

CLINICAL RESEARCH

Clinical Trials

Coronary Computed Tomography Angiography for Early Triage of Patients With Acute Chest Pain

The ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) Trial

Udo Hoffmann, MD, MPH,*† Fabian Bamberg, MD, MPH,*† Claudia U. Chae, MD, MPH,‡ John H. Nichols, BA,* Ian S. Rogers, MD, MBA,* Sujith K. Seneviratne, MBBS,* Quynh A. Truong, MD,* Ricardo C. Cury, MD,*† Suhny Abbara, MD,*† Michael D. Shapiro, DO,* Jamaluddin Moloo, MD,* Javed Butler, MD, MPH,* Maros Ferencik, MD, PhD,* Hang Lee, PhD,§ Ik-Kyung Jang, MD, PhD,‡ Blair A. Parry, BA,|| David F. Brown, MD,|| James E. Udelson, MD,¶ Stephan Achenbach, MD,# Thomas J. Brady, MD,*† John T. Nagurney, MD, MPH||
Boston, Massachusetts; and Erlangen, Germany

Objectives	This study was designed to determine the usefulness of coronary computed tomography angiography (CTA) in patients with acute chest pain.
Background	Triage of chest pain patients in the emergency department remains challenging.
Methods	We used an observational cohort study in chest pain patients with normal initial troponin and nonischemic electrocardiogram. A 64-slice coronary CTA was performed before admission to detect coronary plaque and stenosis ($\geq 50\%$ luminal narrowing). Results were not disclosed. End points were acute coronary syndrome (ACS) during index hospitalization and major adverse cardiac events during 6-month follow-up.
Results	Among 368 patients (mean age 53 ± 12 years, 61% men), 31 had ACS (8%). By coronary CTA, 50% of these patients were free of coronary artery disease (CAD), 31% had nonobstructive disease, and 19% had inconclusive or positive computed tomography for significant stenosis. Sensitivity and negative predictive value for ACS were 100% ($n = 183$ of 368, 95% confidence interval [CI]: 98% to 100%) and 100% (95% CI: 89% to 100%), respectively, with the absence of CAD and 77% (95% CI: 59% to 90%) and 98% ($n = 300$ of 368, 95% CI: 95% to 99%), respectively, with significant stenosis by coronary CTA. Specificity of presence of plaque and stenosis for ACS were 54% (95% CI: 49% to 60%) and 87% (95% CI: 83% to 90%), respectively. Only 1 ACS occurred in the absence of calcified plaque. Both the extent of coronary plaque and presence of stenosis predicted ACS independently and incrementally to Thrombolysis In Myocardial Infarction risk score (area under curve: 0.88, 0.82, vs. 0.63, respectively; all $p < 0.0001$).
Conclusions	Fifty percent of patients with acute chest pain and low to intermediate likelihood of ACS were free of CAD by computed tomography and had no ACS. Given the large number of such patients, early coronary CTA may significantly improve patient management in the emergency department. (J Am Coll Cardiol 2009;53:1642-50) © 2009 by the American College of Cardiology Foundation

Patients who present with acute chest pain that is believed to be of ischemic origin but who have normal initial biochemical markers for myocardial necrosis (troponin or

creatinine kinase) and normal or nondiagnostic electrocardiograms (ECG) represent a major diagnostic challenge to emergency departments (ED) (1-7). As a result, most of

From the *Cardiac MR PET CT Program, †Department of Radiology, ‡Division of Cardiology, §Biostatistics Center, and ||Department of Emergency Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; ¶Cardiology Division, Tufts Medical Center and Tufts University School of Medicine, Boston, Massachusetts; and #Department of Cardiology, University of Erlangen, Erlangen, Germany. This work was supported by the National Institutes of Health (R01 HL080053) and in part supported by Siemens Medical Solutions and GE Healthcare. Drs. Rogers, Truong, Shapiro, and Moloo were supported by the

National Institutes of Health grant T32HL076136. Dr. Hoffmann has received research grants from GE Healthcare and Siemens. Dr. Abbara has received research funding from Bracco and consulting honoraria (minor) from Ezem, Siemens, Partners Imaging, Magellan Health, Perceptive Informatics. Dr. Achenbach has received grant support from Siemens and Bayer Schering Pharma. Dr. Nagurney is funded by Biosite for a biomarker research study.

Manuscript received October 31, 2008; revised manuscript received December 19, 2008, accepted January 12, 2009.

these patients are admitted to the hospital for up to 24 h and undergo serial ECG and troponin testing, as well as a stress test to rule out acute coronary syndrome (ACS), at a cost in excess of \$8 billion annually (8–10).

See page 1651

Coronary computed tomography angiography (CTA) is a rapid diagnostic test that has the unique ability to noninvasively and accurately detect significant coronary artery stenoses (11) and coronary atherosclerotic plaque (12,13). Several smaller studies (14–17) suggest that coronary CTA may be helpful to facilitate early triage in patients with acute chest pain. However, the distribution of CTA findings of coronary artery diseases (CAD) such as plaque and stenosis and their association with ACS is not established. Such knowledge would provide the basis for the assessment of the clinical utility of and the economic implications for using coronary CTA as an early triage tool. Thus, we conducted a prospective observational cohort study to assess the usefulness of coronary CTA in patients with acute chest pain who are being admitted with low to intermediate risk for ACS.

Methods

Patient population. The patient population of the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial consisted of patients who had a chief complaint of acute chest pain lasting >5 min during the past 24 h, normal initial troponin, and an initial ECG without evidence of myocardial ischemia. In all patients, ED physicians had sufficient clinical suspicion for an ischemic origin of chest pain and admitted these patients to the hospital to rule out ACS. Notably, patients with a history of established CAD, defined as stent implantation or coronary artery bypass grafting, were excluded. Detailed inclusion and exclusion criteria are provided in Table 1.

We screened patients who presented with a chief complaint of chest pain to the ED on weekdays from 7 AM to 7 PM (May 2005 to May 2007). All eligible patients who agreed to participate underwent contrast-enhanced coronary CTA before admission to the hospital floor. All physicians, including those in the ED, who were involved in the standard clinical care of the patients remained blinded to the result of coronary CTA. The institutional review board approved the study protocol, and all patients provided written informed consent.

Coronary CTA. The computed tomography (CT) imaging was performed using a 64-slice CT scanner (Sensation 64, Siemens Medical Solutions, Forchheim, Germany). In preparation for the scan, patients with a heart rate >60 beats/min received an intravenous beta-blocker (metoprolol, 5 to 20 mg) unless their systolic blood pressure was <100 mm Hg or other contraindications were present. In addition, patients received 0.6 mg of sublingual nitroglycerin.

All image acquisitions were performed during a single breath-hold in inspiration.

Per standard protocol, a test bolus of 20 ml contrast agent was administered with a flow rate of 5 ml/s to determine the optimal timing of contrast injection. Coronary CTA datasets were acquired with 64×0.6 mm slice collimation, a gantry rotation time of 330 ms, tube voltage of 120 kV, and an effective tube current of 850 mAs using ECG-correlated tube current modulation when appropriate (18). Contrast agent (80 to 100 ml, iodhexodol 320 mg/cm³, Visipaque, General Electric Healthcare, Princeton, New Jersey) was injected intravenously at a rate of 5 ml/s to ensure homogeneous enhancement of the entire coronary artery tree.

Axial images were reconstructed with a slice thickness of 0.75 mm and increment of 0.4 mm using a retrospectively ECG-gated half-scan algorithm with a temporal resolution of 165 ms. Images were initially reconstructed at 60%, 65%, 70%, and 35% of the cardiac cycle (19).

Additional reconstructions were performed to minimize motion artifacts if necessary. All reconstructions were transferred to an offline workstation for analysis (Leonardo, Siemens Medical Solutions, Forchheim, Germany).

Assessment of presence and extent of CAD by coronary CTA. Assessment of coronary CTA datasets for the presence of significant coronary stenosis and the presence of coronary atherosclerotic plaque was performed as a consensus reading by 2 experienced investigators (U.H./M.F. or F.B./M.D.S.) blinded to the subject's clinical presentation and history using a modified 17-segment model of the coronary artery tree (20,21). If a consensus could not be reached, a third expert reader (S.A.) made the final diagnosis. This method has been demonstrated to be highly reproducible (17).

Coronary atherosclerotic plaque. The presence of any coronary atherosclerotic plaque per segment, whether calcified or noncalcified, was determined as described previously (12,13). Briefly, noncalcified plaque was defined as any discernible structure that could be assigned to the coronary artery wall and had CT attenuation below the contrast-enhanced coronary lumen but above the surrounding connective tissue/epicardial fat. Calcified plaque was defined as

Abbreviations and Acronyms

ACS = acute coronary syndrome
AUC = area under the receiver-operating characteristics curve
CAD = coronary artery disease
CI = confidence interval
CT = computed tomography
CTA = computed tomography angiography
ECG = electrocardiogram
ED = emergency department
MACE = major adverse cardiac event(s)
MI = myocardial infarction
NPV = negative predictive value
OR = odds ratio
PPV = positive predictive value
SPECT = single-positron emission computed tomography
TIMI = Thrombolysis In Myocardial Infarction
UAP = unstable angina pectoris

Table 1 Inclusion and Exclusion Criteria

Inclusion criteria	
Age	>18 yrs
	>5 min of chest pain within the previous 24 h
	Admitted to rule out myocardial infarction through standard care protocols
	Sinus rhythm
	Ability to perform a breath hold of 10 to 15 s
Exclusion criteria	
	Elevated troponin I or CK-MB levels in the initial blood sample obtained in the ED
	New diagnostic ECG changes (ST-segment elevation or depression ≥ 1 mm or T-wave inversion > 4 mm in ≥ 2 anatomically contiguous leads)
	Hemodynamic or clinical instability (systolic blood pressure < 80 mm Hg, clinically significant atrial or ventricular arrhythmias, persistent chest pain despite therapy)
	Known allergy to iodinated contrast agent
	Serum creatinine > 1.3 mg/day
	Metformin treatment
	Hyperthyroidism
	Inability to provide informed consent
	Perceived interference with standard clinical care of patients
	History of established CAD, defined as stent implantation or coronary artery bypass grafting

CAD = coronary artery disease; CK-MB = creatine kinase-myocardial band; ECG = electrocardiogram; ED = emergency department.

any structure with a CT attenuation of > 130 HU that could be visually distinguished from the contrast-enhanced coronary lumen.

Coronary artery stenosis. The presence of coronary artery stenosis was defined as a luminal obstruction $> 50\%$ diameter in any coronary segment. If image quality did not permit definite exclusion of the presence of a significant stenosis (owing to the presence of motion artifacts, calcification, or low contrast-to-noise ratio), the segment was classified as indeterminate. For calculation of diagnostic accuracy, such cases were counted as positive.

Clinical End Points

ACS during index hospitalization. We defined ACS as either an acute myocardial infarction (MI) (i.e., patients developed a positive troponin during serial testing [6 h or 9 h after ED presentation] or unstable angina pectoris [UAP] according to the American Heart Association/American College of Cardiology/European Society of Cardiology guidelines (22–24). We defined UAP as clinical symptoms suggestive of ACS (unstable pattern of chest pain at rest, new onset, or crescendo angina), optimally with objective evidence of myocardial ischemia, such as a positive stress test.

Major adverse cardiac events (MACE) during follow-up. A standardized follow-up phone call was conducted 6 months after enrollment to determine the occurrence of MACE (death, MI, and coronary revascularization). In addition, we retrieved medical records for all patients to verify all events potentially corresponding to a MACE, such as a report of recurrent symptoms resulting in medical

consultation, diagnostic testing, or hospital admissions; these events were subsequently validated by review of medical records. Overall, this approach resulted in a follow-up completion rate of 92%. In the remaining 8% of patients, we assessed mortality using the online Social Security Death Index website.

Adjudication. To establish the diagnosis of ACS and MACE, an outcome panel of 2 experienced physicians with more than 10 years' experience (1 ED physician [J.T.N] and 1 cardiologist [S.S.]) reviewed patient data forms containing prospectively collected information on the history and nature of chest pain, risk factors, and medical history, as well as medical records pertaining to the hospital admission. The outcome panel was blinded to the findings of coronary CT. Disagreement was resolved by consensus, which included an additional cardiologist (C.C.) (25).

Clinical covariates. We prospectively collected data on demographics, risk factor profile, Thrombolysis In Myocardial Infarction (TIMI) risk score, and clinical course in all patients. Presence of risk factors (i.e., hypertension, hypercholesterolemia, and diabetes mellitus) was established from actual measurements obtained during the hospitalization or related medication use. Medical records were reviewed to obtain results of all diagnostic tests performed during index hospitalization.

Statistical analysis. Demographics, traditional risk factors, clinical events, and prevalence of plaque and stenosis as detected by coronary CTA are presented as mean \pm SD or median and interquartile range for continuous variables and as percentages for categorical variables.

We determined the utility of coronary CT to guide triage decisions in the ED using 2 different analytic strategies. To determine the accuracy of coronary CTA, we calculated conventional measures of diagnostic accuracy (sensitivity, negative predictive value [NPV], specificity, and positive predictive value [PPV]) and test-positive and -negative likelihood ratios with 95% confidence intervals (CIs) based on a binomial distribution for the absence of plaque and the absence of significant stenosis for the detection of ACS. The chi-square test was used to compare proportions and measures of diagnostic accuracy between groups. To compare the extent of plaque between subjects with and without ACS, Wilcoxon rank-sum test was applied. Further, we performed multivariate logistic regression modeling to examine the association between the extent of coronary atherosclerotic plaque and the presence of stenosis as detected by coronary CTA with the outcome of ACS. The crude models contained the presence of stenosis as a dichotomous variable, or the extent of plaque, defined as the number of coronary segments with any plaque (1–17), as a continuous variable. We then tested whether the association between CT findings and ACS persisted after adjusted for age, sex, and TIMI risk score. Model fit was assessed using c-statistics, equivalent to the area under the receiver-operating characteristic curve (AUC) (26). The asymptotic 95% CIs for the AUCs were estimated using a nonpara-

metric approach that is closely related to the jackknife technique proposed by DeLong et al. (27). Also, we performed a 2-sided asymptotic z-test to compare the AUC of the TIMI risk score and the CT finding, in which the standard error of the test statistics was derived from the asymptotic variance covariance (27).

Sample size calculation. The study was designed to assure a high precision of the estimates of diagnostic accuracy. We aimed to demonstrate lower bounds of 95% CIs for NPV above 90%. Based on our initial experience and published data we assumed the following: 12% prevalence of ACS, 90% sensitivity of significant coronary stenosis for ACS, and sensitivity of 90% and specificity of 85% for coronary CTA to detect significant coronary artery stenoses. Thus, a sample size of 400 patients would assure a tight (<10%) CI of the NPV above 90%.

A 2-sided value of $p < 0.05$ was considered to indicate statistical significance. All analyses were performed using SAS (version 9.1, SAS Institute Inc., Cary, North Carolina).

Results

Patient population. A total of 1,869 patients with a primary complaint of chest pain lasting >5 min were screened during the enrollment period. Exclusion criteria were present in 1,270 patients (impaired renal function [$n = 454$], history of CAD defined as previous stent placement or coronary bypass [$n = 231$], ECG diagnostic for myocardial ischemia or positive initial biomarkers [$n = 209$], arrhythmia [$n = 97$], inability to pause metformin [$n = 68$], enrolled in a different research study or previously included in this study [$n = 63$], history of allergy to iodine [$n = 58$], inability to administer beta-blocker because of asthma [$n = 37$], clinically unstable [$n = 31$], or lack of pregnancy testing [$n = 20$]). In addition, we excluded 231 patients who were ineligible because of interference with standard clinical care ($n = 100$), who refused participation ($n = 124$), or who did not complete the CT exam ($n = 7$). Thus, the study cohort consisted of 368 patients (mean age 52 years, 40% women) (Table 2).

Clinical outcomes. Overall, 8.4% of patients (31 of 368) had ACS (MI: $n = 8$, UAP: $n = 23$), whereas ACS was ruled out in the remaining 337 patients (91.6%). After a mean follow-up of 6.2 ± 2.0 months, none of the 337 subjects without ACS had had a MACE.

Coronary CT angiography. The average time to perform a coronary CTA (door-to-door time, including patient preparation) was 16 ± 7 min. The mean actual scan time to obtain the coronary CTA dataset was 14 ± 2 s. Average time for the interpretation of CT images was 9 ± 7 min (range 3 to 29 min).

Prevalence of Plaque and Stenosis and Diagnostic Accuracy of Coronary CTA

By coronary CTA, 50.3% (183 of 368) of these patients were free of CAD, 31.2% (117 of 368) had plaque but no

Table 2

Baseline Characteristics of 368 Patients Who Presented to the Emergency Department With Acute Chest Pain But Negative Initial Biomarkers and Nonischemic Electrocardiogram

Age (yrs), mean \pm SD	52.7 \pm 12
Male sex, n (%)	223 (61%)
Race, n (%)	
African American	31 (8%)
Caucasian	313 (85%)
Asian	4 (1%)
Other	20 (6%)
Ethnicity, n (%)	
Hispanic	44 (12%)
Non-Hispanic	324 (88%)
BMI (kg/m ²), mean \pm SD	29.0 \pm 6
Diabetes, n (%)	40 (11%)
Hypertension, n (%)	145 (39%)
Hyperlipidemia or statin use, n (%)	135 (37%)
Current or former smoking, n (%)	180 (49%)
No. of risk factors, median (IQR)	2 (1)
Creatinine (mg/dl), mean \pm SD	0.94 \pm 0.2
TIMI score (low/intermediate/high), %	94.3/5.4/0.3
ACS during index hospitalization, n (%)	31 (8%)
Unstable angina pectoris	23 (74%)
Myocardial infarction	8 (26%)
MACE during 6-month follow-up, n (%)	0
Recurrent chest pain	68 (18%)
Outpatient evaluation (PCP)	50 (74%)
Readmission without testing	5 (7%)
Readmission with testing	13 (19%)

ACS = acute coronary syndrome; BMI = body mass index; IQR = interquartile range; MACE = major adverse cardiac events defined as death, myocardial infarction, or revascularization; PCP = primary care physician; TIMI = Thrombolysis In Myocardial Infarction.

stenosis, and 18.5% had a positive CTA (34 were positive for stenosis and 34 rendered inconclusive assessment). The diagnostic test characteristics for ACS are shown in Table 3.

Coronary atherosclerotic plaque. Because none of the patients without plaque had ACS, sensitivity and NPV were excellent (100%). In contrast, specificity and PPV of the presence of coronary plaque was low to moderate because many patients had plaque but no ACS (PPV 17%, specificity 54%). Notably, the specificity of the presence of coronary plaque for ACS was lower in older subjects owing to high prevalence of plaque (21% vs. 59%, $p < 0.0001$, for subjects ≥ 65 years of age vs. < 65 years of age, respectively). Similar findings were seen for the detection of MI (Table 3).

Among 185 subjects in whom any coronary plaque was detected, patients with ACS had significantly more plaque (7.2 ± 3.7 segments vs. 4.2 ± 3.4 segments, $p < 0.0001$) as compared with subjects without ACS. Similar results were seen for calcified plaque and noncalcified plaque (6.5 ± 3.7 segments vs. 3.6 ± 3.5 segments, $p < 0.0001$, and 3.6 ± 3.2 segments vs. 1.8 ± 2.2 segments, $p < 0.0001$, respectively). Among 14 subjects (4%) with exclusively noncalcified plaque, only 1 subject developed ACS (1 of 14, 7.1%).

Coronary artery stenosis. The absence of significant stenosis had excellent NPV of 98%, but sensitivity was limited

Table 3

Diagnostic Accuracy of Coronary CTA for the Detection of Acute Coronary Syndrome and Myocardial Infarction During Index Hospitalization Among Patients With Acute Chest Pain Based on the Presence of Any Coronary Plaque or the Presence of Coronary Artery Stenosis (>50% Luminal Narrowing)

Coronary CTA Finding	Sensitivity [95% CI]	Specificity [95% CI]	PPV [95% CI]	NPV [95% CI]	LR+	LR-
Acute coronary syndrome						
Any plaque	31/31 (100%) [89%–100%]	183/337 (54%) [49%–60%]	31/185 (17%) [12%–23%]	183/183 (100%) [98%–100%]	2.2	0.0
Coronary stenosis	24/31 (77%) [59%–90%]	293/337 (87%) [83%–90%]	24/68 (35%) [24%–48%]	293/300 (98%) [95%–99%]	5.9	0.3
Myocardial infarction						
Any plaque	8/8 (100%) [63%–100%]	183/360 (51%) [46%–56%]	8/185 (4%) [2%–8%]	183/183 (100%) [98%–100%]	2.0	0.0
Coronary stenosis	5/8 (63%) [24%–91%]	297/360 (83%) [78%–86%]	5/68 (7%) [2%–16%]	297/300 (99%) [97%–100%]	3.7	0.45

CI = confidence interval; CTA = computed tomography angiography; LR+ = likelihood ratio given positive test result; LR- = likelihood ratio given negative test result; NPV = negative predictive value; PPV = positive predictive value.

to 77%, as 7 subjects in whom a stenosis was excluded by coronary CTA had ACS (Table 3). Characteristics of these subjects are detailed in Table 4. Because a substantial fraction of patients with a positive CT developed ACS (Fig. 1), PPV and specificity were reasonable and very good and higher than for the absence of plaque (PPV 35%, specificity 87%). Similar findings were seen for the detection of MI (Table 3).

The specificity of the presence of significant stenosis detected by coronary CTA for ACS was lower in older subjects (58% vs. 91%, $p < 0.0001$, for subjects ≥ 65 years of age vs. < 65 years of age, respectively), in whom coronary calcification was more prevalent (84% vs. 39%; $p < 0.0001$). The proportion of patients in whom a stenosis could not be definitely excluded in CT was significantly higher among subjects with ACS as compared with subjects without ACS (24 of 31 [77.4%] vs. 44 of 337 [13.1%], $p < 0.0001$). Remarkably, 14 of 34 patients who had a significant stenosis detected by CT were not diagnosed with ACS. None of them had a MACE after 6 months.

Coronary CT findings for risk stratification. In logistic regression analysis, each additional segment of plaque was

associated with a 37% increased risk of having an ACS (odds ratio [OR]: 1.37, 95% CI: 1.25 to 1.51; $p < 0.001$), whereas the presence of stenosis was associated with a more than 20-fold increased risk of ACS (OR: 22.8, 95% CI: 9.3 to 56.1; $p < 0.0001$). These associations persisted after adjustment for age, sex, and TIMI risk score (OR: 1.28, 95% CI: 1.14 to 1.43; $p < 0.0001$ and OR: 11.69, 95% CI: 4.4 to 31.0; $p < 0.0001$ for the extent of plaque and the presence of stenosis, respectively). The AUC in receiver-operator curves for the prediction of ACS was higher for both the extent of plaque (AUC 0.88, 95% CI: 0.83 to 0.93) and the presence of stenosis (AUC 0.82, 95% CI: 0.74 to 0.89) as compared to TIMI risk score (AUC 0.63, 95% CI: 0.54 to 0.71) (Fig. 2).

Standard care and CTA findings. On average, patients presented to the ED 6.7 ± 7.4 h (range 0.08 to 24.0 h) after the onset of chest pain. For most of these patients, the hospital course was characterized by obtaining serial troponin measurements and resting ECGs over the first 24 h and stress testing the following day. The average hospital length of stay was 40.5 ± 43.2 h (range 2.7 to 381.4 h).

Table 4

Detailed Information on the Results of Standard Care and Coronary CTA Results in Subjects Who Were Determined to Have ACS During Index Hospitalization But in Whom No Significant Stenosis Was Detected by Coronary CTA

Subject	Coronary CTA Finding of Nonobstructive Plaque	Baseline ECG	Troponin	Stress Nuclear Perfusion Imaging	Coronary Angiography/Intervention	Clinical Outcome
76-year-old woman	Proximal RCA, proximal LCX, and proximal and mid LAD	<1 mm ST-segment depression V_5 to V_6	Negative	Inferolateral area of ischemia	None	UAP
78-year-old woman	LM, proximal, mid, and distal LAD; PDA	Nonspecific T-wave changes	Negative	Inferolateral area of ischemia	None	UAP
72-year-old man	Mid RCA	Nonspecific T-wave changes	Negative	Apical area of ischemia, hypokinesia inferolateral region	None	UAP
52-year-old men	Mid LAD	Nonspecific T-wave changes	2nd set pos. (+6.8 h)	None	30% stenosis in mid LAD/none	NSTEMI
63-year-old man	Proximal and mid RCA, mid and distal LAD	New Q waves V_1 to V_2 , nonspecific T-wave changes	3rd set pos. (+5.7 h)	None	95% PLV, 50% 1st septal branch/stent PLV	NSTEMI
53-year-old man	LM and distal LAD	Nonspecific T-wave changes	2nd set pos. (+6.6 h)	None	40% D2 ostium, 70% D3 ostium stenosis/none	NSTEMI
59-year old woman	OM1	<1 mm ST-segment elevation V_2 to V_6	Negative	None	80% PDA stenosis/stent PDA	UAP

ACS = acute coronary syndrome; D2 = second diagonal branch; D3 = third diagonal branch; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; NSTEMI = non-ST-segment elevation myocardial infarction; OM1 = obtuse marginal branch; PDA = posterior descending artery; PLV = posterior left ventricular branch; pos. = > 0.09 ng/ml; RCA = right coronary artery; UAP = unstable angina pectoris; other abbreviations as in Tables 1 and 3.

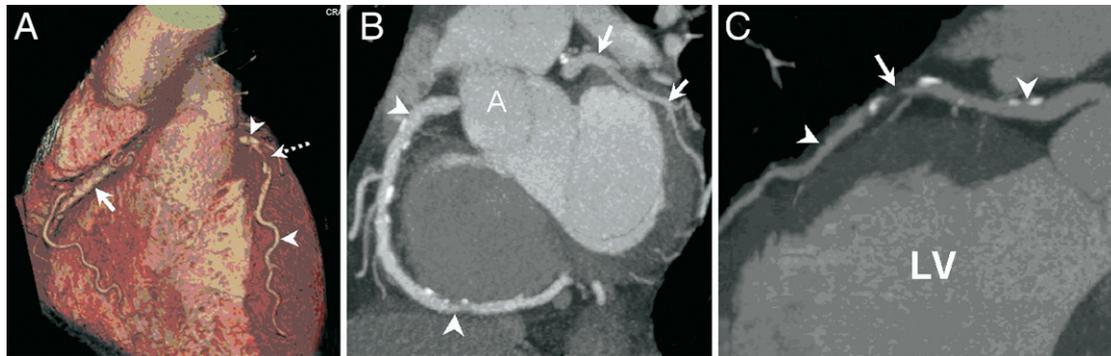


Figure 1 Detection of Significant Coronary Disease in ACS

A 40-year old man presented 3 h after the onset of substernal chest pain and had an inconclusive initial evaluation in the emergency department (ED) with nondiagnostic electrocardiogram and negative initial biomarkers. The patient was determined to have acute coronary syndrome (ACS) after troponin became positive (8 h after ED presentation). The patient subsequently underwent invasive coronary angiography, where an 80% mid left anterior descending coronary artery (LAD) stenosis was detected, and subsequently a stent was placed. Coronary computed tomography angiography (CTA) was performed before hospital admission. This patient was classified as positive for the presence of significant coronary stenosis. **(A)** Volume-rendered 3-dimensional computer tomographic image of the heart depicting the right coronary artery (RCA) (arrows) and the left anterior descending (LAD) coronary artery (arrowheads). **(B)** Maximum intensity projection image of the RCA (arrowheads) demonstrating calcified and noncalcified plaque without the presence of a significant coronary stenosis and the left circumflex coronary artery (arrows) demonstrating calcified and noncalcified plaque with proximal luminal narrowing. A = aortic root. **(C)** Curved multiplanar reformatted image of the LAD reveals a significant coronary stenosis (arrow) in the mid portion of the vessel. Proximal and distal portion demonstrate good luminal contrast enhancement with minimal coronary plaque (arrowheads).

Among the 31 patients with ACS, 20 patients underwent selective invasive coronary angiography, 19 of which revealed significant stenosis. One angiogram revealed a 30%

stenosis that improved with intracoronary nitroglycerin; thus, the patient's non-ST-segment elevation MI was attributed to vasospasm. Two patients had exercise treadmill tests, both of which were positive. Thirteen patients had stress (exercise or adenosine) single-positron emission computed tomography (SPECT) imaging, of which 11 were positive, 1 was negative at a submaximal heart rate, and 1 was indeterminate because of significant attenuation artifact. The 1 patient who had a negative submaximal SPECT was found to have significant stenosis on coronary CTA. The 1 patient who had an indeterminate SPECT also had an inconclusive coronary CTA.

Among the 337 patients (91.6%) in whom ACS was excluded, 13 patients underwent selective invasive coronary angiography, none of which revealed significant stenosis. There were 117 patients who underwent exercise treadmill testing. Two exercise treadmill tests were positive: 1 patient was positive for ischemia but negative on subsequent invasive coronary angiography and negative on coronary CTA, and 1 patient was positive but negative on subsequent SPECT and negative on CTA. A total of 137 patients had stress (exercise or adenosine) SPECT imaging, 3 of whom had ischemia on SPECT but no obstructive disease on invasive coronary angiography or coronary CTA.

Discussion

In this blinded observational cohort study, we demonstrate that 50% of patients who presented with acute chest pain to the ED and were at low to intermediate likelihood of ACS had no CAD by coronary CTA, a finding that has 100% NPV but limited PPV for the subsequent diagnoses of ACS and MACE. In addition, our results indicate that although

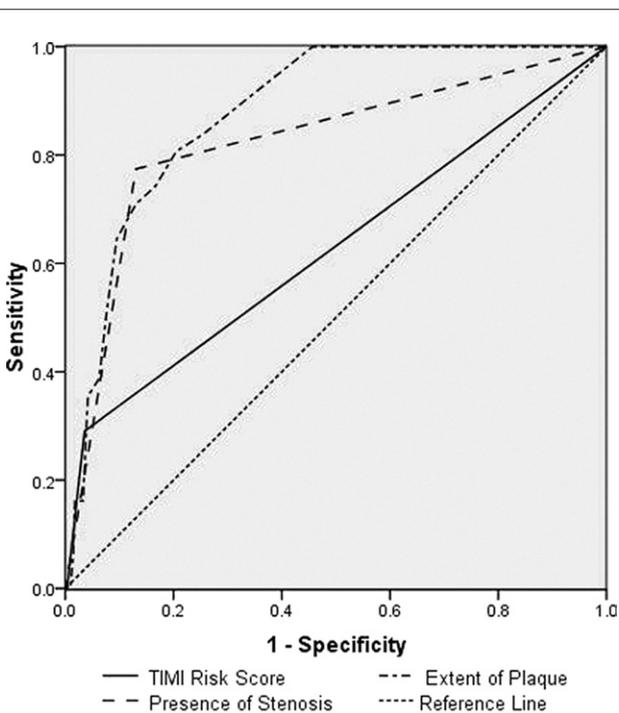


Figure 2 AUCs for the Detection of Acute Coronary Syndromes During Index Hospitalization

Areas under the receiver-operating characteristic curves (AUCs) were higher for both plaque and stenosis as compared to the Thrombolysis In Myocardial Infarction (TIMI) risk score (AUC: 0.88, 0.82, vs. 0.63, respectively).

the NPV remains excellent (98%), the exclusion of significant coronary stenosis by coronary CTA (>50%) has a limited sensitivity (77%) for the detection of ACS owing to a number of false negative findings of lesions in small vessels. Both plaque and stenosis by CT predict ACS independent of cardiovascular risk factors or TIMI risk score (AUC 0.88, 0.82, and 0.63, respectively; all $p < 0.05$). The PPV of coronary CTA is limited in patients >65 years of age. Given the large number of patients with acute chest pain, early coronary CTA may significantly improve patient management in the ED by aiding clinical decision making, specifically early discharge of subjects at low to intermediate likelihood of ACS without CAD.

A number of smaller studies (14,15) have demonstrated that a negative CT, defined variably as the absence of coronary calcification, the absence of CAD, or the absence of nonsignificant stenosis, has a high negative predictive value for ACS. In addition to confirming these findings, we are able to provide robust estimates of diagnostic accuracy with narrower CIs (lower 95% confidence bound >85% for NPV) because of our larger sample size. Importantly, in contrast to previous publications, we also demonstrate that the presence of significant stenosis (defined as >50% luminal narrowing) has reasonable test characteristics for the detection of ACS, although, expectedly, this is not a perfect criterion for ED triage of patients with acute chest pain (sensitivity 77%, $n = 7$ of 31). Possible explanations are rupture or thrombosis in subcritical (28,29) or microvascular disease (30) and limited accuracy of coronary CTA to detect stenosis in small-caliber vessels (<2 mm) (11). Our results suggest that the technique may be less efficient in patients >65 years of age, as the specificity of the plaque triage criterion is significantly limited because most of these patients will have CAD (59% vs. 21% for patients >65 vs. <65 years of age).

In contrast to most published studies, the design of our study permits an unbiased assessment because coronary CTA was not part of standard care, and thus, patient management and subsequent patient outcomes were not affected by CTA (i.e., additional downstream testing such as coronary angiography due to suspected stenosis in CT). As a result, we are able to report the diagnostic accuracy of several CTA patterns of CAD, such as presence of both calcified and noncalcified plaque as well as coronary stenosis <50% for ACS. Interestingly, a significant stenosis by CT was detected in 14 patients who were deemed to not have ACS based on clinical presentation, ECG, biomarkers, and a negative diagnostic test for ischemia. This suggests that CT is more sensitive in detecting significant luminal narrowing, although the hemodynamic significance is unknown. Because none of these patients had a MACE over the following 6 months, the finding of significant CAD as detected by CT may be longstanding and coincidental, with no relation to the patient's acute clinical presentation in the ED. This finding warrants further research specifically

related to the morphologic appearance of these lesions as compared to ACS lesions.

Our data also demonstrate that coronary CTA can risk-stratify patients with acute chest pain and intermediate likelihood of ACS independent of cardiovascular risk factors, TIMI risk score. Although such an analysis is familiar from observational trials using nuclear perfusion imaging at rest in the pre-troponin era (31,32), our results suggest that coronary CTA is superior to nuclear perfusion imaging (OR: 3.83; 95% CI: 2.36 to 6.21 for nuclear imaging vs. OR: 8.65; 95% CI: 3.69 to 20.26 for coronary CTA) (33). This information may guide assessment of the level of care necessary for these patients and, moreover, may improve risk assessment and prevention efforts in patients without ACS who are found to have coronary atherosclerosis. Several studies (34,35) now support that the presence and extent of CAD is also a powerful predictor of future cardiovascular events.

It appears that there is broad agreement (14,15,17) that coronary CTA may improve management of patients with acute chest pain. However, our results demonstrate that the strength of coronary CTA is its high negative predictive value for ACS. Half of all patients in our population had no CAD as detected by coronary CTA. In these patients, alternative diagnostic tests such as exercise stress testing or stress nuclear perfusion imaging were positive in up to 20% of cases, reflecting that they have limited specificity as compared to CT (33,36-38). Because none of these patients had ACS, they may be directly discharged from the ED without further diagnostic testing or hospital admission. Overall, our results may provide the rationale to establish recommendations for the actual clinical use of cardiac CT in populations with a low or intermediate likelihood of ACS, a population in whom diagnostic imaging tests have been generally recommended (22,39).

One of the major limitations of coronary CT is the associated radiation exposure (40). Reduction of radiation exposure using ECG tube modulation or prospective ECG triggering (41) will greatly facilitate acceptance in clinical practice.

Study limitations. This is a single-center study with enrollment limited to weekday daytime hours. However, subjects presenting outside enrollment hours were not significantly different from enrolled subjects with respect to age and sex, which are the strongest predictors of the prevalence of CAD. Because of exclusion of patients with known CAD and renal impairment, very elderly persons are under-represented in this study. In a real-world clinical scenario, many of these patients may be eligible for coronary CTA. Also, we used a CT scanner system from a single manufacturer. However, differences between vendors in the accuracy of coronary CTA for the detection of plaque and stenosis are marginal (11). In addition, coronary CTA exams in our study were performed by a dedicated research team and interpreted by readers with a high level of expertise in the field, having at least 2 years experience with

coronary CTA and more than 800 studies interpreted. Thus, it is possible that our results, including the high reproducibility of CT readings and the small number of inconclusive examinations, may be replicated only in centers with similar levels of expertise.

Conclusions

Both plaque and stenosis by CT predict ACS independent of cardiovascular risk factors or TIMI risk score. In this study, 50% of patients with acute chest pain and low to intermediate likelihood of ACS are free of CAD by CT and have no ACS. Given the large number of such patients, early coronary CTA may significantly improve patient management in the ED.

Acknowledgment

The authors gratefully acknowledge the enthusiastic support in patient enrollment of the team of faculty, residents, and nursing and administrative staff of the Emergency Department Services of the Massachusetts General Hospital.

Reprint requests and correspondence: Dr. Udo Hoffmann, Cardiac MR PET CT Program, Massachusetts General Hospital and Harvard Medical School, 165 Charles River Plaza, Suite 400, Boston, Massachusetts 02114. E-mail: uhoffmann@partners.org.

REFERENCES

1. Lee TH, Rouan GW, Weisberg MC, et al. Clinical characteristics and natural history of patients with acute myocardial infarction sent home from the emergency room. *Am J Cardiol* 1987;60:219-24.
2. Swap CJ, Nagurny JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. *JAMA* 2005;294:2623-9.
3. Limkakeng A Jr., Gibler WB, Pollack C, et al. Combination of Goldman risk and initial cardiac troponin I for emergency department chest pain patient risk stratification. *Acad Emerg Med* 2001;8:696-702.
4. Zimmerman J, Fromm R, Meyer D, et al. Diagnostic marker cooperative study for the diagnosis of myocardial infarction. *Circulation* 1999;99:1671-7.
5. Fesmire FM, Hughes AD, Fody EP, et al. The Erlanger chest pain evaluation protocol: a one-year experience with serial 12-lead ECG monitoring, two-hour delta serum marker measurements, and selective nuclear stress testing to identify and exclude acute coronary syndromes. *Ann Emerg Med* 2002;40:584-94.
6. Hedges JR, Young GP, Henkel GF, Gibler WB, Green TR, Swanson JR. Serial ECGs are less accurate than serial CK-MB results for emergency department diagnosis of myocardial infarction. *Ann Emerg Med* 1992;21:1445-50.
7. Selker HP, Beshansky JR, Griffith JL, et al. Use of the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) to assist with triage of patients with chest pain or other symptoms suggestive of acute cardiac ischemia. A multicenter, controlled clinical trial. *Ann Intern Med* 1998;129:845-55.
8. Tosteson AN, Goldman L, Udvarhelyi IS, Lee TH. Cost-effectiveness of a coronary care unit versus an intermediate care unit for emergency department patients with chest pain. *Circulation* 1996;94:143-50.
9. Conti A, Paladini B, Magazzini S, et al. Chest pain unit management of patients at low and not low-risk for coronary artery disease in the emergency department. A 5-year experience in the Florence area. *Eur J Emerg Med* 2002;9:31-6.
10. Solinas L, Raucci R, Terrazzino S, et al. Prevalence, clinical characteristics, resource utilization and outcome of patients with acute chest pain in the emergency department. A multicenter, prospective, observational study in north-eastern Italy. *Ital Heart J* 2003;4:318-24.
11. Hamon M, Biondi-Zoccai GG, Malagutti P, et al. Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography: a meta-analysis. *J Am Coll Cardiol* 2006;48:1896-910.
12. Achenbach S, Moselewski F, Ropers D, et al. Detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography: a segment-based comparison with intravascular ultrasound. *Circulation* 2004;109:14-7.
13. Leber AW, Knez A, von Ziegler F, et al. Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound. *J Am Coll Cardiol* 2005;46:147-54.
14. Goldstein JA, Gallagher MJ, O'Neill WW, Ross MA, O'Neil BJ, Raff GL. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *J Am Coll Cardiol* 2007;49:863-71.
15. Rubinshtein R, Halon DA, Gaspar T, et al. Usefulness of 64-slice cardiac computed tomographic angiography for diagnosing acute coronary syndromes and predicting clinical outcome in emergency department patients with chest pain of uncertain origin. *Circulation* 2007;115:1762-8.
16. Hollander JE, Litt HI, Chase M, Brown AM, Kim W, Baxt WG. Computed tomography coronary angiography for rapid disposition of low-risk emergency department patients with chest pain syndromes. *Acad Emerg Med* 2007;14:112-6.
17. Hoffmann U, Nagurny JT, Moselewski F, et al. Coronary multidetector computed tomography in the assessment of patients with acute chest pain. *Circulation* 2006;114:2251-60.
18. Hundt W, Rust F, Stabler A, Wolff H, Suess C, Reiser M. Dose reduction in multislice computed tomography. *J Comput Assist Tomogr* 2005;29:140-7.
19. Hoffmann MH, Shi H, Schmitz BL, et al. Noninvasive coronary angiography with multislice computed tomography. *JAMA* 2005;293:2471-8.
20. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975;51:5-40.
21. Hoffmann U, Moselewski F, Cury RC, et al. Predictive value of 16-slice multidetector spiral computed tomography to detect significant obstructive coronary artery disease in patients at high risk for coronary artery disease: patient-versus segment-based analysis. *Circulation* 2004;110:2638-43.
22. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 2002;40:1366-74.
23. Gibler WB, Cannon CP, Blomkalns AL, et al. Practical implementation of the guidelines for unstable angina/non-ST-segment elevation myocardial infarction in the emergency department: a scientific statement from the American Heart Association Council on Clinical Cardiology (Subcommittee on Acute Cardiac Care), Council on Cardiovascular Nursing, and Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Society of Chest Pain Centers. *Circulation* 2005;111:2699-710.
24. Gibler WB, Cannon CP, Blomkalns AL, et al. Practical implementation of the Guidelines for Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction in the emergency department. *Ann Emerg Med* 2005;46:185-97.
25. Nagurny JT, Brown DF, Chae C, et al. Disagreement between formal and medical record criteria for the diagnosis of acute coronary syndrome. *Acad Emerg Med* 2005;12:446-52.

26. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29-36.
27. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837-45.
28. Dokainish H, Pillai M, Murphy SA, et al. Prognostic implications of elevated troponin in patients with suspected acute coronary syndrome but no critical epicardial coronary disease: a TACTICS-TIMI-18 substudy. *J Am Coll Cardiol* 2005;45:19-24.
29. Patel MR, Chen AY, Peterson ED, et al. Prevalence, predictors, and outcomes of patients with non-ST-segment elevation myocardial infarction and insignificant coronary artery disease: results from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines (CRUSADE) initiative. *Am Heart J* 2006;152:641-7.
30. Panting JR, Gatehouse PD, Yang GZ, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002;346:1948-53.
31. Varetto T, Cantalupi D, Altieri A, Orlandi C. Emergency room technetium-99m sestamibi imaging to rule out acute myocardial ischemic events in patients with nondiagnostic electrocardiograms. *J Am Coll Cardiol* 1993;22:1804-8.
32. Kontos MC, Jesse RL, Schmidt KL, Ornato JP, Tatum JL. Value of acute rest sestamibi perfusion imaging for evaluation of patients admitted to the emergency department with chest pain. *J Am Coll Cardiol* 1997;30:976-82.
33. Udelson JE, Beshansky JR, Ballin DS, et al. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. *JAMA* 2002;288:2693-700.
34. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol* 2007;50:1161-70.
35. Pundziute G, Schuijff JD, Jukema JW, et al. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. *J Am Coll Cardiol* 2007;49:62-70.
36. Amsterdam EA, Kirk JD, Diercks DB, Lewis WR, Turnipseed SD. Immediate exercise testing to evaluate low-risk patients presenting to the emergency department with chest pain. *J Am Coll Cardiol* 2002;40:251-6.
37. Fragasso G, Lu C, Dabrowski P, Pagnotta P, Sheiban I, Chierchia SL. Comparison of stress/rest myocardial perfusion tomography, dipyridamole and dobutamine stress echocardiography for the detection of coronary disease in hypertensive patients with chest pain and positive exercise test. *J Am Coll Cardiol* 1999;34:441-7.
38. Hilton TC, Thompson RC, Williams HJ, Saylor R, Fulmer H, Stowers SA. Technetium-99m sestamibi myocardial perfusion imaging in the emergency room evaluation of chest pain. *J Am Coll Cardiol* 1994;23:1016-22.
39. Lee TH, Goldman L. Evaluation of the patient with acute chest pain. *N Engl J Med* 2000;342:1187-95.
40. Einstein AJ, Moser KW, Thompson RC, Cerqueira MD, Henzlova MJ. Radiation dose to patients from cardiac diagnostic imaging. *Circulation* 2007;116:1290-305.
41. Husmann L, Valenta I, Gaemperli O, et al. Feasibility of low-dose coronary CT angiography: first experience with prospective ECG-gating. *Eur Heart J* 2008;29:191-7.

Key Words: cardiac CT ■ emergency department ■ acute chest pain.