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Impact of Coronary Computed Tomographic Angiography Results on Patient and Physician Behavior in a Low-Risk Population

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Background: The impact of screening coronary computed tomographic angiography (CCTA) on physician and patient behavior is unclear.

Methods: We studied asymptomatic patients from a health-screening program. Our study population comprised 1000 patients who underwent CCTA as part of a prior study and a matched control group of 1000 patients who did not. We assessed medication use, secondary test referrals, revascularizations, and cardiovascular events at 90 days and 18 months.

Results: A total of 215 patients in the CCTA group had coronary atherosclerosis (CCTA positive). Medication use was increased in the CCTA-positive group compared with both the CCTA-negative (no atherosclerosis) and control groups at 90 days (statin use, 34% vs 5% vs 8%, respectively; aspirin use, 40% vs 5% vs 8%, respectively), and 18 months (statin use, 20% vs 3% vs 6%, respectively; aspirin use, 26% vs 3% vs 6%, respectively). After

multivariable risk adjustment, the odds ratios for statin and aspirin use in the CCTA-positive group at 18 months were 3.3 (95% confidence interval [CI], 1.3-8.3) and 4.2 (95% CI, 1.8-9.6), respectively. At 90 days, in the total CCTA group vs controls, there were more secondary tests (55 [5%] vs 22 [2%]; $P < .001$) and revascularizations (13 [1%] vs 1 [0.1%]; $P < .001$). One cardiovascular event occurred in each group over 18 months.

Conclusions: An abnormal screening CCTA result was predictive of increased aspirin and statin use at 90 days and 18 months, although medication use lessened over time. Screening CCTA was associated with increased invasive testing, without any difference in events at 18 months. Screening CCTA should not be considered a justifiable test at this time.

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ATHEROSCLEROTIC CORONARY heart disease (CHD) is a major cause of morbidity and mortality.¹ More than 50% of CHD deaths occur in patients who were previously asymptomatic, highlighting the interest in early detection.¹ Individualized risk stratification using noninvasive imaging has

See Invited Commentary at end of article

been suggested by some as an alternative to traditional models.² Coronary computed tomographic angiography (CCTA) is a novel imaging modality, which has high sensitivity for the detection of atherosclerosis.³ Studies have suggested superior prognostic value with CCTA compared with traditional risk factors.^{4,5} While CCTA has limiting risks inherent to contrast and radiation exposure,⁶ it may have a role in the

noninvasive assessment of patients with symptoms,⁷ as well as in screening certain higher-risk asymptomatic subgroups. However, the consequences of CCTA testing also need to be considered.⁸

Given the potential for more widespread use of CCTA in cardiac risk evaluation, we sought to evaluate the downstream implications of CCTA testing. For this purpose, we chose a cohort of asymptomatic patients who had already undergone CCTA as part of a prior study.^{9,10} We prospectively followed this CCTA group along with a matched control group drawn from the same source screening program. To our knowledge, this is the first study to examine the implications of CCTA screening in a large matched cohort study, including its effect on physician prescribing practices and patient use of medications, as well as the impact on downstream secondary testing and cardiac events.

STUDY POPULATION

The CCTA group was drawn from a prior screening study at the Seoul National University Bundang Hospital (SNUBH), Seoul, South Korea, evaluating the burden of subclinical disease detected by 64-slice multidetector CCTA, as well as the influence of cardiac risk factors on CCTA-defined atherosclerotic plaque type.^{9,10} That study population comprised 1074 South Koreans enrolled from the SNUBH Health Promotion Center, who elected to undergo CCTA from December 2005 through May 2006. A total of 74 subjects who underwent CCTA were excluded from our analysis (**Figure 1**). Therefore, the final CCTA study group comprised 1000 asymptomatic subjects.¹⁰

We constructed a matched control group consisting of an equal number of asymptomatic subjects undergoing the same health screening program at SNUBH over approximately the same period. These 1000 matched controls did not opt for screening CCTA and were drawn from a total pool of 6717 subjects participating in the SNUBH program.

The SNUBH institutional review board approved the study protocol, and all patients gave written informed consent.

BASELINE RISK FACTOR ASSESSMENT AND RISK STRATIFICATION

Basic demographic data were acquired during the initial clinical encounter and from a medical record database maintained by the SNUBH Health Promotion Center. Patients were questioned regarding a history of myocardial infarction, angina, hypertension, stroke, diabetes mellitus, and/or smoking and a family history of CHD or stroke. Current medications were documented. Body weight, height, and blood pressure were measured during their index visit. Hypertension was defined as a subject-reported history of hypertension, high blood pressure (>140/90 mm Hg), or the use of antihypertensive medication. Total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose, glycosylated hemoglobin, and serum creatinine levels were measured after a 12-hour fasting period on the same day of the study. Diabetes was defined as a subject-reported history of diabetes, receiving antidiabetic treatment, or having 2 fasting plasma glucose levels of 126 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0555). Dyslipidemia was defined as a reported medical history of dyslipidemia or prior use of a lipid-lowering medication.

DATA ACQUISITION

In patients undergoing CCTA, those with a heart rate higher than 70 beats/min received intravenous esmolol hydrochloride, 10 to 30 mg, before image acquisition. A 64-slice Multi-Detector CT scanner (Brilliance 64; Philips Medical Systems, Eindhoven, the Netherlands) was used to perform CCTA. A standard scanning protocol was applied, with 64 × 0.625-mm section collimation, 420-millisecond rotation time, 120-kV tube voltage, and 800-mA tube current. A bolus of 80-mL iomeprol (Iomeron 400; Bracco, Milan, Italy) was intravenously injected (4 mL/s), followed by a 50 mL of isotonic sodium chloride solution.

The patient's electrocardiogram (ECG) was simultaneously recorded to allow for retrospective segmental data reconstruction. Images were initially reconstructed at mid-diastolic phase (75% of R-R interval) of the cardiac cycle. The mean (SD) radiation exposure of CCTA was 13.21 (0.82) mSv (13.21 [0.83] for male and 13.33 [0.79] for female patients).

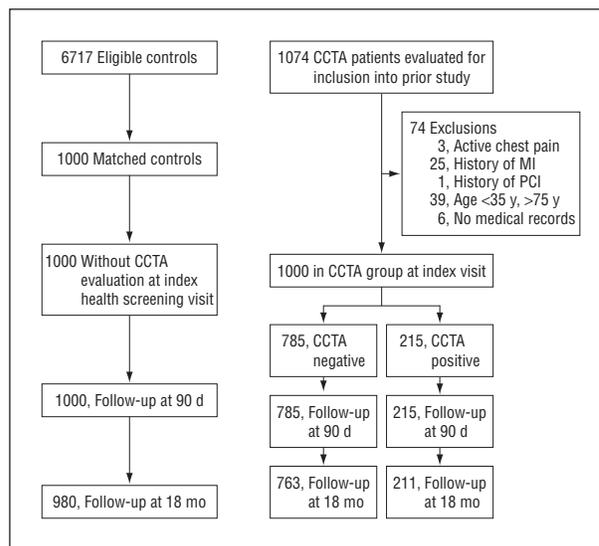


Figure 1. Study overview. CCTA, indicates coronary computed tomographic angiography; MI, myocardial infarction; and PCI, percutaneous intervention.

This exposure is consistent with prior reports using CCTA published from the same period as our study.¹¹

IMAGE ANALYSIS

Scans were analyzed independently on a 3-dimensional (3-D) workstation by 2 experienced investigators (S.I.C. for 5 years; E.J.C. for 3 years), who were blinded to the clinical information. We analyzed plaque characteristics on a per-segment basis according to the modified American Heart Association classification.¹² Plaques were defined as structures larger than 1 mm² within and/or adjacent to the vessel lumen.

Those patients who underwent CCTA were informed of the results at the initial (index) visit after their scan. Patients were provided with 3-D images with a description of the presence of plaque in print. Because the burden of disease was very low in this cohort (see “Results” section), there was insufficient power to conduct subanalysis based on plaque burden and/or stenosis severity. Therefore, we analyzed results in a binary fashion based on whether the scan was positive (any atherosclerotic disease on CCTA) or negative (no disease).

In addition, this provided a simplified framework for analyzing future patient behavior on the basis of the CCTA findings.¹³ Calcium scores were measured as part of the prior study protocol,¹⁰ but because these scores were not reported to the physician or patients, they have not been included in our analysis of downstream behavior.

FOLLOW-UP

We prospectively followed patients over 18 months. At the index visit, medications for the treatment of cardiovascular risk were neither specifically recommended nor provided under the study protocol; all prescriptions were provided at the discretion of the treating physicians at SNUBH.

Follow-up was scheduled at 90 days and 18 months after the index visit. Data regarding medication use, secondary tests (exercise ECG stress testing, single-photon emission computed tomography [SPECT], or coronary angiography [CAG]), and revascularizations (percutaneous intervention [PCI] or coronary artery bypass grafting [CABG]) were obtained from medical records and/or telephone contact using structured questionnaires. These data were obtained for all 2000 patients at

Table 1. Baseline Demographics^a

Characteristic	CCTA Group (n=1000)	Control Group (n=1000)	P Value
Age, mean (SD), y	49.81 (8.88)	49.66 (8.79)	
Male sex	626 (62.6)	628 (62.8)	
FRS, mean (SD), median [range]	5.28 (5.41), 3.00 [29.00]	5.23 (5.07), 3.00 [29.00]	
NCEP risk stratification			
High risk	102 (10.2)	107 (10.7)	.10
Moderate risk	341 (34.1)	295 (29.5)	
Low risk	557 (55.7)	598 (59.8)	
Systolic blood pressure, mm Hg, mean (SD)	117.18 (14.57)	115.78 (14.19)	.03
Diastolic blood pressure, mm Hg, mean (SD)	75.03 (11.78)	74.28 (11.64)	.13
Hypertension	246 (24.6)	232 (23.2)	.45
Diabetes mellitus	73 (7.3)	86 (8.6)	.28
Hypercholesterolemia	142 (14.2)	121 (12.1)	.16
Family history of CAD	129 (12.9)	112 (11.2)	.23
Smoking	331 (33.1)	316 (31.6)	.46
Total cholesterol, mg/dL, mean (SD)	205.62 (35.61)	204.83 (34.33)	.60
LDL-C, mg/dL, mean (SD)	119.38 (32.64)	117.98 (32.23)	.32
HDL-C, mg/dL, mean (SD)	61.58 (15.48)	60.11 (14.16)	.02
Triglycerides, mg/dL, mean (SD)	123.26 (76.31)	133.73 (89.9)	.004
Fasting blood glucose, mg/dL, mean (SD)	97.9 (20.21)	97.56 (24.79)	.73
Glycated hemoglobin, %, mean (SD)	5.72 (0.72)	5.76 (0.76)	.33
Creatinine, mg/dL, mean (SD)	1.09 (0.17)	1.09 (0.17)	.89
Medications			
Antihypertensive agents	149 (14.9)	140 (14.0)	.53
Antidiabetic agents	50 (5.0)	45 (4.5)	.59
Lipid-lowering agents	31 (3.1)	35 (3.5)	.61
Aspirin	69 (6.9)	62 (6.2)	.53

Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomographic angiography; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program.

SI conversion factors: To convert to millimoles per liter, multiply by 0.0259 for cholesterol, 0.0113 for triglycerides, and 0.0555 for glucose. To convert creatinine to micromoles per liter, multiply by 88.4.

^aData are given as number (percentage) of patients unless otherwise specified. The paired *t* test was used for continuous variables, and the McNemar test for categorical variables.

90 days and for 974 (97%) of the CCTA group and 980 (98%) of controls at 18 months.

Medication data were collected for statins, aspirin, antihypertensives, and oral hypoglycemic medications. New cardiac events were also documented at both 90 days and 18 months. Cardiac events were defined as cardiac death, nonfatal myocardial infarction, and unstable angina requiring hospitalization (as diagnosed by history, ECG, and cardiac enzymes).

STATISTICAL ANALYSIS

For the match, logistic regression was used to derive a propensity score summarizing the probabilistic frequency of group assignment based on the following 3 important a priori–defined covariates: age, sex, and Framingham Risk Score.¹⁴ Using this propensity score, we then matched the 1000 CCTA patients with 1000 controls on a 1-to-1 basis. The propensity score matching method enables simultaneous matching over several important potential confounders

(including Framingham Risk Score, a derived calculated variable), while preserving analytical power by combining multiple covariates into 1 score.

For the analysis, baseline continuous variables were expressed as mean (SD) and categorical variables were presented as absolute values and percentages. Because subjects were matched, analyses were performed for paired designs. Differences between continuous variables were analyzed with paired *t* tests, and those between categorical variables using the McNemar test of proportions and the generalized estimating equations method.¹⁵

To further adjust for the effect of potential confounders in this matched sample, conditional multivariable logistic regression was used for modeling medication use in the CCTA group compared with the control group at the 90-day and 18-month follow-up intervals. The model was further adjusted for hypertension, diabetes, smoking, LDL-C level, and a history of dyslipidemia. There were no missing values, and we did not exclude outliers. Interaction terms between study group and model covariates were tested (ie, study group and diabetes) but were discarded owing to nonsignificance. All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

DEMOGRAPHICS

Baseline characteristics of the study groups are given in **Table 1**. The mean (SD) age of the total study population was 50 (9) years, and 63% of the patients were male. The propensity score match provided 2 study groups with nearly identical clinical parameters (C statistic, 0.51; Hosmer-Lemeshow test, 8.21; *P* = .41). However, controls were more likely to have elevated triglyceride levels (*P* = .004) and lower HDL-C levels (*P* = .02). There was also a nominal difference in systolic blood pressure between the groups.

CCTA RESULTS

A comprehensive description of the results of the baseline CCTA screening has been published as part of the prior study.^{9,10} A total of 785 patients (79%) had a normal CCTA result, defined as “CCTA negative.” The remaining 215 patients (21%), defined as “CCTA positive,” had atherosclerotic plaque seen in 392 segments (2±1 segments per subject; range, 1-6 segments). Fifty-two (5%) of these patients had significant (≥50%) stenoses and 21 (2%) had severe (≥75%) stenoses. Forty CCTA-positive patients (4%) and every CCTA-negative patient (100%) had a coronary artery calcification (CAC) score of zero (eTable 1; <http://www.archinternmed.com>). Interobserver agreement for the detection of any plaque per subject and plaque per segment were excellent (Cohen kappa, 0.93 and 0.84, respectively).

MEDICATION USE

Statins

Figure 2B demonstrates baseline statin use prior to study enrollment. There was no difference in use between the

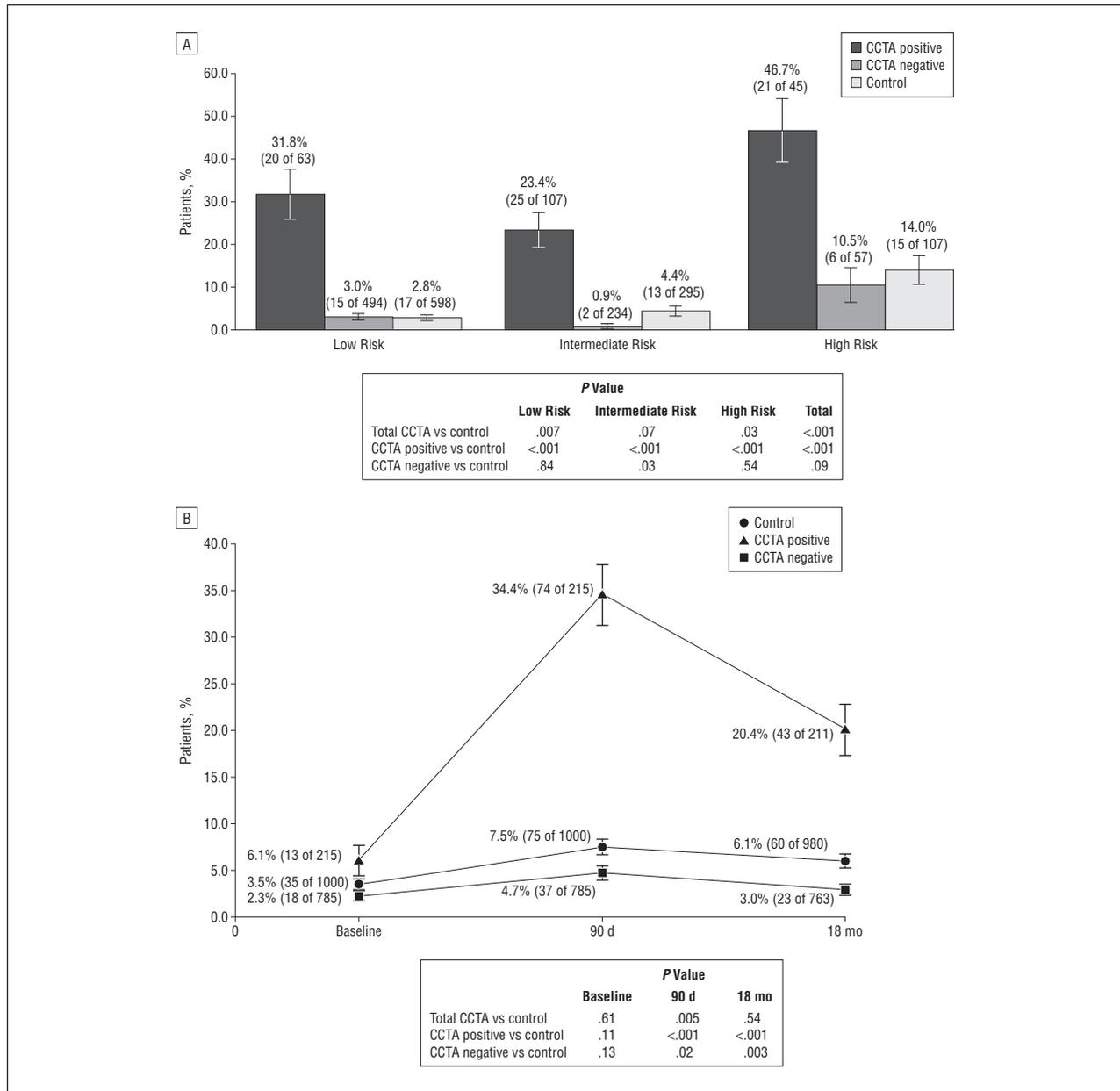


Figure 2. A, Statin prescriptions stratified by National Cholesterol Education Program (NCEP) risk; B, statin use over follow-up. Generalized estimating equations method for analysis of paired data. Error bars indicate SD. CCTA indicates coronary computed tomographic angiography.

entire CCTA group and controls ($P = .60$). We found an association between CCTA results and statin prescriptions at the index visit. Statins were prescribed more often in those with a positive CCTA result compared with the control group ($P < .001$; Figure 2A). This difference persisted when stratified by risk categories defined in the NCEP-ATP (National Cholesterol Education Program-Adult Treatment Program) III guidelines (NCEP risk).¹⁶ Those with a negative CCTA result were less likely than controls to receive a statin prescription if they had intermediate NCEP risk ($P = .03$).

Figure 2B demonstrates that the increased number of prescriptions given to those with a positive CCTA result at the index visit was associated with increased patient statin use at both 90 days (34% vs 8%; $P < .001$) and

18 months (20% vs 6%; $P < .001$) compared with controls. The CCTA-negative group was also less likely to use statins compared with controls at 90 days ($P = .02$) and 18 months ($P = .003$).

In multivariate regression analysis, which included baseline LDL-C level and a history of dyslipidemia, the odds ratio (OR) for statin use in the CCTA-positive group at 90 days was 4.6 (95% confidence interval [CI], 2.3-9.0) compared with controls. By 18 months, this OR was 3.3 (95% CI, 1.3-8.3) (**Table 2**).

Aspirin

We found similar results with aspirin use. Baseline aspirin use was not different between the total CCTA group

Table 2. Odds Ratios (ORs) for Statin and Aspirin Use in the CCTA Group Compared With Controls^a

Study Group	90 Days, OR (95% CI)	P Value	18 Months, OR (95% CI)	P Value
Statins				
CCTA positive vs control	4.588 (2.330-9.036)	<.001	3.307 (1.324-8.258)	.01
CCTA negative vs control	0.707 (0.404-1.237)	.22	0.465 (0.215-1.005)	.051
Aspirin				
CCTA positive vs control	6.784 (3.234-14.231)	<.001	4.193 (1.825-9.635)	<.001
CCTA negative vs control	0.817 (0.453-1.474)	.50	0.489 (0.220-1.084)	.08

Abbreviations: CI, confidence interval; CCTA, coronary computed tomographic angiography.

^aConditional logistic regression. Descriptive variables: dyslipidemia, hypertension, diabetes, smoking, low-density lipoprotein cholesterol.

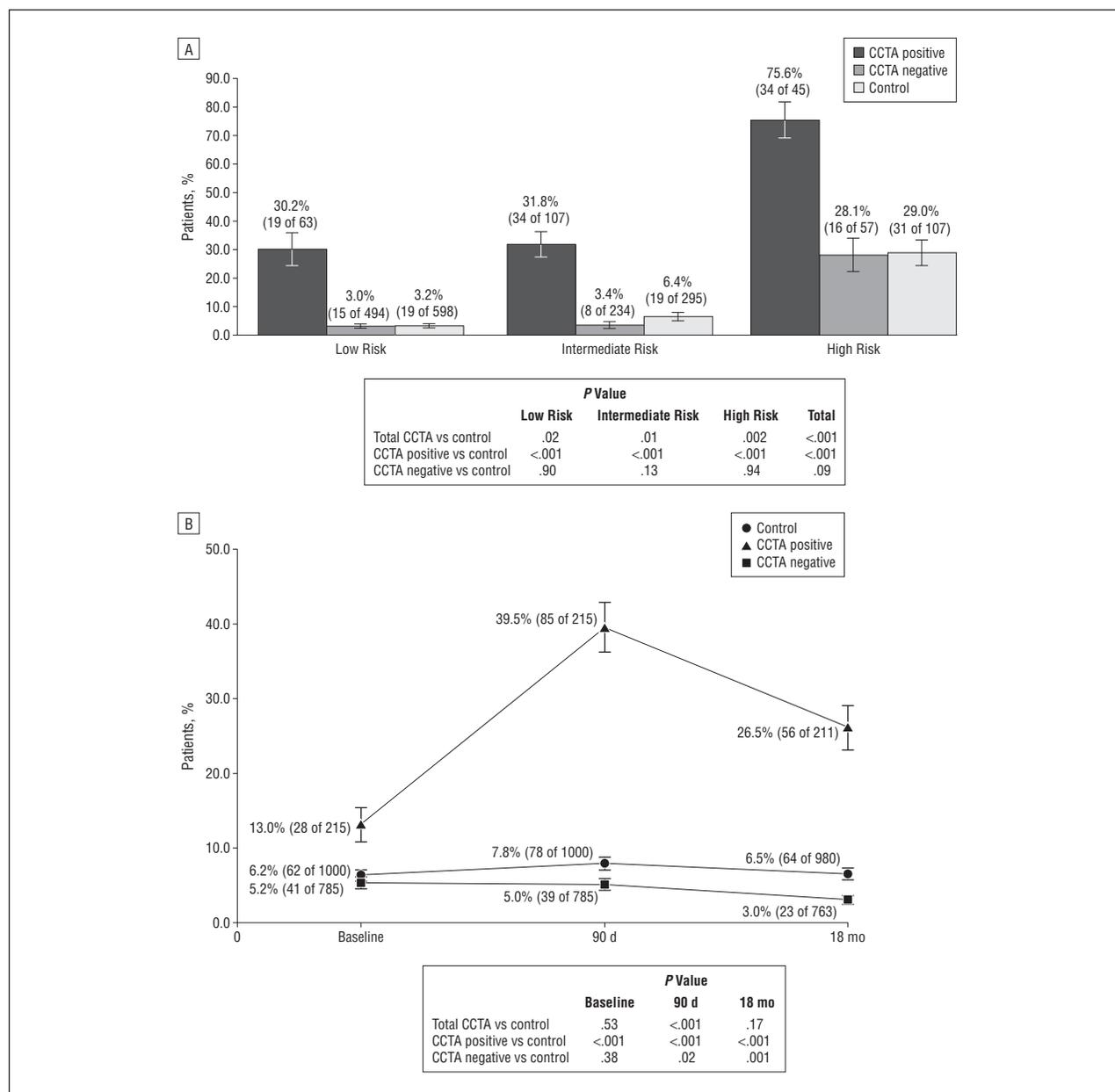


Figure 3. A, Aspirin prescriptions stratified by National Cholesterol Education Program (NCEP) risk; B, aspirin use over follow-up. Generalized estimating equations method for analysis of paired data. Error bars indicate SD. CCTA indicates coronary computed tomographic angiography.

and controls (**Figure 3B**). However, those subsequently found to have a positive CCTA result had higher baseline aspirin use than controls (13% vs 6%; $P < .001$).

Aspirin prescriptions at the index visit were more likely in those with an abnormal CCTA result (Figure 3A). Unlike statins, we did not observe a trend toward less aspi-

Table 3. Secondary Tests (STs), Cardiac Events (CEs), and Revascularizations (RVs)^a

	STs, No. (%; 95% CI)	CEs, No. (%, 95% CI)	RVs, No. (%, 95% CI)	P Value (vs Control Group)
90 Days				
CCTA positive (n=215)	44 (20.5; 15.3-26.5)	0	13 (6.0; 3.2-10.1)	ST, <.001 CE (-) ^b RV, <.001
CCTA negative (n=785)	11 (1.4; 0.7-2.5)	0	0	ST, .22 CE (-) ^b RV (-) ^b
Control (n=1000)	22 (2.2; 1.4-3.3)	0	1 (0.1; 0.0-0.6)	...
18 Months				
CCTA positive (n=211)	0	1 (0.5; 0.01-2.6)	1 (0.5; 0.01-0.6)	ST (-) ^b CE, .26 RV, .49
CCTA negative (n=763)	0	0	0	ST (-) ^b CE (-) ^b RV (-) ^b
Control (n=980)	9 (0.9; 0.4-1.7)	1 (0.1; 0.0-0.6)	2 (0.2; 0.02-0.7)	...

Abbreviation: CCTA, coronary computed tomographic angiography.

^aGeneralized estimating equations method for analysis of paired data.

^bP value is not applicable.

rin prescriptions in those with intermediate NCEP risk and a normal CCTA.

Once again, positive CCTA results were associated with increased aspirin use over follow-up (Figure 3B). Multivariate ORs for aspirin use in the CCTA positive group were 6.8 (95% CI, 3.2-14.2) and 4.2 (95% CI, 1.8-9.6), at 90 days and 18 months, respectively, compared with controls (Table 2).

Antihypertensives and Oral Hypoglycemic Medications

There were no significant differences in the use of these medications between the CCTA group and controls during the study period (eTable 2).

REFERRAL FOR SECONDARY TESTS

Referral for secondary tests was more common in the total CCTA group compared with controls (55 [5.5%] vs 22 [2.2%] patients; $P < .001$) at 90 days. When stratified according to CCTA results, just 1.4% (11 of 785) with a normal CCTA result underwent further testing, whereas 21% (44 of 215) with a positive CCTA result had downstream testing ($P < .001$; **Table 3**).

Of the 55 patients undergoing secondary tests in the total CCTA group, 26 underwent exercise ECG alone, 5 had myocardial SPECT alone, 20 had CAG alone, 2 had both exercise ECG and CAG, and 2 had both SPECT and CAG. Of these 55 patient referrals, 11 occurred in those with a negative CCTA result, with 10 undergoing exercise ECG and 1 undergoing CAG. Of the 22 secondary referrals in the control group; 13 underwent exercise ECG alone, 4 had SPECT alone, 2 had CAG alone, and 3 had both SPECT and CAG.

Stratifying by NCEP risk category revealed that there was an increase in 90-day referral rates for secondary tests in the CCTA group compared with controls as baseline NCEP risk category increased (low risk,

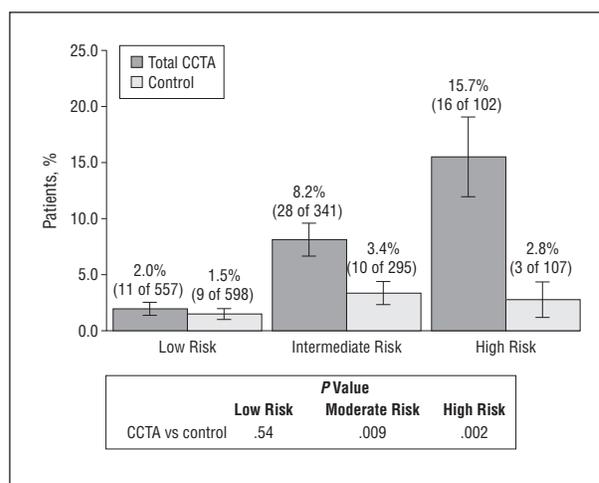


Figure 4. Secondary tests at 90 days stratified by National Cholesterol Education Program (NCEP) risk. Error bars indicate SD. Abbreviation: CCTA indicates coronary computed tomographic angiography.

$P = .60$; moderate risk, $P = .01$; and high risk, $P = .002$) (**Figure 4**).

Despite the increased number of referrals in the whole CCTA group at 90 days, the percentage of abnormal SPECT and CAG test results was no greater than in controls (eTable 3).

REVASCULARIZATIONS AND CARDIAC EVENTS

Revascularization was also more common in the CCTA group than in controls at 90 days (13 vs 1; $P < .001$). Twelve patients had PCI and 1 had CABG in the CCTA group, in contrast to 1 PCI in the control group. There were no differences in revascularizations at 18 months (1 vs 2; $P = .49$).

There were no cardiac events in the first 90 days. After 18 months, there was 1 admission for unstable angina in the CCTA group and 1 unspecified cardiac death in the control group.

In our study of 2000 asymptomatic matched patients, an abnormal CCTA result was associated with more aspirin and statin prescriptions, as well as increased patient medication use at 90 days and 18 months. However, medication use lessened with time. Performance of CCTA was also associated with significantly more secondary testing and invasive revascularization procedures in this asymptomatic cohort, without any difference in cardiac events at 18 months. Thus, the potential benefit of increased medication use in the CCTA group is tempered by the risk of further testing in low-risk patients without any evidence-based indication.

PRESCRIPTIONS AND MEDICATION USE

Whether imaging tests can augment patient compliance with preventive cardiac therapies remains unclear. In particular, the literature reporting the effects of CCTA on medication compliance is limited. Prior reports documenting the relationship between CCTA and medication use have focused on symptomatic patients. LaBounty et al¹⁷ demonstrated that higher grades of CCTA documented atherosclerosis severity were associated with greater post-CCTA use of aspirin (OR, 3.2 per grade) and statins (OR, 3.6 per grade) but not antihypertensive medications.

In a similar series, Blankstein et al¹⁸ reported that CCTA may generally influence medical management, although to varying degrees according to different health care providers. Results of CCTA influenced changes in medical therapies for 31% of patients, with significant increases in initiation of therapy, as well as dose escalation. Our study reaffirms these findings but also adds to them by providing the first report to our knowledge of the association between abnormal CCTA results and longitudinal patient medication use over 18 months (in addition to postscan prescriptions only). We also found a reduction in statin and aspirin use in those with a normal CCTA result. Whether this will prove to be cost-effective or potentially harmful owing to a false sense of reassurance is currently unknown.

Our study has methodological strengths that overcome some limitations of these prior CCTA reports, which had small sample sizes. In addition, ours is the only study that incorporates a control group that did not receive imaging. This control group allows for differentiation between the effects of the health screening encounter and the CCTA imaging test itself.

Given that it appears that physicians and patients may dramatically change practice based on CCTA findings, our findings argue for randomized trials in this area.¹⁹ This is of particular importance for patients with higher pretest probability of significant disease. Currently, at least 4 randomized trials of CCTA are under way. These include PROMISE (PROspective Multicenter Imaging Study for Evaluation of chest pain; NCT01174550), PROSPECT (Study Comparing CT Scan and Stress Test in Diagnosing Coronary Artery Disease in Patients Hospitalized for Chest Pain; NCT00705458), RESCUE (Randomized Evaluation of Patients With Stable Angina Comparing Diagnostic

Examinations; NCT01262625), and ROMICAT-II (Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography; NCT01084239).

Our findings are also compatible with some prior studies of CAC scoring, where abnormal results were associated with greater initiation of aspirin and statins.^{20,21} As with our study, these studies have found a general trend toward reduced medication use over time since the initial abnormal CAC scan.²²⁻²⁴

These findings serve as a reminder that medication compliance is a complex phenomenon determined only in part by a single health care interaction (such as an imaging test like a CCTA) and may be more influenced by numerous encounters in a longitudinal physician-patient relationship.²⁵

SECONDARY TESTS AND REVASCULARIZATION

While it is reassuring that those with a negative CCTA result had a trend toward decreased downstream testing compared with controls (1.4% vs 2.2%; $P = .22$), we did find significantly increased referrals in those with positive test results despite their asymptomatic status and low mean Framingham Risk Score (placing most patients in a low 10-year risk group).

This finding may reflect a variation of the so-called oculo-stenotic reflex²⁶ (an angiographic term for when a coronary stenosis is invasively corrected on the basis of visual severity and not clinical significance). This raises great concern regarding the use of CCTA imaging in low-risk groups. These concerns are highlighted by the findings of COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), which showed that aggressive medical and lifestyle interventions led to similar outcomes compared with PCI in patients with stable CHD.²⁷ In such, we found that the evidence-free performance of CCTA in asymptomatic patients was associated with further evidence-free testing and interventions.

These findings highlight the need to consider the pretest probability of disease before performing imaging tests in patients who may be subsequently exposed to potentially harmful downstream procedures with questionable prognostic benefit.^{28,29} Further concerns also relate to the finding of incidental abnormalities in these asymptomatic patients,³⁰ as well as the anecdotal phenomenon of liberalized lifestyle decisions in those with normal imaging results. We stress that our results do not apply to those with angina symptoms, when CCTA may have benefit in resource utilization.^{31,32} They also do not apply to CAC testing in asymptomatic patients, where downstream resource utilization is minimal in those with scores lower than 400 Agatston units.³³

STUDY LIMITATIONS

This is a nonrandomized study of self-referred patients and is thus subject to allocation bias, selection bias, and residual confounding. Specifically, the control group did not opt for CCTA screening and may have also been less likely to fill prescriptions and undergo any recommended secondary testing. We attempted to minimize these sources of bias by matching and adjusting for

other variables in the multivariate logistic regression models.

This was a racially homogenous Korean population, which may limit external generalization. Our study is also limited by a small number of events and relatively short follow-up (18 months), which are insufficient to form conclusions about cardiac events in a low-risk cohort.

Additional data on cost and risk factor control at follow-up visits were not available. Events were not externally adjudicated. We do not have data regarding the reasons for drug discontinuation in either group over time. In addition, we relied on self-reported medication use for follow-up, which tends to overestimate actual compliance.³⁴

Owing to the low burden of disease we were unable to assess medication use or secondary tests by stenosis severity. The use of CCTA for risk assessment in an asymptomatic population is not currently supported by clinical guidelines and for now remains a research tool.¹¹ Finally, we note that the radiation exposure of CCTA carries a future cancer risk.⁶

CONCLUSIONS

We demonstrate that a screening CCTA suggesting coronary atherosclerosis was associated with a sustained increase in aspirin and statin use. However, an abnormal result was also associated with more resource-intensive secondary tests and invasive revascularizations outside of evidence-based guidelines. The clinical implications of these results may rely on the debate regarding the utility of statins and aspirin in primary prevention. Randomized trials of CCTA use with longer follow-up are needed to assess whether these effects can alter outcomes. Our data concurs with the prevailing notion that screening CCTA does not have a role in low-risk patients.

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Author Contributions: Dr Chang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* McEvoy, Blaha, Yoon, E. K. Choi, Cho, Rivera, Blumenthal, and Chang. *Acquisition of data:* E. K. Choi, Cho, Chun, S.-I. Choi, and Chang. *Analysis and interpretation of data:* McEvoy, Blaha, Nasir, Cho, Chun, Rivera, Blumenthal, and Chang. *Drafting of the manuscript:* McEvoy, Blaha, and Chang. *Critical revision of the manuscript for important intellectual content:* McEvoy, Blaha, Nasir, Yoon, E. K. Choi, Cho, Chun, S.-I. Choi, Rivera, Blumenthal, and Chang. *Statistical analysis:* McEvoy, Blaha, Nasir, and Yoon. *Administrative, technical, and material support:* McEvoy. *Study supervision:* Nasir, Rivera, Blumenthal, and Chang.

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Online-Only Material: The eTables are available at <http://www.archinternmed.com>.

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INVITED COMMENTARY

ONLINE FIRST

Pseudodisease, the Next Great Epidemic in Coronary Atherosclerosis?

Between 1995 and 2000, public health authorities in 6 of 16 German states offered urine screening for neuroblastoma to the parents of more than 2.5 million 1-year-old infants.¹ Nearly 1.5 million infants underwent screening, leading to a diagnosis of neuroblastoma in 149. Physicians diagnosed neuroblastoma twice as often in the 6 screening states as in the 10 nonscreening states, yet the rates of stage 4 neuroblastoma diagnoses were virtually identical, as were death rates from neuroblastoma, in states that screened as those that did not. As reported by Schilling et al,¹ screening succeeded in increasing diagnosis of early disease, yet had no impact on reducing rates of advanced or fatal disease. Investigators in Japan and Canada reported similar findings: screening led to more diagnoses and more interventions but failed to prevent advanced disease or deaths.^{1,2}

How could this be? Physicians and public health authorities who instituted neuroblastoma screening believed it to be an invariably progressive disease. Once a tumor is detectable, it was thought that it must be treated because otherwise it will expand, metastasize, and eventually kill. In fact, the screening stories in Germany, Canada, and Japan revealed that most of the detected early neuroblastomas would have regressed spontaneously and never have presented a threat had they only been left alone. While our diagnostic technologies were good enough to detect early disease, they were not able to distinguish between those tumors that represented a genuine threat to a child's life and those that did not.

This phenomenon is now well described and is known as "overdiagnosis."³ Some have referred to it as the diagnosis of pseudodisease, which, as defined by Black and Czum,^{4(p295)} is "a condition that would not have become clinically significant if it had not been detected by screen-

ing." Pseudodisease can regress spontaneously, remain permanently subclinical, or progress so slowly that another disease kills the patient first.

Overdiagnosis is a serious problem because it leads to a number of harms, while by its very nature it cannot offer benefit. Physicians cannot easily ignore diagnoses made with screening tests because it is impossible for them to determine whether their patients have real disease or pseudodisease. Therefore, physicians prescribe tests, medications, procedures, or even surgical procedures, all of which carry inherent risks. In the neuroblastoma story, for example, there were documented cases of children who died from treatment rather than disease.¹

Overdiagnosis is threatening to become an increasingly important public health problem because of the enthusiasm for and proliferation of unproven screening tests.⁵ In this issue of the *Archives*, McEvoy et al⁶ present their observations of 1000 low-risk asymptomatic adults who were self-referred to coronary computed tomographic angiography (CCTA) as a screening test for coronary atherosclerosis. Using an elegant propensity-matched design, the authors compared the clinical courses of these 1000 people to 1000 similar adults who chose not to undergo screening. They found that more than 20% of the screened adults had evidence of coronary atherosclerosis and that over the next 18 months these adults were much more likely to take statins and aspirin and were much more likely to undergo subsequent testing and invasive coronary revascularization procedures. However, the rates of major coronary events were extremely low (0.1% over 18 months) and identical irrespective of screening.

The report by McEvoy et al⁶ serves as a powerful reminder of the 2-edged effects of screening.⁷ As they articulate in their discussion, their principle finding was