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Changes in Preventive Medical Therapies and CV Risk Factors After CT Angiography

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OBJECTIVES The aim of the study was to determine the association of coronary computed tomographic angiography (CTA)–identified coronary artery disease (CAD) with post-test aspirin, statin, and antihypertensive medication use and changes in cholesterol and blood pressure (BP).

BACKGROUND The relationship of CTA findings to subsequent changes in preventive cardiovascular medication prescribing patterns and risk factors is largely unknown.

METHODS We studied 1,125 consecutive patients without known CAD referred for coronary CTA. CAD was defined as none, nonobstructive (<50%), or obstructive (≥50%). Prescriptions were queried in the 6 months pre- and post-CTA for comparison of aspirin, statin, and BP treatment. Medication intensification was defined as initiation, dose increase, or, for statins, change to a more potent formulation. Lipid and BP values were obtained at 12 months pre- and post-CTA.

RESULTS Patients were 50 ± 12 years of age (59% men), with 34%, 47%, and 33% on baseline statin, BP medication(s), and aspirin, respectively. Relative to patients without CAD (n = 617), patients with nonobstructive (n = 411) and obstructive CAD (n = 97) demonstrated significant intensification in unadjusted rates of statin (26%, 46%, and 46% of patients; $p < 0.001$), BP (11%, 21%, and 24%; $p < 0.001$), and aspirin therapies (9%, 29%, and 40%; $p < 0.001$), and significant improvements in total cholesterol (−6.7, −14.7, and −24.7 mg/dl; p = 0.008), low-density lipoprotein cholesterol (−5.6, −14.1, and −24.6 mg/dl; p = 0.001), systolic (+0.1, −1.4, and −4.9 mm Hg; p = 0.002), and diastolic BP (−0.6, −1.0, and −3.4 mm Hg; p = 0.012), respectively. Adjusted for baseline risk factors and medications, CAD was independently associated with increased aspirin, statin, and BP medication use rates in CTA-identified nonobstructive CAD (odds ratio [OR]: 6.9, 95% confidence interval [CI]: 4.7 to 10.2; OR: 6.6, 95% CI: 3.0 to 14.3; OR: 1.6, 95% CI: 1.1 to 2.2, respectively; $p < 0.05$), and aspirin and statin use in obstructive CAD (OR: 42.4, 95% CI: 15.8 to 113.9; OR: 30.3, 95% CI: 3.2 to 289.2, respectively; $p < 0.05$).

CONCLUSIONS CAD presence and severity on CTA are associated with increased use of preventive cardiovascular medications and improvements in cholesterol and BP. (J Am Coll Cardiol Img 2013;6:574–81) © 2013 by the American College of Cardiology Foundation

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Significant data have demonstrated that coronary artery disease (CAD) burden shown on coronary computed tomographic angiography (CTA) predicts future cardiac events and death (1–3). Although studies have shown that the presence and severity of calcified coronary atherosclerosis visualized using coronary artery calcium testing in asymptomatic patients are associated with significant changes in cardiovascular preventive medication prescribing patterns and improvements in cardiovascular risk factors (4,5), similar studies reporting the impact of CAD visualized on CTA are limited (6–9). For any imaging modality to ultimately result in improved outcomes, patient management and behavior must be significantly affected and potentially guided in intensity by the results of the test. Because both obstructive and nonobstructive CAD on CTA are associated with a substantial increase in adverse event rates (2), providers may elect to intensify cardiovascular preventive medications for CAD visualized on CTA; however, the magnitude of these changes and their effect on cardiovascular risk factors as related to CTA disease severity is largely unknown. This is particularly important because a significant proportion of patients undergoing coronary CTA according to appropriate use criteria will have subclinical nonobstructive CAD, leaving providers with questions on how to optimally treat these patients, especially those at low risk according to standard global risk scores (10). We compared pre- and post-CTA prescription patterns of aspirin, statin, and antihypertensive medications, and subsequent changes in serum cholesterol and blood pressure (BP) measures, stratified according to CAD severity among patients clinically referred for coronary CTA.

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METHODS

Study population. We retrospectively identified 1,125 consecutive adult patients without known CAD who underwent coronary CTA between May 2006 and December 2010 for possible angina at Walter Reed Army Medical Center. Previous CAD was defined as history of a myocardial infarction (MI), coronary revascularization, or diagnosis of obstructive (≥50% stenosis) CAD. Patient demographic information, medical history, medications at the time of CTA, test indication, scan parameters, and CTA findings were prospectively collected. Hypertension was defined as a documented history of high BP or treatment with antihypertensive medications. Diabetes mellitus was defined by diagnosis of diabetes made previously by a physician and/or use of insulin or oral hypoglycemic agents. Dyslipidemia was defined as known but untreated dyslipidemia or treatment with lipid-lowering medications. Current smoking was defined as any cigarette use within the past month. Family history of early CAD was defined as clinically manifest CAD involving a male first-degree relative younger than 55 years of age or a female first-degree relative younger than 65 years of age. Individual 10-year risk of MI and coronary death was calculated using the Framingham risk score (11). The study was approved by the local institutional review board.

Coronary CTA. According to institutional protocol, all patients were prescribed variable doses (typically 50 to 100 mg) of oral metoprolol to be taken 1 h before the scheduled scan. Intravenous metoprolol was administered as needed before coronary CTA to obtain a goal pre-scan heart rate of <65 beats/min. Nitroglycerin 0.4 to 0.8 mg sublingual was given 1 min before contrast image acquisition. All patients were in sinus rhythm. Coronary CTA studies were performed with a 64-slice computed tomography scanner system (LightSpeed VCT, GE Healthcare, Waukesha, Wisconsin) in accordance with published guidelines (12). Coronary CTA scans were interpreted jointly (consensus) by a cardiologist and radiologist, each level 2 or 3 certified in the interpretation of coronary CTA (13). Coronary lesions were characterized according to institutional protocol by the maximal luminal diameter stenosis as none (no atherosclerosis and no stenosis), mild (atherosclerosis with 0% to 49% stenosis), moderate (50% to 69%), and severe (70% to 100%) in ≥1 major epicardial vessel.

Outcomes. After coronary CTA, comprehensive prescription, laboratory data, and clinical follow-up information (including death) were queried by an independent data extractor, blinded to the coronary CTA results and baseline risk factors, using all available electronic health databases (inpatient, outpatient, laboratory, radiological) of the Department of Defense Military Healthcare System, a large closed international health care network providing comprehensive and accessible health care and access to medications.

ABBREVIATIONS AND ACRONYMS

BP = blood pressure
CAD = coronary artery disease
CI = confidence interval
CTA = computed tomographic angiography
LDL-C = low-density lipoprotein cholesterol
MI = myocardial infarction
OR = odds ratio

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To evaluate changes in CAD medications attributed to coronary CTA findings, pre- and post-CTA aspirin, statin, and BP medication prescriptions were retrospectively queried using the Department of Defense worldwide pharmacology database to include any prescriptions in the 6 months before and 6 months immediately after coronary CTA. Medication assessment was done for all patients at least 6 months after coronary CTA by investigators blinded to CTA findings. Changes in therapy were defined as no change, less intensive, or more intensive treatment. Intensification of therapy was defined as the initiation of aspirin, initiation or increase in the BP medication dose, and/or the initiation or increase in the dose of a statin or change to a more potent statin preparation based on the expected percentage of low-density lipoprotein cholesterol (LDL-C) decrease (14,15). Independent associations of pre- and post-CTA medication use were performed adjusting for baseline medication use and CAD risk factors (age, sex, hypertension, diabetes, tobacco use, and dyslipidemia), and results were stratified by CAD severity on CTA, defined as no CAD, nonobstructive (<50% stenosis), and obstructive CAD (≥50%).

To evaluate the control of traditional CAD risk factors pre- and post-CTA, systolic and diastolic BP values and lipid profiles were queried in a similar blinded fashion to include total, LDL-C, and high-density lipoprotein cholesterol. The most recent lipid profile in the 12 months pre-CTA (mean 1.6 ± 1.6 months) was compared with the most recent available post-test lipid profile ≥4 weeks, but <12 months, post-CTA (mean 6.3 ± 4.5 months) to allow adequate time to permit meaningful changes in cholesterol values in a manner consistent with previous research (7). Similarly, the most recent BP results in the 12 months pre-CTA (mean 1.5 ± 1.7 months) were compared with the most recent BP measure ≥4 weeks, but <12 months, post-CTA (mean 3.7 ± 2.3 months). When BP readings were available from 2 separate visits, the mean was used from the 2 most recent visits.

Major adverse cardiac events were assessed to include combined rates of death from any cause, MI, and coronary revascularization, with results stratified by CAD severity on CTA. Nonfatal MI was ascertained by a review of clinical notes for a diagnosis of MI and confirmed using the World Health Organization definition (16). Revascularization was defined as coronary artery bypass graft surgery or percutaneous coronary intervention >90 days from coronary CTA. Revascularizations ≤90 days from coronary CTA were censored because previous studies demonstrated that these interventions are performed based on the results of the index coronary CTA, whereas coronary revascularizations >90 days from coronary CTA were considered to be new events related to disease worsening (17). The Social Security Death Index was screened to ensure no deaths were missed, and clinical outcomes were adjudicated independently by 2 cardiologists who were unaware of coronary CTA results and changes in medications.

Statistical analysis. Continuous variables with normal distributions were expressed as mean ± 1 SD and compared with the Student *t* test for independent groups and 1-way analysis of variance for between-group comparisons. Categorical variables were expressed as frequencies (%) and compared by Pearson chi-square test. A 2-tailed p value ≤0.05 was considered significant. Changes in medication use from pre- to post-CTA (dependent variable) were assessed using multivariable logistic regression adjusting for covariate pretest medication use and baseline CAD risk factors (age, sex, hypertension, diabetes, and dyslipidemia). A linear mixed-effects model was used to evaluate for changes in continuous dependent variables pre- and post-CTA, with subjects and pre- and post-coronary CTA status as random effects, and medication intensification and CTA severity (no CAD, <50%, ≥50%) as fixed effects (18). All analyses were performed with SPSS for Windows (version 19.0, SPSS Inc., Chicago, Illinois) and Stata (version 12.1, StataCorp, College Station, Texas).

RESULTS

Patient characteristics. Baseline patient characteristics are displayed in Table 1. Patients (N = 1,125) were of mean age 50 ± 12 years, 59% men, and were followed for a mean period of 24 ± 13 months. The group was predominantly low risk (mean Framingham risk score, 4.5 ± 5.5%), with 33%, 34%, and 47% taking aspirin, statin, and BP treatment at baseline, respectively. Baseline significant differences in patients with no CAD, <50% stenosis, and ≥50% stenosis were present, where increasing CAD severity on coronary CTA was associated with increased cardiovascular risk factors; greater likelihood of baseline aspirin, statin, and BP medication use; and significant differences in baseline HDL-C and systolic BP. A significant portion of patients with nonobstructive and obstructive CAD were not taking aspirin (55% and 45%, respectively), a statin (55% and 31%, respectively),

Table 1. Baseline Patient Characteristics

	All Patients (N = 1,125)	No CAD (n = 617)	<50% Stenosis (n = 411)	≥50% Stenosis (n = 97)	p Value
Age, yrs	50 ± 12	46 ± 12	55 ± 10	58 ± 10	<0.001
Follow-up, months	24 ± 13	24 ± 13	24 ± 13	26 ± 15	0.23
Men	59	53	65	74	<0.001
Body mass index, kg/m^2	29 ± 5	29 ± 5	29 ± 5	29 ± 5	0.86
Hypertension	49	39	59	73	<0.001
Hyperlipidemia	51	36	64	89	<0.001
Diabetes mellitus	10	6	14	20	<0.001
Family history of CAD	27	26	29	23	0.77
Tobacco use in past 30 days	12	11	13	17	0.41
Total cholesterol (n = 841), mg/dl	191 ± 38	193 ± 38	189 ± 39	181 ± 38	0.08
LDL cholesterol (n = 1,068), mg/dl	115 ± 33	116 ± 31	116 ± 35	108 ± 33	0.08
HDL cholesterol (n = 1,068), mg/dl	52 ± 17	55 ± 18	50 ± 15	46 ± 14	<0.001
Systolic BP (n = 1,002), mm Hg	127 ± 14	125 ± 14	129 ± 14	130 ± 13	<0.001
Diastolic BP (n = 1,002), mm Hg	79 ± 8	78 ± 8	79 ± 9	78 ± 8	0.82
Framingham risk score (10 yr CHD)	4.5 ± 5.5	2.7 ± 3.7	6.2 ± 6.1	8.5 ± 7.6	<0.001
Typical angina	8	8	6	14	0.045
Aspirin use	33	21	45	55	<0.001
Statin use	34	21	45	69	<0.001
BP medication use	47	32	52	56	<0.001

Values are mean ± 1 SD or %.
BP = blood pressure; CAD = coronary artery disease; CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

or BP medication (43% and 36%, respectively) at the time of coronary CTA. On the basis of worst stenosis in any coronary segment, 54.8% of patients (n = 617) had no CAD, 36.5% (n = 411) had nonobstructive CAD (<50% stenosis), and 8.6% (n = 97) had obstructive CAD (≥50% stenosis).

Outcomes. Compared with those with no CAD, patients with nonobstructive and obstructive CAD demonstrated significant intensification in aspirin (9% no CAD, 29% nonobstructive CAD, and 40% obstructive CAD; $p < 0.001$), statin (26%, 46%, and 46% of patients; $p < 0.001$), and BP medication (11%, 21%, and 24%; $p < 0.001$) (Table 2, Online Fig. 1). Controlling for baseline risk factors and medication use, CAD severity was independently associated with aspirin and statin use in patients with nonobstructive CAD (odds ratio [OR]: 6.91, 95% confidence interval [CI]: 4.69 to 10.20; OR: 6.58, 95% CI: 3.02 to 14.33; $p < 0.001$ for aspirin and statin, respectively) and obstructive CAD (OR: 42.44, 95% CI: 15.81 to 113.89, $p < 0.001$; OR: 30.35, 95% CI: 3.18 to 289.23; $p = 0.003$), and with BP medication use in patients with nonobstructive CAD (OR: 1.57, 95% CI: 1.10 to 2.24; $p = 0.013$) (Fig. 1). Absolute rates of all therapies significantly increased post-CTA in patients with nonobstructive and obstructive CAD (Table 2).

Complete pre- and post-CTA measurements of total, LDL-C, and high-density lipoprotein cholesterol were available in 37% of patients (n = 412). Pre- and post-CTA systolic and diastolic BP measurements were available in 85% of patients (n = 959). When BP readings were available from 2 separate visits before or after CTA, the mean was

Table 2. Unadjusted Medication Rates Pre- Versus Post-Coronary CTA

	No CAD (n = 617)	<50% Stenosis (n = 411)*	≥50% Stenosis (n = 97)*	p Value
Statin pre-CTA	21	45	69	<0.001
Less intensive	18	10	4	<0.001
Statin started	6	24	24	0.013
More intensive†	26	46	46	<0.001
Statin post-CTA	21	60	86	<0.001
BP medication pre-CTA	32	52	56	<0.001
Less intensive	1	1	1	0.99
BP medication started	3	4	9	<0.001
More intensive†	11	21	24	<0.001
BP medication post-CTA	35	56	64	<0.001
Aspirin pre-CTA	21	45	55	<0.001
Aspirin stopped	5	1	0	<0.001
Aspirin started	9	29	40	<0.001
Aspirin post-CTA	25	73	95	<0.001

Values are %. *$p < 0.05$ comparing unadjusted rates of pre- versus post-CTA medication use. †Intensification defined as initiation or increase in dose of a medication or, in the case of statin therapy, change to more potent statin.
CTA = computed tomographic angiography; other abbreviations as in Table 1.

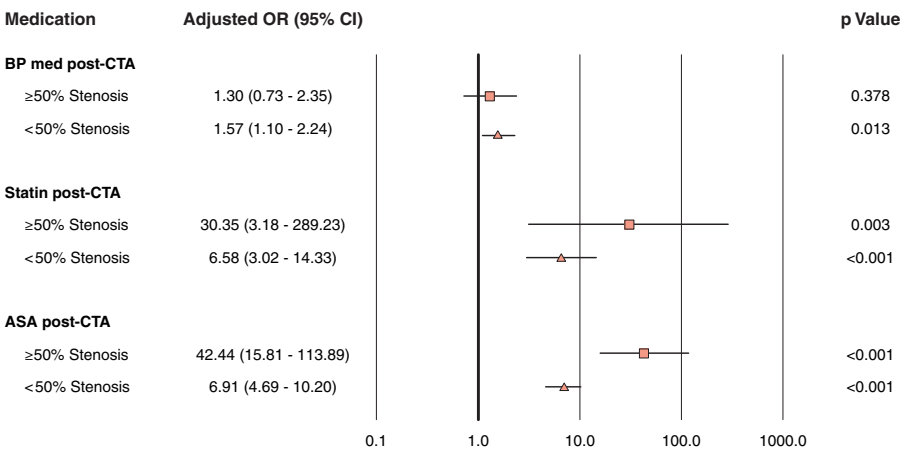

Figure 1. Adjusted Post-CTA Medication Use Stratified by CAD Severity

Controlling for baseline medication use and coronary artery disease (CAD) risk factors (age, sex, hypertension, diabetes, tobacco use, and dyslipidemia), CAD severity demonstrated on coronary computed tomographic angiography (CTA) was independently associated with aspirin (ASA), statin, and blood pressure (BP) medication use in patients with nonobstructive CAD and with aspirin and statin use in patients with obstructive CAD. **Horizontal lines** represent 95% confidence intervals (CIs). OR = odds ratio.

used of the most recent measurements; at least 2 BP results were available for 916 of 959 patients before CTA and in 852 of 959 patients after CTA.

Comparing pre- and post-CTA cardiovascular risk factor control, relative to patients with no CAD, patients with <50% and ≥50% stenosis demonstrated significant improvements in total cholesterol (no CAD, −6.7 mg/dl; nonobstructive CAD, −14.7 mg/dl; obstructive CAD, −24.7 mg/dl; p = 0.008), LDL-C (−5.6, −14.1, −24.6 mg/dl; p = 0.001) (Fig. 2), systolic BP (+0.1, −1.4, −4.9 mm Hg; p = 0.002), and diastolic BP (−0.6, −1.0, −3.4 mm Hg; p = 0.012) (Fig. 3). When compared with patients with no change in medical therapy, a significant improvement in total cholesterol and systolic BP were noted in patients with both nonobstructive and obstructive CAD when therapy was intensified (Fig. 4).

During 24 ± 13 month follow-up, there were 6 deaths, 3 MIs, and 6 late coronary revascularizations. There was 1 event in the no CAD group

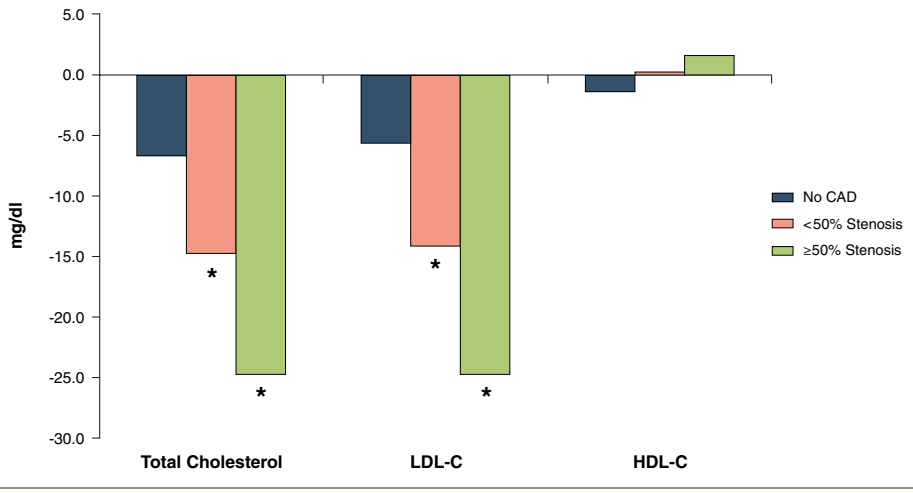

Figure 2. Mean Change in Cholesterol Values After Coronary CTA

Relative to patients with no CAD, patients with <50% and ≥50% stenosis demonstrated significant improvements in total cholesterol and low-density lipoprotein cholesterol (LDL-C), but no change in high-density lipoprotein cholesterol (HDL-C) after coronary CTA. *p < 0.05 versus no CAD. Abbreviations as in Figure 1.

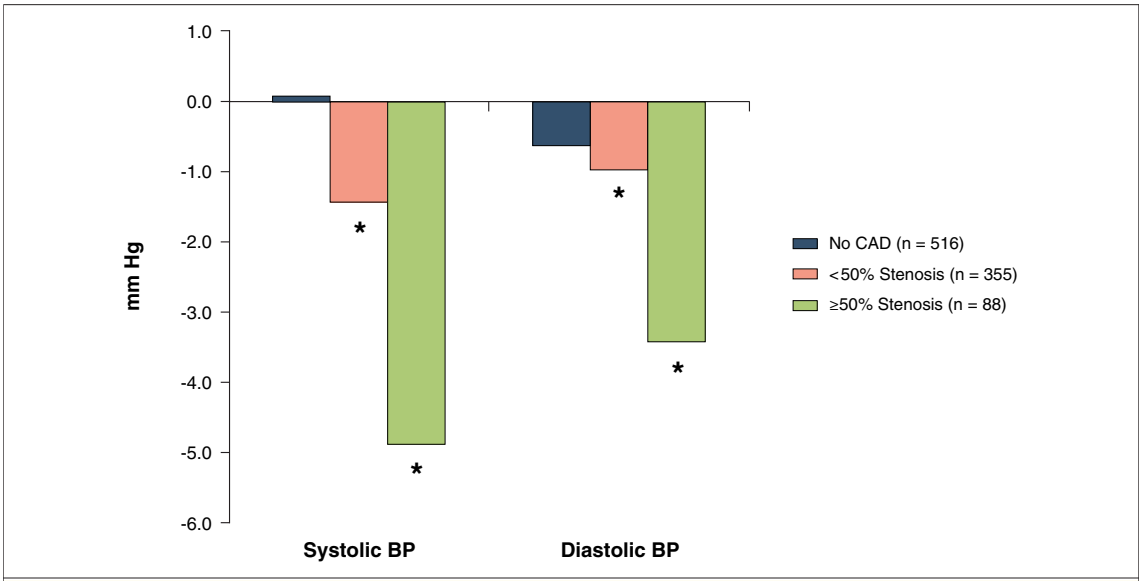

Figure 3. Mean Change in BP Values After Coronary CTA

Relative to patients with no CAD, patients with <50% and ≥50% stenosis demonstrated significant improvements in systolic and diastolic BP after coronary CTA. *p < 0.05 versus no CAD. Abbreviations as in Figure 1.

(0.08%/year), 4 events in the nonobstructive group (0.5%/year), and 10 events in patients with obstructive CAD (4.3%/year) ($p < 0.001$). Due to low event rates, an analysis of the impact of medication changes on adverse events was underpowered.

DISCUSSION

In this study, the largest reported to date to examine the relationship of CAD demonstrated on coronary CTA to changes in medication use and measured risk variables, we observed that the presence and severity of CAD on coronary CTA were independently associated with intensification of aspirin, statin, and antihypertensive medications within 6 months after CTA among a low-risk symptomatic cohort. These changes in provider prescribing patterns were associated with significant improvements in total cholesterol, LDL-C, and BP measures. Importantly, the absence of CAD was not associated with significant changes in cardiovascular preventive medication use.

Our results from a low-risk, symptomatic cohort with a low prevalence of obstructive CAD (8%) suggest that providers may be initiating and adjusting cardiovascular preventive therapies based on coronary CTA findings and beyond that indicated by baseline risk factor burden. In contrast, Hachamovitch et al. (9) prospectively compared baseline and post-imaging medication rates of patients at intermediate to high pre-test likelihood for CAD referred for single-photon emission computed tomography (n = 565), positron emission tomography (n = 548), or coronary CTA (n = 590). Although medical therapy increased proportionally to the degree of abnormal noninvasive test findings, the authors concluded that there was significant undertreatment of patients with high-risk imaging findings across all modalities during 90-day follow-up. Specifically, among patients with the most severe test abnormalities, 20% to 30% did not receive aspirin and 20% to 25% did not receive a lipid-lowering agent at 90 days after the index test. The discrepancy between the higher prescription rates observed in our population versus the lower rates seen in their higher risk cohort may be, in part, attributable to fewer comorbidities in our population allowing for fewer contraindications to medications, use of filled prescriptions as opposed to patient interviews to measure medication changes, more complete prescription and health care cost coverage, and complete in-hospital and within-network referral sources where referring providers are systematically provided direct, electronic CTA reports. In the current health care cost environment, it is important to examine the association of noninvasive cardiovascular test results with subsequent changes in medical treatment in the context of socioeconomic factors and access to medical care because noninvasive tests for CAD may have hetero-

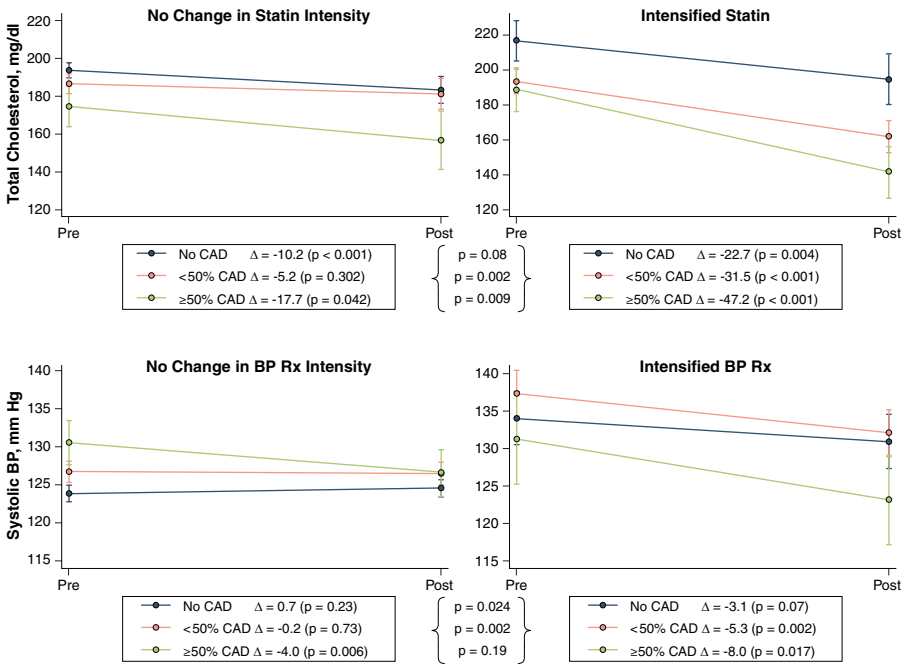

Figure 4. Effect of Medication Intensification on Changes in Total Cholesterol and Systolic BP Stratified by CAD Severity on Coronary CTA

Compared with patients with no change in medical therapy, significant improvements in total cholesterol and systolic BP were noted in patients with nonobstructive and obstructive CAD when medical therapy was intensified. **Vertical bars** represent 95% confidence intervals. *p values shown for in-group and between-group comparisons. Rx = prescription; other abbreviations as in Figure 1.

geneous follow-up related to health care system differences. This hypothesis requires further study.

Numerous trials have demonstrated important reductions in adverse event rates in the treatment of modifiable CAD risk factors (15,19). In the absence of long-term outcomes and cost-effectiveness data, debate endures as to whether changes in preventive medication therapies are justified based on CTA findings alone, particularly in patients with nonobstructive CAD at low global cardiovascular risk (20,21). We observed that nonobstructive CAD was associated with significant intensification in cardiovascular preventive therapies among a low-risk symptomatic cohort. Although the mainstay of cardiovascular risk reduction is and should remain therapeutic lifestyle modification, trials are needed to assess the long-term impact of aspirin and statin therapies on patients with CAD, particularly nonobstructive CAD, diagnosed using coronary CTA, perhaps accounting for measures of plaque risk (e.g., degree of vessel remodeling or presence of low-attenuation plaque) (22).

Study limitations. We recognize several limitations to our study. The study was retrospective, performed at a single center, and underpowered to assess for the effect of medication changes on outcomes. Due to the observational nature of our analysis, follow-up for measured post-test risk factors was variable (excellent for BP and lower for lipids), reflecting a real-world evaluation of patients after CTA. Although data were meticulously obtained from all available military health care system electronic health records, there is the potential for incomplete data. Although patients studied here have the benefit of complete cost coverage for medications obtained within our network, prescriptions outside of the military health care system and over-the-counter aspirin may not have been captured. Further, although our analysis draws associations between changes in medication prescriptions and subsequent risk factors, medication compliance rates, and other potential contributing factors such as changes in diet, exercise, and nonstatin prescriptions were not captured, and direct causation cannot be determined. As this study limited the window to ascertain medication changes to 6 months after CTA to limit potential confounders, long-term changes in treatment patterns, adverse effects of therapies, and effects on CAD outcomes and cost-effectiveness require further study.

CONCLUSIONS

The presence and severity of CAD on coronary CTA are associated with significant intensification in aspirin, statin, and BP medications and improvements in total cholesterol, LDL-C, and BP.

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Key Words: aspirin ■ coronary artery disease ■ coronary CT angiography ■ dyslipidemia ■ hypertension.

▶APPENDIX

For a supplemental figure, please see the online version of this article.