapies in 44% of patients.\textsuperscript{3} 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.\textsuperscript{6} Finally, Cheezum et al\textsuperscript{5} recently reported an important retrospective analysis of 1,125 patients who underwent CCTA. In that study when compared to those with normal CCTA, those with non-obstructive CAD were 6.9 times more likely to receive aspirin therapy, 6.6 times more likely to be treated with statin therapy, and 1.6 times more likely to receive blood pressure lowering therapy. Similarly, those with obstructive CAD were 42 times more likely to receive aspirin therapy and 30 times 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, while systolic blood pressure was reduced by 1.4 mmHg and 4.9
mmHg, respectively.\textsuperscript{5} Due to few adverse events, Cheezum’s study was underpowered for assessing the impact of these changes on patient outcomes.

Extending the observations of these single center studies, the SPARC multi-center registry showed sub-optimal 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 increased from 64.7 to 79.4, compared with 71 to 90\% in our cohort.\textsuperscript{7} 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).\textsuperscript{24} Also, SPARC primarily evaluated patients who underwent CCTA in the year 2006, a time of early clinical experience when less knowledge on how to define interventions based on the CCTA results existed. Our study, on the other hand, enrolled patients from 2004-2011; 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 the CCTA results and prognosis was published in 2007)\textsuperscript{25}, 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 in the prior paragraphs 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 post-CCTA rates of aspirin and lipid therapies are not even higher. While patient factors (adverse effects, non-adherence, patient preference) may partially explain this finding, a breakdown in communication of results from imagers to clinicians or the failure of the treating clinician to alter medical therapy when indicated may play a role. Thus, improvements in these processes of care may help to improve rates of preventive medical therapies in patients identified to be at risk but not treated.26

While 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. While coronary artery calcium 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 therapies27 with subsequent beneficial changes in risk factors28. Similarly, among symptomatic patients referred for nuclear myocardial perfusion imaging, the presence of coronary artery calcium is associated with intensification of medical therapies.29

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 in order to reach adequate statistical power to demonstrate the benefit of statin therapy.30 On the basis of our sample size calculation (Supplemental Data), the event rates observed for our sample of 2,839 subjects has only 9% power to detect a difference in CV death and 14% power for CV 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 (HR = 0.81, p = 0.75), an analysis of which had limited power due to few patients (10%) not
treated with statin. In addition, statin therapy in those with no CAD was not significant (HR = 1.83, p = 0.62), an analysis which had limited power due to 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 pre-treated patients (with lower absolute risk due to lower LDL) likely results in a lower absolute risk reduction than initiation of new therapy among statin naïve patients (with higher baseline LDL and higher absolute risk).31

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 CV death or MI) and 0.82 (for non-fatal MI).32 Based upon the sample size and event rate in our study, a hazard ratio of at least 0.38 (CV death) or 0.51 (CV death and MI) in favor of statin intensification would have been required for statistical power. While 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, non-obstructive CAD.

While prior studies have shown that CCTA is associated with changes in medical therapy and risk factors, our analysis is the first to show a sub-group in whom medical therapy post-CCTA was associated with improved prognosis. Nevertheless, our findings regarding the potential reduction in CV death or MI among patients who have at least 4 segments of non-obstructive plaque should only be viewed as hypothesis generating, and require confirmation in future prospective trials. However, given that most MI occur due to plaque rupture at sites of non-obstructive 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, while subject to inherent limitations from the retrospective nature of our study, suggest that further studies are
needed in order to investigate whether patients with extensive non-obstructive CAD should be treated more aggressively. Studying the potential role of CCTA in identifying and treating such individuals is important, particularly since 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 (i.e. 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 that were treated with different doses.

In conclusion, in patients without known prior CAD who are clinically referred for CCTA, diagnosis of non-obstructive and obstructive CAD are strongly associated with intensification of preventive medical therapy prescriptions. Such changes in management are subsequently associated with improvement in cholesterol labs that are sustained at 4 years of follow-up and may improve long-term cardiovascular risk. Propensity weighted analysis of statin
therapy post-CCTA in those with extensive, non-obstructive 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

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Table 1. Demographics. Columns represent n(%) for proportions and mean(sd) for pre-test probability of ≥50% Stenosis (as predicted by Morise Score).

<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>
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<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>
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<td>Male gender</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 CP</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 CP</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 CP</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>
Table 2. Test of propensity score weighting. Unweighted regression coefficients are shown for variables associated with statin therapy post-CCTA. Propensity weighted regression coefficients demonstrate adequacy of adjustment.

<table>
<thead>
<tr>
<th></th>
<th>Unweighted Coefficient</th>
<th>p-value</th>
<th>Propensity Weighted Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, 10 years</td>
<td>0.62 (0.55 - 0.69)</td>
<td>&lt;0.001</td>
<td>-0.001 (-0.012 - 0.01)</td>
<td>0.81</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.43 (0.28 – 0.58)</td>
<td>&lt;0.001</td>
<td>0.03 (-0.21 – 0.28)</td>
<td>0.78</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2.68 (2.48 - 2.87)</td>
<td>&lt;0.001</td>
<td>-0.09 (-0.41 - 0.23)</td>
<td>0.59</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.1 (0.83 - 1.36)</td>
<td>&lt;0.001</td>
<td>0.05 (-0.32 - 0.42)</td>
<td>0.80</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.27 (1.1 - 1.43)</td>
<td>&lt;0.001</td>
<td>-0.01 (-0.27 - 0.24)</td>
<td>0.91</td>
</tr>
<tr>
<td>Baseline statin</td>
<td>3.6 (3.35 - 3.86)</td>
<td>&lt;0.001</td>
<td>0.17 (-0.31 - 0.65)</td>
<td>0.48</td>
</tr>
<tr>
<td>Early Revascularization</td>
<td>2.04 (1.55 - 2.53)</td>
<td>&lt;0.001</td>
<td>0.26 (-0.33 - 0.84)</td>
<td>0.39</td>
</tr>
<tr>
<td>≥ 50% CCTA Stenosis</td>
<td>2.04 (1.77 - 2.3)</td>
<td>&lt;0.001</td>
<td>0.18 (-0.18 - 0.54)</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Table 3. Adverse Cardiovascular Events. Columns represent absolute events and (percent annualized incidence). P-value <0.001 comparing CCTA subgroups No CAD vs. <50% Stenosis vs. ≥50% Stenosis.

<table>
<thead>
<tr>
<th></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 (0.49)</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>19 (1.79)</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>
Table 4. Propensity weighted cox proportional hazards univariable (top) and multivariable model for cardiovascular death and myocardial infarction. Pretest probability defined continuously per 1 percentage point of pretest probability as predicted by the Morise score.

<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(1.20-9.0)</td>
<td>0.051</td>
</tr>
<tr>
<td>Statin post-CCTA</td>
<td>2.39(1.3-4.41)</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:

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Univariable HR</th>
<th>p-value</th>
<th>Multivariable HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin Post-CCTA x Extent of CAD by CCTA (SIS)</td>
<td>-</td>
<td>0.50</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Statin post-CCTA x Extent of CAD by CCTA (SIS)</td>
<td>-</td>
<td>0.003</td>
<td>-</td>
<td>0.022</td>
</tr>
<tr>
<td>Statin post-CCTA (SIS≤4, worst stenosis &lt;50%)</td>
<td>2.25(0.49-10.29)</td>
<td>0.29</td>
<td>1.44(0.27-7.68)</td>
<td>0.67</td>
</tr>
<tr>
<td>Statin post-CCTA (SIS&gt;4, worst stenosis &lt;50%)</td>
<td>0.24(0.07-0.82)</td>
<td>0.023</td>
<td>0.18(0.05-0.67)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

* excluded from MV model: did not add to global chi-squared and no significant interaction.
Figure Legends

Figure 1. Proportion prescribed primary preventive aspirin therapy, pre- and post-CCTA. Using McNemar test to compare pre- and post prevalence of aspirin use, p<0.001 for No CAD, <50% Stenosis, and ≥ 50% Stenosis. CAD = coronary artery disease; CCTA = coronary computed tomography angiography.

Figure 2. Changes in lipid lowering therapy and LDL levels pre and post-CCTA. CAD = coronary artery disease; CCTA = coronary CT angiography; Rx = prescription; LDL = low density lipoprotein.

Figure 3. Changes in aspirin and statin therapy were associated with CCTA findings, after adjusting for age, gender, dyslipidemia, hypertension, diabetes, pre-CCTA statin therapy, and revascularization early after CCTA (within 90 days) (p<0.001 compared to normal CCTA as a reference group). CCTA = coronary computed tomography angiography; OR = odds ratio.

Figure 4. Change in low density lipoprotein (LDL) levels over time according to CCTA and statin intensification. LDL is reported in mg/dL. Percent changes in LDL on the table are compared for each time frame with the baseline (pre-CCTA) LDL. p-value <0.001 for comparison of pre-CCTA LDL with 2 year post-CCTA LDL level by statin intensification according to no CAD, any CAD, non-obstructive CAD, or obstructive CAD. CAD = coronary artery disease; CCTA = coronary CT angiography.

Figure 5. Event free survival from cardiovascular death or MI according to presence or absence of statin therapy post-CCTA among those with non-obstructive CAD, stratified by extent of disease according to Segment Involvement Score (SIS).
No CAD  Non-Obstructive CAD  ≥ 50% CAD

% Lipid Rx pre  Lipid Rx post - intensified  Lipid Rx post - no change

Pre-CCTA  Post-CCTA  Pre-CCTA  Post-CCTA  Pre-CCTA  Post-CCTA

No CAD (n=1147)  <50% CAD (n=1068)  ≥50% CAD (n=624)

32%  18%  57%  25%  71%  63%

LDL (mg/dL)

Pre-LDL  Post-LDL  Pre-LDL  Post-LDL  Pre-LDL  Post-LDL

No Lipid Rx Post  Lipid Rx Post- Intensified  Lipid Rx Post - No Change
Changes in Medical Therapy Post-CCTA

<table>
<thead>
<tr>
<th>Medication</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin Post-CCTA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50% Stenosis</td>
<td>2.52</td>
<td>1.96 - 3.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥50% Stenosis</td>
<td>6.33</td>
<td>4.31 - 9.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Intensified Statin Post-CCTA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50% Stenosis</td>
<td>3.93</td>
<td>3.12 - 4.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥50% Stenosis</td>
<td>6.63</td>
<td>5.05 - 8.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Intensified Lipid Rx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50% Stenosis</td>
<td>3.55</td>
<td>2.86 - 4.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥50% Stenosis</td>
<td>5.59</td>
<td>4.31 - 7.27</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Coronary Artery Disease Detected by Coronary CT Angiography Is Associated with Intensification of Preventive Medical Therapy and Lower LDL Cholesterol

Edward Hulten, Marcio Sommer Bittencourt, Avinainder Singh, Daniel O’Leary, Mitalee P. Christman, Wafa Osmani, Suhny Abbara, Michael Steigner, Quynh A. Truong, Khurram Nasir, Frank Rybicki, Josh Klein, Jon Hainer, Thomas J. Brady, Udo Hoffmann, Brian 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

Edward Hulten, MD MPH1, 2*; Marcio Sommer Bittencourt, MD1, 3*; Avinainder Singh, BS1; Daniel O'Leary, BS1; Mitalee P. Christman, BS1; Wafa Osmani1; Suhny Abbara, MD4; Michael Steigner, MD1; Quynh A. Truong, MD5; Khurram Nasir, MD MPH6; Frank Rybicki, MD1; Josh Klein, BS1; Jon Hainer, BS1; Thomas J. Brady, MD4; Udo Hoffmann, MD3; Brian Ghoshhajra, MD3; Rory Hachamovitch7, Marcelo F. Di Carli, MD1; Ron Blankstein, MD1

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3. Heart Institute (InCor) – University of São Paulo, São Paulo, Brazil

4. Cardiac MR PET CT Program, Department of Radiology, Division of Cardiac Imaging, Massachusetts General Hospital; Harvard Medical School, Boston, MA

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6. Center for Wellness and Prevention Research, Baptist Health South Florida, Miami, FL

7. Cleveland Clinic Foundation, Cleveland, Ohio
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<tr>
<td>Supplemental Figure 3</td>
<td>8</td>
</tr>
</tbody>
</table>
**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.

References:
