Impact of Coronary Calcification on Clinical Management in Patients With Acute Chest Pain

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Background**—**Coronary artery calcification (CAC) may impair diagnostic assessment of coronary computed tomography angiography (CTA). We determined whether CAC affects efficiency of coronary CTA in patients with suspected acute coronary syndrome (ACS).

Methods and Results**—**This is a pooled analysis of ACRIN-PA (American College of Radiology Imaging Network–Pennsylvania) 4005 and the ROMICAT-II trial (Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography) comparing an initial coronary CTA strategy to standard of care in acute chest pain patients. In the CTA arms, we investigated appropriateness of downstream testing, cost, and diagnostic yield to identify patients with obstructive coronary artery disease on subsequent invasive coronary angiography across CAC score strata (Agatston score: 0, >0–10, >10–100, >100–400, >400). Out of 1234 patients (mean age 51±8.8 years), 80 (6.5%) had obstructive coronary artery disease (≥70% stenosis) and 68 (5.5%) had ACS. Prevalence of obstructive coronary artery disease (1%–64%), ACS (1%–44%), downstream testing (4%–72%), and total (2337–8484 US$) and diagnostic cost (2310–6678 US$) increased across CAC strata (P<0.001). As the increase in testing and cost were lower than the increase of ACS rate in patients with CAC>400, cost to diagnose one ACS was lowest in this group (19 283 US$ versus 464 399 US$) as compared with patients without CAC. The diagnostic yield of invasive coronary angiography was highest in patients with CAC>400 (87% versus 38%).

Conclusions**—**Downstream testing, total, and diagnostic cost increased with increasing CAC, but were found to be appropriate because obstructive coronary artery disease and ACS were more prevalent in patients with high CAC. In patients with acute chest pain undergoing coronary CTA, cost-efficient testing and excellent diagnostic yield can be achieved even with high CAC burden.

Clinical Trial Registration**—**URL: http://www.clinicaltrials.gov. Unique identifiers: NCT01084239 and NCT00933400.
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Coronary artery calcification (CAC) is an indicator of coronary atherosclerosis and can be noninvasively assessed using ECG-gated noncontrast computed tomography (CT) of the heart.[1] There is a positive association between the presence and extent of CAC and prevalence of obstructive coronary artery disease (CAD) by coronary CT angiography (CTA)[2] as well as risk of future cardiovascular events.[3,4]

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In the assessment of coronary arteries, a high burden of CAC can reduce the diagnostic performance of coronary CTA (especially through reduction in specificity and positive predictive value) and subsequently might be less effective to identify patients without significant coronary artery stenosis, as shown by data from Arbab-Zadeh et al[5] in 371 patients undergoing coronary CTA and cardiac catheterization. A meta-analysis from 19 studies with over 1600 patients also demonstrated a decrease in diagnostic accuracy to detect significant coronary artery stenosis using 64-slice coronary CTA in patients with a CAC score >400.[6] Increased extent of CAC was also shown to be associated with higher rates of downstream testing and cost in asymptomatic patients,[7] and some guidelines recommend invasive assessment rather than coronary CTA in symptomatic patients with a CAC score >400.[8] However, limited information is available about the effect of CAC on downstream testing and cost in symptomatic patients presenting to the emergency department (ED) with suspected obstructive CAD or acute coronary syndrome (ACS). Also not known is whether differences between men and women exist.

We pooled 2 large randomized multicenter trials that studied the clinical effectiveness of coronary CTA versus the standard of care for the management of acute chest pain in the ED and determined differences in clinical management (and specifically downstream testing) and cost after coronary CTA across increasing CAC strata in the overall cohort, in a subpopulation with obstructive CAD and in men and women.

Methods

Study Design

This study is an observational cohort analysis of pooled data from the 2 largest randomized, controlled, multicenter trials (ACRIN-PA [American College of Radiology Imaging Network–Pennsylvania] 4005[9] and ROMICAT II [Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography])[10] using individual patient-level data. Both trials evaluated low-to-intermediate risk patients presenting to the ED with suspected ACS comparing coronary CTA as initial diagnostic strategy to standard of care. In both trials, subsequent clinical management was directed by physicians' discretion. Detailed descriptions of the studies have been published previously.[9,10]

Study Population

Individuals presenting with acute chest pain or anginal equivalent to the ED were recruited at 14 hospitals [5[9] and 9 hospitals[10]] in the United States and were randomized to either a diagnostic strategy incorporating coronary CTA or a standard diagnostic strategy alone. Inclusion and exclusion criteria were described in detail elsewhere.[9,10] Briefly, subjects ≥30 years[9] and 40 to 74 years[10] were included, presenting with symptoms suspicious for ACS, requiring further risk stratification according to the attending physician. Included patients had ECG and initial troponin test without signs of acute myocardial ischemia or necrosis. Patients with impaired renal function (>1.5 mg/dL serum creatinine), known allergy to iodinated contrast agent, clinically unstable condition, or nonsinus rhythm were excluded. For this analysis, we included patients randomized to the CTA arm from both source trials. We excluded patients with missing CTA or missing noncontrast CAC data.

Studies were approved by local institutional review boards, and all participants provided written informed consent.

Study Protocol

Eligible patients were enrolled and randomly assigned in a 1:1[10] or 2:1[9] fashion to coronary CTA as part of the initial evaluation in the ED or a standard of care strategy, chosen by the treating emergency physician. Coronary CTA results were provided to caregivers in real-time and used for clinical decision-making, although there was no protocol mandating subsequent care.

Follow-up was performed at 28 days after discharge[10] or at least 30 days after enrollment[9] to determine patient safety outcomes.

CT Imaging and Image Interpretation

Coronary image acquisition was performed using 64-multidetector row or newer CT scanners. The imaging protocol included a topogram and a noncontrast coronary calcium scan preceding the contrast enhanced coronary CTA. CT scans were performed in accordance with the current guidelines.[11]

For the analysis, the presence of significant coronary artery stenosis was defined using ≥50% and ≥70% stenosis thresholds in at least 1 of the 17 coronary segments. The ≥70% stenosis threshold was defined as ≥50% stenosis in the left main and ≥70% stenosis in other major epicardial vessels. The presence of plaque on coronary CTA or a CAC>0 without ≥50% stenosis was defined as mild disease (coronary CTA 1%–49%). Individuals with a CAC of zero and no detectable plaque on CTA were regarded normal (coronary CTA 0%). If the presence of a significant stenosis could not be ruled out, for example, because of image quality (motion artifacts, calcification, image noise), the coronary segment was classified as indeterminate.

CAC score was quantified by study sites using Agatston method on a dedicated workstation.[12] For this analysis, data were stratified by CAC score strata (Agatston score: 0, >0–10, >10–100, >100–400, >400)[13] to display the association of results with the extent of CAC. To separate the influence of CAC from stenosis on additional testing, patients with obstructive CAD (≥50%) by coronary CTA were stratified by CAC (Agatston score: ≤100, >100–400, >400) in a subgroup analysis.

Study End Points

To assess the effect of CAC on the management of patients with acute chest pain, we used 2 end points.

- Primary end point: We determined the frequency of all downstream tests (beyond coronary CTA), total, and diagnostic cost across CAC strata. The appropriateness of invasive downstream testing was determined by frequency of invasive coronary angiography (ICA) related to the number of ACS and the number of revascularizations (ratios: ICA/ACS and ICA/revascularization). Detailed definitions of ACS can be found in Appendix in the Data Supplement.
- Secondary end point: Diagnostic yield of ICA was a ratio of the number of ICAs showing obstructive CAD divided by the overall number of ICA.
- Safety end points were major adverse cardiovascular events, defined as cardiac death and MI within 30 days after presentation[9] and death, MI, unstable angina pectoris, or urgent coronary revascularization within 28 days after index hospitalization.[10]

Statistical Analysis

All statistical analyses, including data pooling, were performed by an independent data-coordinating center. Definitions of all core variables with respect to CT findings, outcomes, and risk categories were identical, and no modifications were required. Continuous variables are presented as mean±standard deviation or median with interquartile range. Categorical variables are expressed as frequencies and percentages. Trends regarding CAC groups were tested using the Wilcoxon rank-sum test or an extension developed by Cuzick (for nonbinary variables).[14] For comparisons between included and excluded patients (Data Supplement), an independent sample *t* test for continuous variables, Fisher exact test for categorical variables, and the Wilcoxon rank-sum test for ordinal variables was used. To determine the impact of CAC on the likelihood of positivity for ACS, ICA, and downstream testing, we performed additional analysis using logistic regression models, including age, sex, and CAC score categories, as independent variables. For cost analysis, we focused on healthcare costs during index hospitalization, assessed from reports

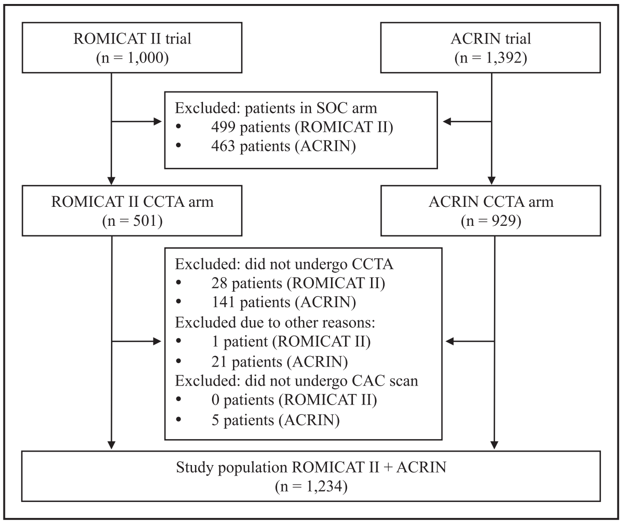

Figure 1. Flow chart demonstrating study population of the 2 source trials (ROMICAT II and ACRIN; n=1234). ACRIN indicates American College of Radiology Imaging Network; CAC, coronary artery calcification; CCTA, coronary computed tomography angiography; ROMICAT, Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography; and SOC, standard of care.

from hospital cost-accounting systems and physician billing records. Costs were available for ROMICAT II patients only. A multiple linear regression model with total cost as outcome variable and detailed diagnostic test and intervention data (all from ROMICAT II) as independent variables was used to estimate cost for ACRIN patients. Total cost included all occurring costs. Diagnostic cost included any diagnostic test (coronary CTA, exercise treadmill testing, nuclear myocardial perfusion imaging, stress echocardiography, or ICA). Cost per ACS was defined as sum of total cost per group divided by the number of patients with ACS in this individual group and reflects the cost to diagnose and treat 1 patient with ACS during index hospitalization. A 2-sided *P* value of <0.05 was considered to indicate statistical significance. All analyses were performed using Stata (Version SE 13.1; StataCorp LP, College Station, TX).

Results

Overall Patient Cohort

Out of a total of 2392 symptomatic patients enrolled in ROMICAT II (n=1000) and ACRIN-PA 4005 (n=1392) with suspected ACS, 1430 patients (59.8%) were randomized to coronary CTA. One thousand two hundred and thirty-four individuals (51.6%) finally underwent coronary CTA, including a preceding noncontrast CAC scan (Figure 1).

Baseline characteristics of all included patients are shown in Table 1 (mean age, 51.0±8.8 years; 49.5% women). Out of 1234 patients, 5.5% (n=68) were diagnosed with ACS during the index hospitalization, of whom 0.7% (n=9) had MI and 4.8% (n=59) had unstable angina pectoris. The prevalence of coronary artery stenosis ≥50% and ≥70% was 13.1% (n=162) and 6.5% (n=80), respectively. During the index hospitalization, 15.9% (n=196) of all patients had at least 1 test in addition to coronary CTA; 6.5% (n=80) of them had ICA. The proportion of patients undergoing ICA showing no obstructive disease was 27.5% (n=22), leading to an overall invasive diagnostic yield of 72.5%. Subsequently, 3.3% (n=41) of all patients underwent revascularization (see Table 2 for details).

Baseline characteristics of patients not included in the analysis as compared with those included in the analysis are summarized in Table I in the Data Supplement.

CAC Distribution and Its Association to Cardiovascular Risk Profile, ACS, and CAD

Among 1234 patients, 64.4% (n=795) had no detectable coronary calcium, 7.4% (n=91) had a CAC score of >0 to 10, 15.8% (n=195) had a CAC score of >10 to 100, 8.3% (n=103) had a CAC score of >100 to 400, and 4.1% (n=50) had a CAC

Table 1. Patient Characteristics, Cardiovascular Risk Factors, Thrombolysis in Myocardial Infarction Risk Score, and Radiation Exposure in Various Coronary Artery Calcification Score Strata

	CAC Score Strata						
Characteristics	Full Cohort (n=1234)	0 (n=795)	>0–10 (n=91)	>10–100 (n=195)	>100–400 (n=103)	>400 (n=50)	*P* Value
Age, y	51.0±8.8	48.8±8.3	52.2±8.1	54.0±8.1	56.5±7.6	60.2±8.3	<0.001
Male sex, %	623 (50.5)	342 (43.0)	58 (63.7)	118 (60.5)	67 (65.0)	38 (76.0)	<0.001
Smoker, %	608 (49.3)	362 (45.5)	41 (45.1)	111 (56.9)	65 (63.1)	29 (58.0)	<0.001
Diabetes mellitus, %	183 (14.8)	87 (10.9)	15 (16.5)	41 (21.0)	24 (23.3)	16 (32.0)	<0.001
Dyslipidemia, %	426 (34.5)	222 (27.9)	36 (40.0)	90 (46.1)	46 (44.7)	32 (64.0)	<0.001
Hypertension, %	644 (52.2)	361 (45.4)	47 (51.7)	129 (66.2)	67 (65.1)	40 (80.0)	<0.001
Family history of CAD	352 (28.5)	230 (28.9)	28 (30.8)	56 (28.7)	22 (21.4)	16 (32.0)	0.549
Radiation dose, mSv	7.8±4.5	7.6±4.5	7.4±4.2	8.0±4.9	8.7±4.3	9.8±4.0	0.001
TIMI score							<0.001
0	674 (54.6)	481 (60.5)	54 (59.3)	85 (43.6)	41 (39.8)	13 (26.0)	
1	407 (33.0)	233 (29.3)	27 (29.7)	78 (40.0)	44 (42.7)	25 (50.0)	
2	149 (12.1)	81 (10.2)	10 (11.0)	30 (15.4)	18 (17.5)	10 (20.0)	
3	4 (0.3)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	2 (4.0)	

CAC indicates coronary artery calcification; CAD, coronary artery disease; and TIMI, Thrombolysis in Myocardial Infarction.

Table 2. Extent of Coronary Artery Disease by Computed Tomography Angiography, Rate of Acute Coronary Syndrome at Discharge, Downstream Testing, Revascularization, and Predicted Cost According to Coronary Artery Calcification Score Strata

Characteristics	CAC Score Strata						*P* Value
	Full Cohort (n=1234)	0 (n=795)	>0–10 (n=91)	>10–100 (n=195)	>100–400 (n=103)	>400 (n=50)	
Indeterminate	68 (5.5)	39 (4.9)	8 (8.8)	14 (7.2)	4 (3.9)	3 (6.0)	0.367
CCTA 0%	660 (53.5)	660 (83.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	…
CCTA 1%–49%	344 (27.9)	83 (10.4)	67 (73.4)	136 (69.7)	54 (52.4)	4 (8.0)	<0.001
CCTA ≥50%	162 (13.1)	13 (1.6)	16 (17.6)	45 (23.1)	45 (43.7)	43 (86.0)	<0.001
CCTA ≥70%	80 (6.5)	4 (0.5)	3 (3.3)	24 (12.3)	17 (16.5)	32 (64.0)	<0.001
ACS at discharge	68 (5.5)	4 (0.5)	5 (5.5)	20 (10.3)	17 (16.5)	22 (44.0)	<0.001
MI	9 (0.7)	1 (0.1)	0 (0.0)	1 (0.5)	4 (3.9)	3 (6.0)	<0.001
UAP	59 (4.8)	3 (0.4)	5 (5.5)	19 (9.7)	13 (12.6)	19 (38.0)	<0.001
MACE at 28 day, f/u	3 (0.2)	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.0)	1 (2.0)	0.011
Additional testing during index visit	196 (15.9)	31 (3.9)	20 (22.0)	60 (30.8)	49 (47.6)	36 (72.0)	<0.001
Noninvasive testing							
SPECT	86 (7.0)	17 (2.1)	13 (14.3)	21 (10.8)	24 (23.3)	11 (22.0)	<0.001
ETT	13 (1.1)	3 (0.4)	1 (1.1)	7 (3.6)	2 (1.9)	0 (0.0)	0.004
Stress ultrasound	36 (2.9)	7 (0.9)	3 (3.3)	14 (7.2)	7 (6.8)	5 (10.0)	<0.001
Invasive testing							
ICA	80 (6.5)	8 (1.0)	5 (5.5)	26 (13.3)	18 (17.5)	23 (46.0)	<0.001
No of ICA showing no obstructive disease	22 (27.5)	5 (62.5)	2 (40.0)	6 (23.1)	6 (33.3)	3 (13.0)	0.034
Diagnostic yield of ICA, %	72.5	37.5	60.0	76.9	66.7	87.0	
Revascularization	41 (3.3)	3 (0.4)	3 (3.3)	14 (7.2)	8 (7.8)	13 (26.0)	<0.001
PCI	37 (3.0)	3 (0.4)	3 (3.3)	12 (6.2)	6 (5.8)	13 (26.0)	<0.001
CABG	4 (0.3)	0 (0.0)	0 (0.0)	2 (1.0)	2 (1.9)	0 (0.0)	0.004
Cost							
Total cost							<0.001
Mean±SD	3295±4300	2337±1319	3307±3503	4601±6739	5688±7917	8484±6558	
Median (IQR)	2111 (2111–2111)	2111 (2111–2111)	2111 (2111–2111)	2111 (2111–3959)	2649 (2111–4552)	4803 (2111–16 679)	
Diagnostic cost							<0.001
Mean±SD	2948±2342	2310±1057	3078±2444	3736±3190	4455±3332	6678±4172	
Median (IQR)	2111 (2111–2111)	2111 (2111–2111)	2111 (2111–2111)	2111 (2111–3959)	2649 (2111–4552)	4803 (2111–9732)	
Ratios (95% CI)							
ICA/ACS	1.17 (0.97–1.38)	2.00 (0.04–3.96)	1.00 (0.21–1.79)	1.30 (0.91–1.69)	1.06 (0.67–1.45)	1.05 (0.77–1.32)	
ICA/Revasc.	1.95 (1.53–2.37)	2.67 (0.28–5.06)	1.67 (0.47–2.87)	1.86 (1.19–2.52)	2.25 (1.08–3.42)	1.77 (1.13–2.41)	
Cost per ACS	59 793 (48 632–70 953)	464 399 (18 297–910 501)	60 186 (16 803–103 568)	44 862 (31 305–58 419)	34 465 (22 675–46 255)	19 283 (15 218–23 348)	

Additional testing was defined as any subsequent test in addition to coronary computed tomography angiography (CCTA) and includes all multiple possible occurrences of invasive coronary angiography, exercise tolerance test (ETT), single-photon emission computed tomography (SPECT), and stress echocardiography/ultrasound during index hospitalization. Costs in US$ are provided as means±standard deviations and as medians with interquartile ranges. Ratios are provided as mean (95% confidence intervals). ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; CAC, coronary artery calcification; CI, confidence interval; CTA, computed tomography angiography; ICA, invasive coronary angiography; IQR, interquartile range; MACE, major adverse cardiovascular event; MI, myocardial infarction; PCI, percutaneous coronary intervention; and UAP, unstable angina pectoris.

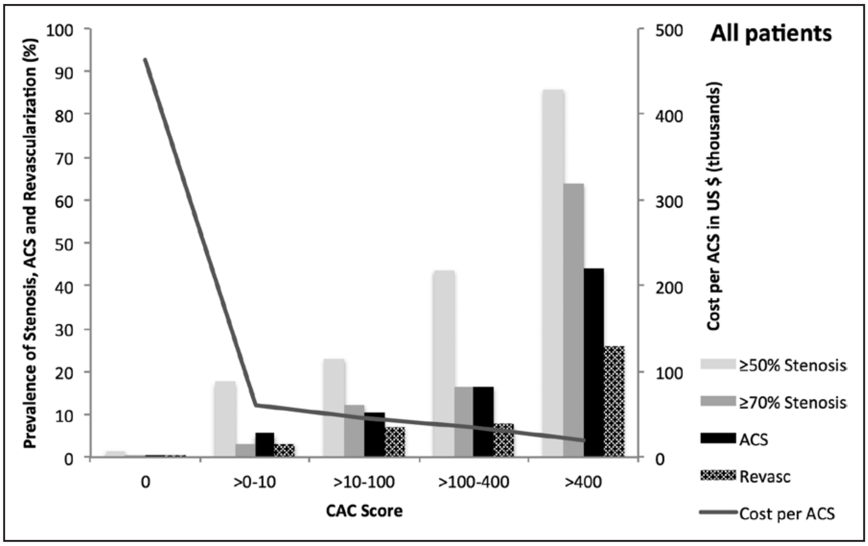

Figure 2. Prevalence of coronary artery stenosis (≥50% and ≥70%), incidence of acute coronary syndrome (ACS) during the index hospitalization, and frequency of revascularization (all trends $P<0.001$) in relation to cost per ACS stratified by coronary artery calcification (CAC) score in all patients.

score >400. Across CAC groups, the proportion of male sex as well as number of cardiovascular risk factors increased with increasing extent of CAC ($P<0.001$; Table 1).

The incidence of ACS during the index hospitalization increased significantly with increasing extent of CAC (0 to >400) from 0.5% (n=4) to 44.0% (n=22), respectively ($P<0.001$), with the highest incidence in patients with a CAC>400, as depicted in Figure 2. The prevalence of obstructive CAD (≥70% stenosis) also significantly increased across CAC groups (from 0.5% [n=4] to 64.0% [n=32]; $P<0.001$; Figure 2).

Association of CAC With Downstream Testing, ICA Yield, and Cost

The number of patients undergoing a second test significantly increased across CAC strata ($P<0.001$) as shown in Table 2. The frequency of downstream testing was lowest in patients without CAC (3.9%) and highest in patients with CAC>400 (72.0%), corresponding to an 18-fold increase in the frequency of downstream testing. The frequency of ICA also increased significantly across CAC groups (from 1.0% to 46.0%; $P<0.001$), as did the rate of revascularization (from 0.4% to 26.0%; $P<0.001$; Figure 2). The number of ICA performed per ACS, as well as per revascularization, did not increase across CAC score strata in the overall cohort (2.0–1.05 and 2.67–1.77, respectively, $P=0.35$ and $P=0.48$). The proportion of ICA showing no obstructive disease significantly decreased with increasing extent of CAC ($P=0.034$). Subsequently, the invasive diagnostic yield to identify obstructive CAD increased across CAC strata, with the lowest yield in patients without CAC (38%) and the highest yield in patients with CAC>400 (87%).

Total cost and cost for diagnostic testing significantly increased with increasing extent of CAC (both $P<0.001$). Both cost variables were highest in groups with CAC>400. In contrast, when relating cost to the incidence of ACS as an intention to diagnose (cost per ACS), cost was highest in patients with CAC of 0 (ACS=4; US$ 464 399 per ACS) and decreased across CAC strata (Figure 2), with the lowest cost per ACS in patients with CAC>400 (US$ 19 283 per ACS), as 22 out of 50 patients were diagnosed with ACS (Table 2).

CAC Independently Predicts ACS, ICA, and Downstream Testing

In multivariable analysis, CAC score independently predicted ACS (odds ratio, 2.88; 95% confidence interval [CI], 2.27–3.56; $P<0.001$), ICA (odds ratio, 2.59; 95% CI, 2.10–3.20; $P<0.001$), and downstream testing (odds ratio, 2.76; 95% CI, 2.37–3.22; $P<0.001$) after adjustment for age and sex. Age and sex were not predictive for ACS, ICA, and downstream testing. Similar results were seen for CAC categories, showing increasing risk for higher CAC categories (Table III in the Data Supplement).

Effect of CAC on Management in Patients With Obstructive CAD

In this subgroup analysis, we included 162 patients with obstructive CAD (≥50%), of whom 45.7% (n=74) had a CAC score ≤100, 27.8% (n=45) had a CAC score >100 to 400, and 26.5% (n=43) had a CAC score >400 (Table 3). A total of 39.5% (n=64) of patients were diagnosed with ACS and 77.8% (n=126) of patients underwent additional testing without differences across CAC strata ($P=0.357$ and $P=0.660$, respectively). The frequency of ICA and revascularization ($P=0.703$ and $P=0.809$, respectively), as well as the predicted cost ($P=0.894$), also did not significantly vary with increasing extent of CAC.

Sex-Specific Differences

With increasing extent of CAC in both sexes, the incidence of ACS increased significantly (all $P<0.001$), with the highest rate of ACS in men and women with CAC>400 (41.7% versus 44.7%; Figure 3A and 3B). In the group with CAC=0, 4 patients were diagnosed with ACS (0.5%; 95% CI, 0.1%–1.3%). All 4 patients were women (0.9%; 95% CI, 0.2%–2.3%); no men without CAC were diagnosed with ACS (0.0%; 95% CI, 0.0%–1.1%). The prevalence of obstructive CAD (≥70% stenosis) also significantly increased across CAC strata, with the highest prevalence in men and women with CAC>400 (65.8% and 58.3%; both $P<0.001$).

Across CAC strata, the lowest rate of downstream testing was found in men and women with no CAC (3.5% and 4.2%, respectively) and significantly increased in both sexes

Table 3. Differences in Incidence of Acute Coronary Syndrome, Frequency of Downstream Testing, and Cost in Patients With Obstructive Coronary Artery Disease (≥50%) Stratified by Coronary Artery Calcification

	CAC Score				
Characteristics	Full Cohort (n=162)	≤100 (n=74)	>100–400 (n=45)	>400 (n=43)	*P* Value
ACS at discharge	64 (39.5)	28 (37.8)	15 (33.3)	21 (48.8)	0.357
MI	8 (4.9)	2 (2.7)	3 (6.7)	3 (7.0)	0.255
UAP	56 (34.6)	26 (35.1)	12 (26.7)	18 (41.9)	0.669
Additional testing during index visit	126 (77.8)	57 (77.0)	34 (75.6)	35 (81.4)	0.660
Noninvasive testing					
SPECT	45 (27.8)	20 (27.0)	14 (31.1)	11 (25.6)	0.973
ETT	3 (1.9)	3 (4.05)	0 (0.0)	0 (0.0)	0.078
Stress ultrasound	18 (11.1)	8 (10.8)	5 (11.1)	5 (11.6)	0.895
Invasive testing					
ICA	71 (43.8)	33 (44.6)	16 (35.6)	22 (51.2)	0.703
No of ICA showing no obstructive disease	16 (22.5)	8 (24.2)	5 (31.3)	3 (13.6)	0.449
Revascularization	39 (24.1)	20 (27.0)	7 (15.6)	12 (27.9)	0.809
PCI	35 (21.6)	18 (24.3)	5 (11.1)	12 (27.9)	0.998
CABG	4 (2.5)	2 (2.7)	2 (4.4)	0 (0.0)	0.508
Cost					
Total cost					0.894
Mean±SD	9341±9417	9742±10 030	8896±10 769	9115±6561	
Median (IQR)	4552 (2649–15 117)	4552 (2649–16 679)	4552 (2649–9732)	9732 (2649–16 679)	
Diagnostic cost					0.899
Mean±SD	6787±4077	6899±4235	6228±3752	7176±4158	
Median (IQR)	4552 (2649–9732)	4552 (2649–9732)	4552 (2649–9732)	9732 (2649–9732)	
Cost per ACS (95% CI)	23 643 (19 792–27 495)	25 746 (19 337–32 155)	26 689 (16 750–36 628)	18 664 (14 573–22 755)	

Additional testing was defined as any subsequent test in addition to coronary computed tomography angiography (CCTA) and includes all multiple possible occurrences of invasive coronary angiography, exercise tolerance test (ETT), single-photon emission computed tomography (SPECT) and stress echocardiography/ultrasound during index hospitalization. Costs in US$ are provided as means±standard deviations and as medians with interquartile ranges. ACS indicates acute coronary syndrome; CABG: coronary artery bypass graft; CAC, coronary artery calcification; CAD, coronary artery disease; CI, confidence interval; ICA, invasive coronary angiography; IQR, interquartile range; MACE, major adverse cardiovascular event; MI, myocardial infarction; PCI, percutaneous coronary intervention; and UAP, unstable angina pectoris.

(*P*<0.001; Figure 3A and 3B). In men, 10% of all downstream tests were performed in patients without CAC, in whom no ACS occurred. In women, 25% of all downstream tests were performed in patients without CAC, in whom 24% of all cases of ACS occurred. The frequency of ICA showed a significant increase across CAC strata (1.2%–47.4% and 0.9%–41.7% in men and women, respectively; both *P*<0.001), as did the rate of revascularization (0.3%–21.1% and 0.4%–41.7%, respectively; both *P*<0.001). The number of ICA performed per ACS (ICA/ACS), as well as per revascularization (ICA/revascularization), did not increase in male patients across CAC groups. In contrast, we observed higher ratios in women in the group with mild CAC (CAC score 1–100) as demonstrated in Table IIA and IIB in the Data Supplement, indicating that the frequency of testing did not mirror the low prevalence of disease in this group of women, in whom 42% downstream tests were performed, but only 18% ACS occurred.

The invasive diagnostic yield for obstructive CAD was higher in men and women with CAC>400 (83% in men and 100% in women) as compared with patients without CAC (25% in men and 50% in women) as depicted in Figure 4.

While total as well as diagnostic cost significantly increased with increasing extent of CAC in both sexes similarly (both *P*<0.001), cost per ACS decreased and was lower in men at any level of CAC. In both sexes, cost per ACS was lowest with CAC>400 (Figure 3A and 3B).

Discussion

In this pooled analysis from 2 large multicenter studies, we observed a significant increase in downstream testing and cost across CAC strata, which was found to be appropriate because of the strong association of CAC with CAD severity and incidence of ACS in patients with acute chest pain presenting to the ED. In patients undergoing coronary CTA, cost-efficient

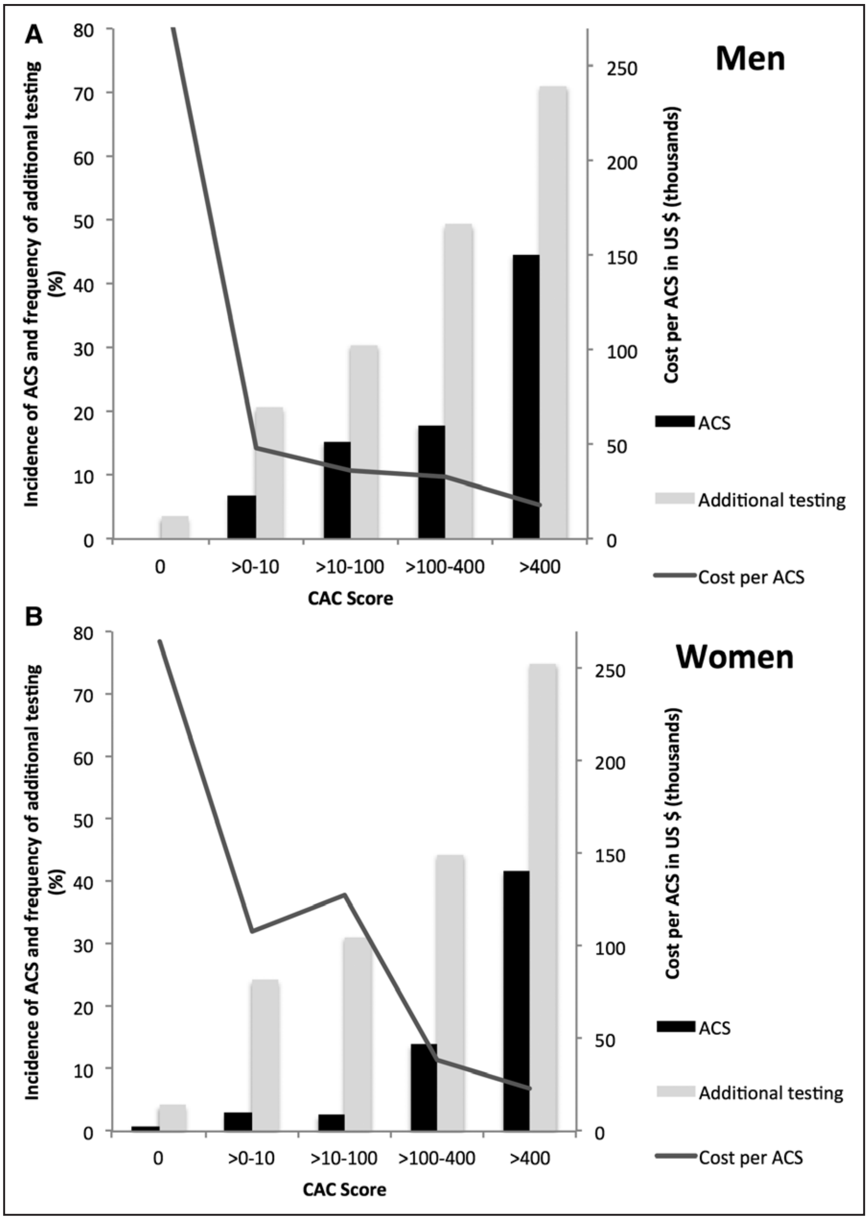

Figure 3. Incidence of acute coronary syndrome (ACS) and frequency of additional testing (all trends $P<0.001$) in relation to cost per ACS stratified by coronary artery calcification (CAC) score in (**A**) men and (**B**) women.

testing can be achieved even in patients with high burden of CAC. Moreover, the diagnostic yield to identify patients with obstructive CAD on subsequent ICA was the highest in patients with CAC>400. The increase in diagnostic testing, ICA, and revascularizations with increasing CAC levels was more appropriate in men as compared with women.

Appropriateness of Testing

In this cohort of acute chest pain patients, we confirmed the strong association of cardiovascular risk factors, obstructive CAD, and ACS with the extent of CAC, as previously described in asymptomatic[15] and stable symptomatic patients.[2] Along with that, a strong association with the increased frequency of downstream testing was seen, which is consistent with results in asymptomatic patients.[7] The observed increase in downstream testing across CAC groups (0–>400) seems to be appropriate because the 18-fold increase in the number of patients undergoing downstream testing is balanced by an 88-fold increase in the incidence of ACS and a 128-fold increase in the prevalence of obstructive CAD. As a surrogate for the appropriateness of invasive testing, we used the ratio of the frequency of ICA to the number of ACS and the ratio of the frequency of ICA to the number of revascularization in the underlying analysis. In fact, we found no increase in these ratios across CAC score strata, suggesting that invasive testing was appropriate. In patients with obstructive CAC only, we also did not observe any differences in the frequency of testing and revascularization across CAC groups, indicating that higher rates of testing are driven by the presence of obstructive CAD rather than by the extent of CAC.

Diagnostic Yield

Among other downstream tests, the frequency of ICA also significantly increased across CAC strata ($P<0.001$), with the highest rate of ICA in patients with CAC>400 (46%). However, the lower efficiency to detect significant coronary artery stenosis in patients with high CAC scores, as demonstrated in previous studies,[5,6] was not seen in this contemporary ED

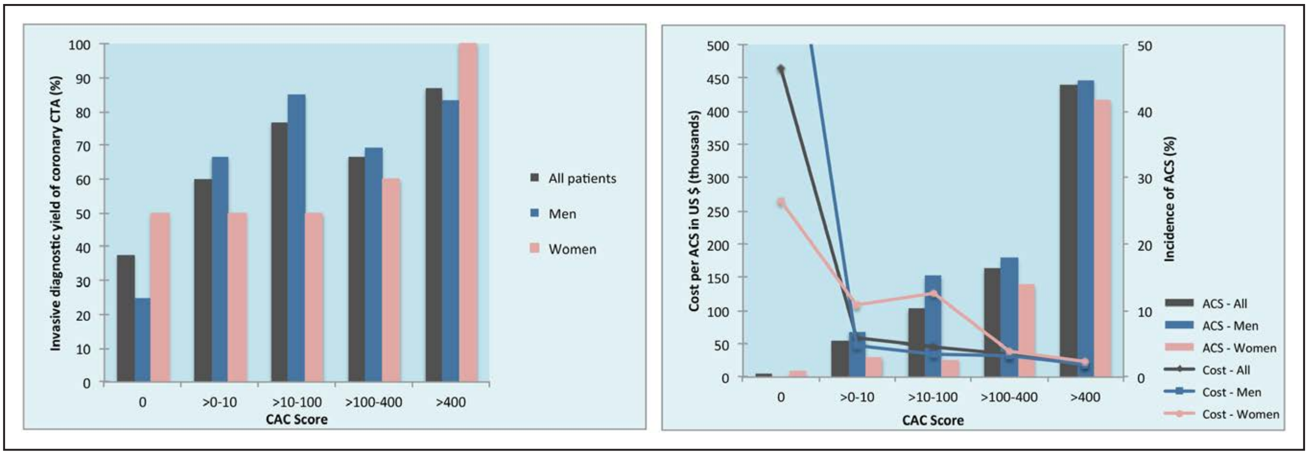

Figure 4. Invasive diagnostic yield of coronary computed tomography angiography (CTA) and cost per acute coronary syndrome (ACS) stratified by coronary artery calcification (CAC) in men and women**.** CAC may impair the diagnostic accuracy to detect obstructive coronary artery disease (CAD) on coronary CTA and is thought to be associated with inefficient patient management. This pooled analysis looked at resource utilization (downstream testing including ICA and cost) across CAC strata in patients with suspected ACS undergoing coronary CTA. Disease burden, adverse health outcomes, and additional testing increased with increasing extent of CAC (Table 2; trend *P*<0.001) but did not vary in patients with obstructive CAD across CAC strata (Table 3). The diagnostic yield of invasive angiography to detect obstructive CAD was used as measure of effectiveness for a strategy using coronary CTA. The invasive diagnostic yield increased across CAC strata and was higher in patients with CAC>400 as compared with patients with CAC of zero, similar in men and women (**left**). While total and diagnostic cost increased with increasing extent of CAC (Table 2; *P*<0.001), cost to diagnose one ACS (cost per ACS) decreased across CAC strata and was lowest in patients with high extent of CAC, also seen in men and women (**right**). In conclusion, in patients undergoing a strategy with coronary CTA, cost-efficient testing and excellent invasive diagnostic yield can be achieved in patients with high burden of CAC.

cohort with acute chest pain. In fact, the number of ICA showing no obstructive CAD (defined as <50% stenosis) significantly decreased with increasing extent of CAC (*P*=0.034). This translated into a higher diagnostic yield to identify patients with obstructive CAD on subsequent ICA (87%) in the subgroups with CAC>400 as compared with patients with no CAC (25%). The overall diagnostic yield of anatomic testing in our study was 73% and is comparable to published results from the PROMISE trial[16] (Prospective Multicenter Imaging Study for Evaluation of Chest Pain; 72%), which compared the effectiveness of coronary CTA and functional testing as initial diagnostic test in 10 003 patients with suspicion for stable CAD.

CAC of Zero

The role of noncontrast cardiac CT and the value of a CAC score of zero for the prediction of functionally relevant CAD and clinical events has been previously studied.[15,17–19] The absence of CAC was predictive of normal myocardial perfusion on cardiac PET examination among patients with acute chest pain admitted to the chest pain unit.[20] Importantly, CAC score of zero was associated with low event rates, for example, <1% in a prospective observational study with a 7-year follow-up[17] and 0.3% (95% CI, 0.04%–1.1%) in another acute chest pain cohort of 1031 patients.[19] Subsequently, some authors concluded that the absence of CAC could justify the discharge from the ED without further testing.[19] A recently published meta-analysis that included over 3500 patients reevaluated the role of CAC testing in acute chest pain patients and confirmed a low event rate (0.8%/year) in patients with CAC score of zero.[20] Similarly, CAC score of zero indicated low risk of ACS during the index hospitalization in our analysis (0.5%; 95% CI, 0.1%–1.3%). However, the upper limit of the 95% CI for the risk of ACS includes the threshold of 1%, which is typically accepted as the minimum for the safe discharge by emergency physicians. The upper bound of the 95% CI was >1.0% in both men and women, although no man with CAC of zero was diagnosed with ACS in our study. All 4 patients with a CAC score of zero who were subsequently diagnosed with ACS were women (ACS event rate 0.9%; upper limit of the 95% CI, 2.3%). This finding emphasizes the importance of coronary CTA testing, especially in female patients without CAC, and supports the clinical value of an early coronary CTA strategy in women, as previously suggested by the sex-specific analysis in the ROMICAT-II trial,[21] irrespective of a low CAC score.

In this context, it is important to restate that a contrast-enhanced coronary CTA has the ability to visualize noncalcified plaque, as well as high-risk plaque features, shown to increase the risk for ACS independent of significant coronary stenosis.[22] Hence, a CAC scan should be followed by another test in patients with acute chest pain. Whether a CAC of zero can still have value in special scenarios, for example, in medical centers without the ability of advanced cardiac imaging and whether the low event rate in men holds true in larger cohorts, needs to be evaluated in future studies.

Sex-Specific Differences in Downstream Testing

Overall, the rate of downstream testing was 1.6-fold lower in women as compared with that in men. This seems to be out of proportion to the incidence of ACS and prevalence of obstructive CAD in women, which was almost 3-fold lower. To determine whether CAC is likely to cause inefficiency of testing in women, we also stratified by the extent of CAC in both sexes individually.

Ultimately, the discrepancy between men and women was caused by a disproportionately high frequency of testing in women with low CAC scores (>0–100), as 42% of all additional tests were performed in this group, but only 18% of all ACS diagnoses occurred. Interestingly, the rate of indeterminate scans was highest in these groups (CAC>0–100). The reasons for that remain unknown; however, this finding may explain the higher rate of additional testing. In fact, if high CAC scores were to account for higher proportion of indeterminate coronary CTA scans, we would expect the highest rates of indeterminate scans in subgroups with the highest extent of CAC, which was not found in our analysis. Finally, more diagnostic uncertainty seems to exist for women than for men. In men, testing seems proportionate in relation to events because all events occurred in those with CAC, with increasing incidence across CAC strata.

Cost

Our data confirm increasing cost with increasing extent of CAC, as shown previously in asymptomatic patients,[7] most likely because of an increasing burden of CAD, subsequent downstream testing, and revascularizations. Beyond that, we demonstrated that costs related to the incidence of ACS (cost per ACS) decreased across CAC strata, as the increase in the incidence of ACS was higher as compared with the increase in cost in patients with high burden of CAC. In other words, the higher number needed to diagnose one ACS drove the cost in patients without CAC higher because of the low incidence of ACS. Although diagnostic cost was lower in women as compared with that in men, cost per ACS was higher in women overall and across CAC strata, most pronounced in the subgroup of women with CAC>0 to 100, as displayed in Figure 4. This again reflects that testing is more efficient in men because testing adequately increased with burden of CAD. Knowledge of patient subgroups with increased resource utilization may ultimately help to improve testing efficiency.

Limitations

Our study has a couple of limitations. First, the overall number of individuals in categories with high calcification and the number of patients with the diagnosis of ACS were small, despite pooling data from the 2 largest trials performed in the ED using coronary CTA. Nevertheless, this analysis represents the largest effort to evaluate the effect of the presence and extent of CAC on downstream testing and predicted cost in an acute chest pain population to this date. Second, this study was limited to the intervention arms of both trials, and all information pertaining to the standard-of-care arms was omitted. While this strategy did not allow for direct comparison of outcomes and efficiency of testing between arms, we wanted to provide a more clinically relevant and detailed analysis in respect to the efficiency of testing across CAC groups within the CTA arm. Third, because of the low prevalence of obstructive CAD and low incidence of ACS, especially in the cohort without CAC, sex-specific conclusions are limited. However, the goal of these analyses was to provide a framework for understanding the predictive impact of CAC in men and women on subsequent clinical management (downstream testing, ICA, and revascularization) and associated cost during an acute chest pain presentation. Fourth, costs were available for ROMICAT II patients only and estimated for ACRIN-PA patients using a multiple linear regression model. Finally, both source trials were not designed for long-term follow-up. Nevertheless, follow-up was performed at 28 days after discharge[10] or at least 30 days after enrollment[9] to determine patient safety outcomes.

Conclusions

Downstream testing and total as well as diagnostic cost increased with increasing CAC, but were found to be appropriate because obstructive CAD and adverse outcomes were more prevalent in patients with high CAC. In patients undergoing a strategy with coronary CTA, cost-efficient testing and excellent invasive diagnostic yield can be achieved in patients with high burden of CAC.

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CLINICAL PERSPECTIVE

Among patients presenting with acute chest pain, identification and quantification of coronary artery calcification (CAC) can predict resource utilization based on the strong association with obstructive coronary artery disease and acute coronary syndrome. Our analyses suggest that the increase in downstream testing in patients with high burden of CAC seems to be appropriate. CAC does not seem to significantly impair diagnostic assessment of a strategy with coronary computed tomography angiography because excellent diagnostic yield to identify patients with obstructive coronary artery disease on subsequent invasive coronary angiography can be achieved in patients with high burden of CAC. From a cost perspective, coronary computed tomography angiography seems to be efficient in patients with high extent of CAC because of a higher incidence of acute coronary syndrome as compared with patients without CAC. Multicenter randomized trials are needed to determine whether the assessment of CAC by noncontrast computed tomography of the heart can be used to optimize clinical management in men and women in respect to further noninvasive and invasive testing and improve resource utilization as compared with the standard of care in symptomatic patients with acute chest pain.

Circulation
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Impact of Coronary Calcification on Clinical Management in Patients With Acute Chest Pain

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Supplemental Materials for publication

Supplemental Table 1: Characteristics of patients randomized to coronary CTA but excluded from the analysis

	Randomized to CTA (n=1,409)	Included in analysis (n=1,234)	Excluded from analysis (n=175)	P value
Age (years) , mean ± SD	50.8 ± 8.9	51.0 ± 8.8	49.2 ± 9.5	0.016
Male (%)	704 (50.0)	611 (49.5)	93 (53.1)	0.375
Race				
Caucasian	691 (49.0)	631 (51.1)	60 (34.3)	<0.001
Afro-American	664 (47.1)	554 (44.9)	110 (62.9)	<0.001
Asian	29 (2.1)	25 (2.0)	4 (2.3)	0.776
Other/unknown	25 (1.8)	24 (1.9)	1 (0.6)	0.353
Hispanic Ethnicity	80 (5.7)	75 (6.1)	5 (2.9)	0.114
Smoker (%)	686 (48.7)	608 (49.3)	78 (44.6)	0.258
Diabetes Mellitus (%)	216 (15.3)	183 (14.8)	33 (18.9)	0.178
Dyslipidemia (%)	479 (34.0)	426 (34.5)	53 (30.3)	0.306
Hypertension (%)	732 (52.0)	644 (52.2)	88 (50.3)	0.686
Family history of CAD	403 (28.6)	352 (28.5)	51 (29.1)	0.859
TIMI Score, n (%)				0.715
Low (0-1)	1236 (87.7)	1081 (87.6)	155 (88.6)	
Intermediate (2-4)	173 (12.3)	153 (12.4)	20 (11.4)	
High (>4)	0 (0.0)	0 (0.0)	0 (0.0)	
Diagnosis, n (%)				
Acute coronary syndrome	80 (5.7)	68 (5.5)	12 (6.9)	0.484
Unstable angina pectoris	63 (4.5)	59 (4.8)	4 (2.3)	0.171
Myocardial infarction	17 (1.2)	9 (0.7)	8 (4.6)	<0.001
MACE at 28 day f/u	3 (0.2)	3 (0.2)	0 (0.0)	1.000

CAD: coronary artery disease; TIMI: thrombolysis in myocardial infarction; MACE: major adverse cardiovascular event.

Supplemental Table 2a: Extent of coronary artery disease by CTA, rate of ACS at discharge, downstream testing, revascularization and predicted cost according to CAC score strata - **MEN ONLY**

Characteristics	CAC score strata						
	Full cohort (n=623)	***0* (n=342)**	***>0-10* (n=58)**	***>10-100* (n=118)**	***>100-400* (n=67)**	***>400* (n=38)**	***P value***
Indeterminate	31 (5.0)	18 (5.3)	3 (5.2)	5 (4.2)	3 (4.5)	2 (5.3)	0.729
CCTA 0%	280 (44.9)	280 (81.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	---
CCTA 1-49%	202 (32.4)	40 (11.7)	43 (74.1)	82 (69.5)	35 (52.2)	2 (5.3)	<0.001
CCTA ≥50%	110 (17.7)	4 (1.2)	12 (20.7)	31 (26.3)	29 (43.3)	34 (89.5)	<0.001
CCTA ≥70%	60 (9.6)	1 (0.3)	3 (5.2)	19 (16.1)	12 (17.9)	25 (65.8)	<0.001
ACS at discharge	51 (8.2)	0 (0.0)	4 (6.9)	18 (15.3)	12 (17.9)	17 (44.7)	<0.001
MI	8 (1.3)	0 (0.0)	0 (0.0)	1 (0.9)	4 (6.0)	3 (7.9)	<0.001
UAP	43 (6.9)	0 (0.0)	4 (6.9)	17 (14.4)	8 (11.9)	14 (36.8)	<0.001
MACE at 28 day f/u	2 (0.3)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (2.6)	0.127
Additional testing during index visit	120 (19.3)	12 (3.5)	12 (20.7)	36 (30.5)	33 (49.3)	27 (71.1)	<0.001
Non-invasive testing							
SPECT	48 (7.7)	5 (1.5)	8 (13.8)	14 (11.9)	15 (22.4)	6 (15.8)	<0.001
ETT	9 (1.4)	2 (0.6)	1 (1.7)	4 (3.4)	2 (3.0)	0 (0.0)	0.082
Stress Ultrasound	18 (2.9)	3 (0.9)	1 (1.7)	5 (4.2)	4 (6.0)	5 (13.2)	<0.001
Invasive testing							
ICA	58 (9.3)	4 (1.2)	3 (5.2)	20 (17.0)	13 (19.4)	18 (47.4)	<0.001
No. of ICA showing no obstructive disease	14 (24.1)	3 (75.0)	1 (33.3)	3 (15.0)	4 (30.8)	3 (16.7)	0.236
Revascularization	31 (5.0)	1 (0.3)	2 (3.5)	13 (11.0)	7 (10.5)	8 (21.1)	<0.001
PCI	28 (4.5)	1 (0.3)	2 (3.5)	11 (9.3)	6 (9.0)	8 (21.1)	<0.001
CABG	3 (0.5)	0 (0.0)	0 (0.0)	2 (1.7)	1 (1.5)	0 (0.0)	0.058
Cost							
Total Cost	3748 ± 5167	2340 ± 1286	3325 ± 3638	5447 ± 8254	5834 ± 7572	8104 ± 6354	<0.001
Diagnostic Cost	3230 ± 2732	2320 ± 1101	3086 ± 2516	4077 ± 3572	4575 ± 3398	6642 ± 4293	<0.001
Ratios (95%CI)							
ICA / ACS	1.14 (0.92-1.36)	---	0.75 (0.01-1.49)	1.11 (0.83-1.39)	1.08 (0.63-1.54)	1.06 (0.70-1.42)	
ICA / Revasc.	1.87 (1.42-2.32)	4.00 (-2.81-10.81)	1.50 (0.29-2.71)	1.54 (1.04-2.04)	1.86 (0.91-2.80)	2.25 (1.07-3.43)	

Cost per ACS	45780 (36574-54986)	---	48216 (9752-86680)	35711 (25376-46045)	32571 19824-45317)	18116 (13357-22874)

Supplemental Table 2b: Extent of coronary artery disease by CTA, rate of ACS at discharge, downstream testing, revascularization and predicted cost according to CAC score strata - **WOMEN ONLY**

Characteristics	CAC score strata						
	Full cohort (n=611)	***0* (n=453)**	***>0-10* (n=33)**	***>10-100* (n=77)**	***>100-400* (n=36)**	***>400* (n=12)**	***P value***
Indeterminate	37 (6.1)	21 (4.6)	5 (15.2)	9 (11.7)	1 (2.8)	1 (8.3)	0.033
CCTA 0%	380 (62.2)	380 (83.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	---
CCTA 1-49%	142 (23.2)	43 (9.5)	24 (72.7)	54 (70.1)	19 (52.8)	2 (16.7)	<0.001
CCTA ≥50%	52 (8.5)	9 (2.0)	4 (12.1)	14 (18.2)	16 (44.4)	9 (75.0)	<0.001
CCTA ≥70%	20 (3.3)	3 (0.7)	0 (0.0)	5 (6.5)	5 (13.9)	7 (58.3)	<0.001
ACS at discharge	17 (2.8)	4 (0.9)	1 (3.0)	2 (2.6)	5 (13.9)	5 (41.7)	<0.001
MI	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.560
UAP	16 (2.6)	3 (0.7)	1 (3.0)	2 (2.6)	5 (13.9)	5 (41.7)	<0.001
MACE at 28 day f/u	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	0.042
Additional testing during index visit	76 (12.4)	19 (4.2)	8 (24.2)	24 (31.2)	16 (44.4)	9 (75.0)	<0.001
Non-invasive testing							
SPECT	38 (6.2)	12 (2.7)	5 (15.2)	7 (9.1)	9 (25.0)	5 (41.7)	<0.001
ETT	4 (0.7)	1 (0.2)	0 (0.0)	3 (3.9)	0 (0.0)	0 (0.0)	0.033
Stress Ultrasound	18 (3.0)	4 (0.9)	2 (6.1)	9 (11.7)	3 (8.3)	0 (0.0)	<0.001
Invasive testing							
ICA	22 (3.6)	4 (0.9)	2 (6.1)	6 (7.8)	5 (13.9)	5 (41.7)	<0.001
No. of ICA showing no obstructive disease	8 (36.4)	2 (50.0)	1 (50.0)	3 (50.0)	2 (40.0)	0 (0.0)	0.108
Revascularization	10 (1.6)	2 (0.4)	1 (3.0)	1 (1.3)	1 (2.8)	5 (41.7)	<0.001
PCI	9 (1.5)	2 (0.4)	1 (3.0)	1 (1.3)	0 (0.0)	5 (41.7)	<0.001
CABG	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	0.042
Cost							
Total Cost	2833 ± 3118	2334 ± 1345	3275 ± 3308	3304 ± 2871	5418 ± 8629	9689 ± 7327	<0.001
Diagnostic Cost	2661 ± 1819	2303 ± 1024	3064 ± 2351	3214 ± 2426	4233 ± 3240	6794 ± 3940	<0.001
Ratios (95%CI)							
ICA / ACS	1.29 (0.78-1.80)	1.00 (0.02-1.98)	2.00 (-0.82-4.82)	3.00 (-1.19-7.19)	1.00 (0.20-1.80)	1.00 ---	
ICA / Revasc.	2.20 (1.19-3.21)	2.00 (0.03-3.97)	2.00 (-0.82-4.82)	6.00 (-4.83-16.83)	5.00 (-3.91-13.91)	1.00 ---	

Cost per ACS	101831 (59619-144043)	264324 (14306-514342)	108066 (-73073-289205)	127222 (-37684-292127	39011 12417-65604	23253 16247-30258

Supplemental Table 3: Additional logistic regression analysis to determine independent predictors for ACS (Model1), invasive angiography (Model 2) and additional testing (Model 3) treating CAC as categories (CAC categories as dummy variables)

	Model 1 ACS (Yes/No)		Model 2 ICA (Yes/No)		Model 3 Additional Testing (Yes/No)	
Independent Variables	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Female	0.56 (0.30-1.05)	0.070	0.60 (0.34-1.05)	0.074	1.07 (0.73-1.55)	0.738
Age	1.01 (0.97-1.04)	0.768	1.01 (0.98-1.04)	0.556	1.00 (0.98-1.02)	0.860
CAC = 0	Base Case		Base Case		Base Case	
CAC >0-10	10.12 (2.64-38.86)	0.001	5.02 (1.59-15.87)	0.006	7.09 (3.79-13.23)	<0.001
CAC >10-100	20.08 (6.63-60.85)	<0.001	13.28 (5.77-30.59)	<0.001	11.20 (6.84-18.33)	<0.001
CAC >100-400	33.61 (10.60-106.58)	<0.001	17.52 (7.07-43.39)	<0.001	23.04 (13.06-40.67)	<0.001
CAC >400	125.41 (37.17-423.09)	<0.001	65.33 (24.54-173.94)	<0.001	66.28 (30.39-144.56)	<0.001

Definition of myocardial infarction and unstable angina pectoris

Myocardial Infarction: In subjects with no recent revascularization in whom normal biomarkers were never elevated or have been documented to return to normal after a qualifying (or recent) MI who meet the following criteria:

1. Typical cardiac biomarker rise and/or fall AND at least one of the following: a) Ischemic discomfort at rest lasing ≥10 minutes b) ECG changes indicative of ischemia (ST elevation ≥0.1 mV or ST depression ≥0.05 mV, or new T-wave inversions. OR;
2. Development of new, abnormal Q waves (≥30 msec in duration and ≥1 mm in depth) in >2 contiguous precordial leads or ≥2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction. OR;
2. Pathologic findings of an acute MI
3. Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

In subjects with percutaneous coronary intervention within 48 hours, an elevation of CK-MB >3x ULN distinct from a prior event will be considered to be a procedural MI. In subjects with CABG within 48 hours, an elevation of CK-MB > 10x ULN distinct from a prior event will be considered to be a procedural MI. For subjects with elevated cardiac biomarkers at the time of a suspected new event, the new event must be demonstrated to be distinct from a previous event including demonstration that cardiac biomarkers are falling and that the new event is associated with a rise in biomarkers of at least 50% above a the previous value.

For each MI identified by the CEC, a Type of MI will be assigned using the following guidelines:

Type 1: Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

Type 2: Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

Type 4a: Myocardial infarction associated with PCI

Type 4b: Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

Type 5: Myocardial infarction associated with CABG

Unstable Angina: An event not meeting the definition of myocardial infarction and with the following characteristics. Chest pain or anginal equivalent at rest or in accelerating pattern AND at least one of the following objective signs:

a) New and/or dynamic ST-depression ≥ 0.05 mV, ST-elevation ≥ 0.1 mV, or symmetric T wave inversion ≥ 0.2 mV on a resting ECG.
b) Definite evidence of ischemia on stress echocardiography, myocardial scintigraphy (e.g., an area of clear reversible ischemia), or ECG-only stress test (e.g., significant dynamic ST shift, horizontal or downsloping).
c) Angiographic evidence of epicardial coronary stenosis of ≥70% diameter reduction and/or evidence for intraluminal arterial thrombus.
d) Positive stress test without imaging resulting in increased anginal medication
e) CT angiography showing > 50% stenosis with regional LV dysfunction or > 70% stenosis