

CLINICAL RESEARCH

Clinical Trial

The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) Trial

James A. Goldstein, MD,* Kavitha M. Chinnaiyan, MD,* Aiden Abidov, MD, PhD,†
Stephan Achenbach, MD,‡ Daniel S. Berman, MD,§ Sean W. Hayes, MD,§ Udo Hoffmann, MD,||
John R. Lesser, MD,¶ Issam A. Mikati, MD,# Brian J. O'Neil, MD,** Leslee J. Shaw, PhD,††
Michael Y. H. Shen, MD,‡‡ Uma S. Valeti, MBBS,§§ Gilbert L. Raff, MD,*
for the CT-STAT Investigators

*Royal Oak and Detroit, Michigan; Tucson, Arizona; Giessen, Germany; Los Angeles, California;
Boston, Massachusetts; Minneapolis, Minnesota; Chicago, Illinois; Atlanta, Georgia; and Fort Lauderdale, Florida*

- Objectives** The purpose of this study was to compare the efficiency, cost, and safety of a diagnostic strategy employing early coronary computed tomographic angiography (CCTA) to a strategy employing rest-stress myocardial perfusion imaging (MPI) in the evaluation of acute low-risk chest pain.
- Background** In the United States, >8 million patients require emergency department evaluation for acute chest pain annually at an estimated diagnostic cost of >\$10 billion.
- Methods** This multicenter, randomized clinical trial in 16 emergency departments ran between June 2007 and November 2008. Patients were randomly allocated to CCTA (n = 361) or MPI (n = 338) as the index noninvasive test. The primary outcome was time to diagnosis; the secondary outcomes were emergency department costs of care and safety, defined as freedom from major adverse cardiac events in patients with normal index tests, including 6-month follow-up.
- Results** The CCTA resulted in a 54% reduction in time to diagnosis compared with MPI (median 2.9 h [25th to 75th percentile: 2.1 to 4.0 h] vs. 6.3 h [25th to 75th percentile: 4.2 to 19.0 h], p < 0.0001). Costs of care were 38% lower compared with standard (median \$2,137 [25th to 75th percentile: \$1,660 to \$3,077] vs. \$3,458 [25th to 75th percentile: \$2,900 to \$4,297], p < 0.0001). The diagnostic strategies had no difference in major adverse cardiac events after normal index testing (0.8% in the CCTA arm vs. 0.4% in the MPI arm, p = 0.29).
- Conclusions** In emergency department acute, low-risk chest pain patients, the use of CCTA results in more rapid and cost-efficient safe diagnosis than rest-stress MPI. Further studies comparing CCTA to other diagnostic strategies are needed to optimize evaluation of specific patient subsets. (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment [CT-STAT]; [NCT00468325](#)) (J Am Coll Cardiol 2011;58:1414–22) © 2011 by the American College of Cardiology Foundation

More than 8 million U.S. patients present annually to emergency departments (ED) with chest pain suspicious for ischemia and/or acute coronary syndrome (ACS) (1–3).

However, only a minority of “low-risk” chest pain patients are actually suffering from coronary artery disease (CAD) symptoms. In the past, ED triage based on history, serial

From the *Division of Cardiology, William Beaumont Hospital, Royal Oak, Michigan; †Division of Cardiology, University of Arizona, Tucson, Arizona; ‡Department of Cardiology, University of Giessen, Giessen, Germany; §Departments of Imaging and Cardiology, Cedars-Sinai Medical Center, Los Angeles, California; ||Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; ¶Minneapolis Heart Institute, Minneapolis, Minnesota; #Division of Cardiology, Northwestern University Medical School, Chicago, Illinois; **Department of Emergency Medicine, Wayne State University Medical School, Detroit, Michigan; ††Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia; ‡‡Division of Cardiology, Cleveland Clinic Florida, Fort Lauderdale, Florida; and the §§University of

Minnesota, Minneapolis, Minnesota. This study was funded by a research grant from Bayer Pharmaceuticals. Bayer Pharmaceuticals did not design, conduct, analyze, or interpret this study, nor did it prepare or review this manuscript. Dr. Abidov has served on the Speakers' Bureau of Astellas Pharma and has received grant support from Sarver Heart Center. Drs. Achenbach and Lesser have received research grants and speaker honoraria from Siemens. Dr. O'Neil is on the Speakers' Bureau of Bristol Myers-Squibb and Sanofi-Aventis; and is an unpaid consultant for HeartScape and ZOLL Circulation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 20, 2011; revised manuscript received March 21, 2011, accepted March 22, 2011.

electrocardiogram (ECG), and biomarkers alone resulted in the discharge of 2% of patients who were later diagnosed with ACS; such patients have higher mortality rates (4–8). Accordingly, it is now standard in many EDs and chest pain centers to evaluate such patients with a “rule-out myocardial infarction” strategy followed by stress testing and/or cardiac imaging; this approach has reduced diagnostic error but can be time-consuming and resource-intensive (2,6,9). It has been estimated that the diagnosis of acute ED chest pain costs \$10 to \$12 billion annually in this country alone (7,10). At a time when economic resources are constrained while healthcare demand is increasing, it is important to assess the comparative effectiveness of diagnostic methodologies not only in terms of safety and accuracy, but also for efficiency and diagnostic cost.

See page 1423

Advances in coronary computed tomographic angiography (CCTA) have made it possible to image the coronary vasculature rapidly and noninvasively, with excellent accuracy for detecting the presence and determining the severity of luminal stenoses and extraluminal plaque (11–17). To determine whether CCTA has the potential to safely increase efficiency and reduce the ED costs of care, the present randomized multicenter trial compared a diagnostic strategy incorporating CCTA to a strategy including rest-stress single-proton emission computed tomography scanning (myocardial perfusion imaging [MPI]) for evaluation of low-risk acute chest pain patients (6).

Methods

Study design. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) study was a multicenter, randomized, comparative effectiveness trial contrasting a diagnostic strategy including CCTA to a strategy incorporating rest-stress MPI for evaluation of acute low-risk chest pain at 11 university and 5 community hospital sites. Rest-stress MPI was selected as the comparator noninvasive test because: 1) it was the noninvasive cardiac imaging method used for low-risk chest pain at most (13 of 16) of our study sites; and 2) it is designated as appropriate for the diagnosis of possible ACS patients at low, intermediate, and high risk according to the multiple society appropriate use criteria for cardiac radionuclide imaging (18). The study protocol was developed and supervised by an executive steering committee and a data safety monitoring board, and received institutional review board approval at the coordinating institution (Beaumont Hospital) and at all participating study sites. All enrolled patients gave informed consent.

Patients. Patients were all acute chest pain patients admitted to the ED sequentially whenever research coordinators were present. Low- to intermediate-risk patients, as defined

below, who had symptoms suspicious for ischemia were prospectively enrolled and randomized, according to the method detailed in the Statistics section, to evaluation by CCTA or MPI (Fig. 1). Inclusion criteria included the following: 1) chest pain suspicious for angina based on an ED physician's history taking and physical examination; 2) age ≥ 25 years; 3) time from onset of chest pain to presentation ≤ 12 h; 4) time from ED presentation to randomization ≤ 12 h; 5) normal or nondiagnostic rest ECG at the time of enrollment, without ECG evidence of ischemia (i.e., ST-segment elevation or depression ≥ 1 mm in 2 or more contiguous leads, and/or T-wave inversion ≥ 2 mm); and 6) TIMI (Thrombolysis In Myocardial Infarction) risk score ≤ 4 for unstable angina or non-ST-segment elevation myocardial infarction (MI) (19–21). Exclusion criteria included the following: 1) known coronary artery disease; 2) elevated serum biomarkers including creatine kinase-myocardial band, myoglobin, and/or troponin I (e.g., Advia Centaur assay, Bayer Healthcare, Tarrytown, New York); 3) ischemic ECG changes, as denoted in the preceding text; 4) previously known cardiomyopathy, with an estimated ejection fraction $\leq 45\%$; 5) contraindication to iodinated contrast and/or beta-blocking drugs; 6) atrial fibrillation or markedly irregular rhythm; 7) body mass index ≥ 39 kg/m²; 8) elevated serum creatinine levels (creatinine ≥ 1.5 mg/dl); and 9) CT imaging or contrast administration within the past 48 h.

Endpoints. The primary study outcome was diagnostic efficiency, defined as time to diagnosis (time from randomization to when test results of CCTA or MPI were called to ED physicians). The time of randomization, scanning, and time of call with diagnosis were recorded on case report forms. Randomization could occur whenever study coordinators were present, including hours when neither scanner was available; the time and ED costs associated with waiting were included in the time to diagnosis. From these data, time of scanner availability for each modality was also analyzed.

Secondary outcomes included ED costs of care and safety. Cost was estimated from detailed hospital billing records incorporating the period from ED admission to discharge either to home or to inpatient hospitalization beyond the index noninvasive test. Because a complete analysis of direct and indirect costs could not be obtained at most sites, ED costs of care were estimated from the total billed charges multiplied by the Medicare cost-to-charge

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
AMI = acute myocardial infarction
CAD = coronary artery disease
CCTA = coronary computed tomographic angiography
ECG = electrocardiogram
ED = emergency department
ICA = invasive coronary angiography
MACE = major adverse coronary event(s)
MI = myocardial infarction
MPI = myocardial perfusion imaging
PCI = percutaneous coronary intervention

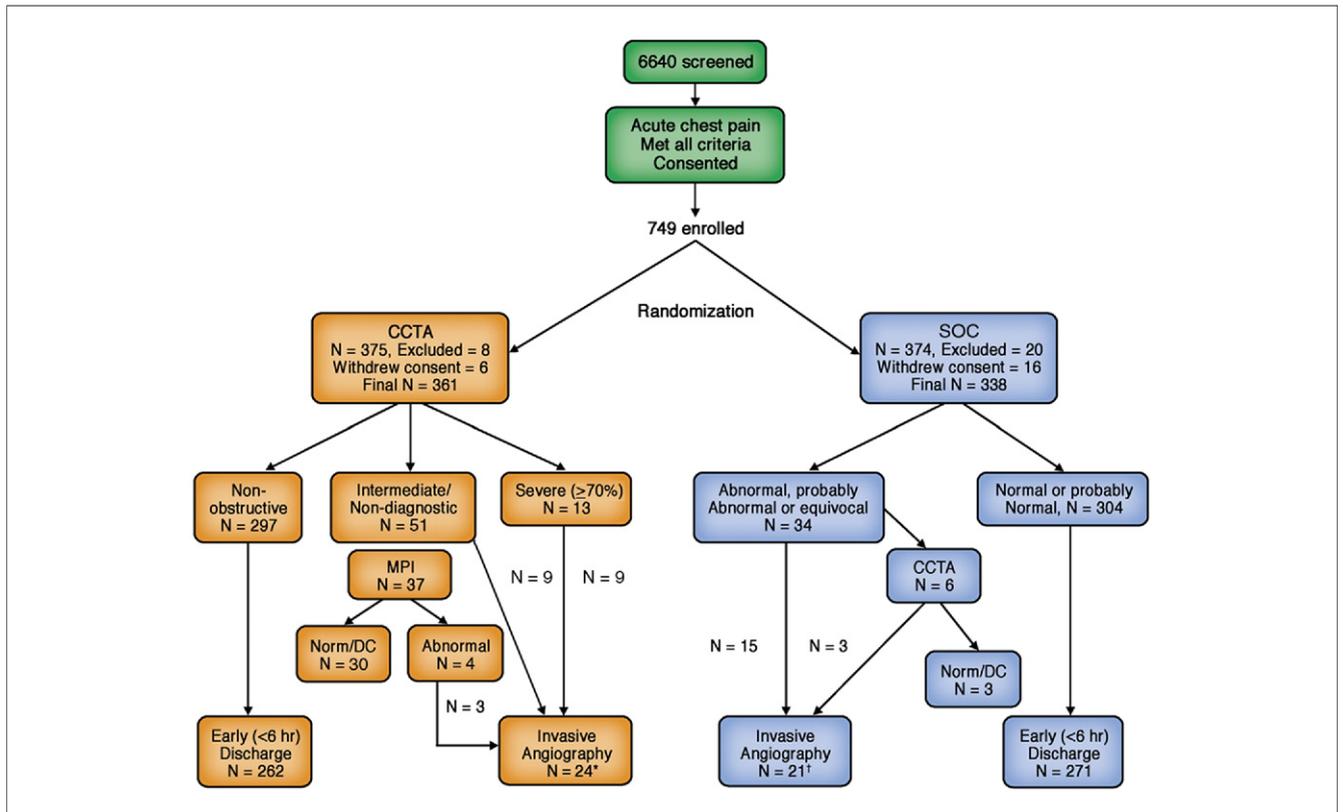


Figure 1 Study Algorithm

Coronary computed tomographic angiography (CCTA) arm (orange): *invasive coronary angiography = 24 patients (18 = abnormal CCTA, 3 = abnormal myocardial perfusion imaging [MPI], 3 = physician discretion). MPI = 37 patients (24 = abnormal CCTA, 13 = physician discretion). Standard of care (SOC) arm (blue): †invasive coronary angiography = 21 patients (15 = abnormal MPI, 3 = abnormal CCTA, 3 = physician discretion). DC = discharge. Figure illustration by Craig Skaggs.

ratio of each site. This ratio assigns a cost value per dollar billed and is site-specific. All charges including therapeutics were part of this calculation. If a patient required inpatient admission to complete the index noninvasive test, the charges incurred during hospitalization were included until the time when the noninvasive diagnosis was called to the attending physician. For patients undergoing both CCTA and MPI, the additional time and charges consequent to both tests were included.

Safety was defined as the absence of “unsafe” events, namely, major adverse cardiac events (MACE) over 6 months in patients designated as having a normal or near-normal index noninvasive test. These unsafe events included ACS (acute myocardial infarction [AMI] documented by cardiac enzymatic and electrocardiographic criteria or unstable angina), cardiac death, or revascularization in patients with a normal index test. Because revascularizations were not driven by the normal index test, in these patients, they were regarded as unsafe events due to misdiagnosis. The number of unsafe events was counted as 1 per patient even if that patient had multiple MACE events. The MACE events were adjudicated by a blinded clinical events committee using standard American College of Cardiology Foundation/American Heart Association criteria (4). Clin-

ical events were determined by evaluation of hospital and medical office records in each patient at the 6-month anniversary of the index ED visit, as well as late telephone interviews with all patients employing a structured questionnaire. Mortality was confirmed by the Social Security Death Index.

CCTA procedure. The CCTA was performed by previously published methods (22). The CCTA could be done immediately after enrollment. Briefly, in patients not receiving beta-blocking drugs, metoprolol 50 to 100 mg orally (or equivalent) and/or 5 to 30 mg intravenously were administered to achieve a heart rate <65 beats/min. Nitroglycerin 0.4 mg sublingual was given 1 min before image acquisition. Imaging was performed on CCTA scanners available at each institution including 64- to 320-slice scanners. Contrast-enhanced images were obtained using 60 to 100 ml Ultravist 300 (Bayer HealthCare, Montville, New Jersey) injected through an antecubital vein followed by a saline chaser. The CT datasets were read immediately by an experienced physician and findings were communicated to the ED physician. Coronary artery stenoses were evaluated per segment for all vessels having an estimated reference diameter of at least 1.5 mm, using a standardized 18-segment model (23). Maximal diameter stenosis was defined as the

most severe reduction in the coronary artery contrast column visualized using multiplanar reconstructions in a transverse arterial section, compared to the nearest normal lumen. The following severity categories were used: 0 = no stenosis; 1 = 1% to 25% stenosis; 2 = 26% to 50% stenosis; 3 = 51% to 70% stenosis; 4 = 71% to 99% stenosis; and 5 = total occlusion.

Rest-stress MPI procedure. Standard same-day rest-stress MPI was performed according to previously published methodology (24). These protocols were implemented according to the standards practice at participating sites, including the choice of isotopes. Rest imaging studies could be done immediately after enrollment. Stress testing was done only if the resting studies were normal; these included symptom-limited standard exercise treadmill or pharmacologic (adenosine or dipyridamole) stress MPI depending on physicians' clinical judgment (25). The MPI clinical readings were performed immediately and results called in to ED physicians.

The MPI findings for clinical decision making were analyzed at each institution according to standard methodology using qualitative and semiquantitative visual analysis and a standard 17-segment model (26). Final results were classified as normal, probably normal, equivocal, probably abnormal, and abnormal, on the basis of stress/rest perfusion imaging and functional data (27) as well as hemodynamic response to stress, including symptoms (typical angina pectoris during exercise), ECG response (>1 mm flat or downsloping ST-segment depression 80 ms after the J point, >1 mm of ST-segment elevation 80 ms after the J point, or sustained ventricular tachycardia), exercise duration when applicable, and blood pressure response (28).

Radiation dose analysis. The CCTA radiation doses were estimated by previously described methods (29). Each scan included a protocol summary report containing the dose-length product of each image, summing all phases of the examination, such as the topogram, monitoring or test dose, calcium score, and CCTA. Effective radiation dose was derived from the summed dose-length product multiplied by the standard conversion factor (0.014 mSv/mGray × cm).

The MPI radiation was calculated based on the administered radioisotope amount from both phases of the study. In the case of Tc-99m, a conversion factor of 0.0085 mSv/mBq was used, whereas 0.22 mSv/mBq was used for thallium-201 chloride.

Invasive coronary angiography. For patients referred for invasive coronary angiography (ICA), angiograms for clinical decision making were performed according to the standard practices at participating sites (22). Images were analyzed independently by blinded quantitative angiographic analysis of stenosis severity with an automated edge detection system (QuantCor QCA, Pie Medical Systems, Maastricht, the Netherlands). Lesions were classified by the maximal luminal diameter stenosis according to a qualitative severity scale: 0 = no stenosis; 1 = 1% to 25% stenosis; 2 =

26% to 50% stenosis; 3 = 51% to 70% stenosis; 4 = 71% to 99% stenosis; and 5 = total occlusion.

Clinical decision algorithms. On the basis of results of the index noninvasive test, study investigators recommended further management as outlined in Figure 1. In the CCTA arm, investigators recommended triage as follows: patients with coronary arterial stenoses 0% to 25% and/or calcium score <100 Agatston units were eligible for discharge home; patients with stenoses >70% were referred for ICA; and patients with intermediate lesions (stenosis 26% to 70% or calcium score >100 Agatston units) or uninterpretable scans were recommended to cross over for a rest-stress MPI. In the MPI arm, investigators recommended that patients with a normal or probably normal MPI were eligible for discharge home; and patients with ischemic ECG abnormalities, elevated biomarkers, and equivocal or abnormal MPI were to be referred for admission and/or ICA. A CCTA after an equivocal MPI was not dictated by the study protocol but was ordered by attending physicians' discretion in some patients. All patients underwent serial ECGs and cardiac biomarkers before enrollment and at 4 and 8 h thereafter before discharge. Although investigators provided diagnostic interpretation and standardized recommendations, all clinical management decisions including ICA, admission, immediate discharge, or a second noninvasive test were at the discretion of attending physicians.

Statistical methods. This study was powered to achieve a 90% probability to demonstrate a 25% reduction in the time to diagnosis; the sample size was determined at 704 patients. An additional 46 patients were included to account for patients who might not complete the protocol or were lost to follow-up. The randomization scheme was generated in a 1:1 ratio stratified (by site), alternating block design. All sites received their own site-specific, randomization envelopes. Once a patient was enrolled and the consent form had been signed, the next sequentially numbered envelope was opened and included the randomization arm and the patient's unique study identification number.

All categorical variables were examined using Pearson's chi-square or Fisher exact tests where appropriate and are reported as counts and percentage frequencies. Continuous variables were tested for normality and normally distributed variables were analyzed using a 2-sample *t* test. Variables that were not normally distributed were examined using a Wilcoxon rank sum test, including the secondary outcome of time to diagnosis. All continuous variables are shown as mean ± SD as well as median (25th to 75th percentile). All analyses used the SAS System for Windows (version 9.2, SAS Institute, Cary, North Carolina).

Results

Patient population. From June 2007 to November 2008, a total of 6,640 ED acute chest pain patients were screened, and 749 were enrolled (Fig. 1). The most common reasons for exclusion were as follows: prior known CAD (22.0%);

unwillingness or inability to provide consent (12.7%); ED physician discretion (8.7%); ≥ 24 h since last chest pain (7.6%); creatinine ≥ 1.5 mg/dl (7.3%); age ≤ 25 years (6.8%); ECG ischemia or positive biomarkers (5.2%); prior contrast within previous 48 h (5.1%); irregular rhythm (2.5%); contrast allergy (2.7%); and contraindications to beta-blockers (2.6%). Among the 749 enrolled cases, 50 (7.2%) patients either failed to complete the protocol or withdrew consent; these patients were excluded from analysis, leaving 699 patients with complete early results (361 patients in the CCTA group; 338 in the MPI group). Over the next 6 months, 72 (10.3%) patients were lost to follow-up for nonfatal MACE (CCTA = 30 of 361 [8.3%], MPI = 42 of 338 [12.4%], $p = 0.13$) leaving a total of 627 patients (CCTA, $n = 330$; MPI, $n = 297$) with complete 6-month results. All-cause mortality data were available from the Social Security Death Index for 698 of 699 (99.9%) patients (CCTA = 361 of 361, MPI = 337 of 338). Demographic variables were comparable between the CCTA arm and the MPI arm for early and late time periods (Table 1).

Findings on index studies and clinical outcomes. CCTA GROUP. Among 361 patients, CCTA ruled out the presence of more than minimal coronary artery disease in 297 of 361 (82.2%) cases; at least 1 $>70\%$ stenosis was detected in 13 (3.6%) patients; intermediate stenosis (25% to 70%) was found in 37 (10.2%) patients; and scans were not fully interpretable in 14 (3.9%) cases (Fig. 1). Of the patients with normal or minimally abnormal coronaries, 262 of 297 (88.2%) were then discharged home within 6 h. Rest-stress MPI was performed in 37 (10.2%) CCTA patients; of these, 23 had either intermediate lesions or nondiagnostic scans, 10 had normal CCTA, and 4 showed $>50\%$ narrowing. ICA was performed in 24 (6.6%) cases (18 because of CT findings, 3 because of ischemia seen in subsequent MPI, and 3 per physician discretion) (Fig. 2, Table 2). Among CCTA patients undergoing ICA during the index visit, 13

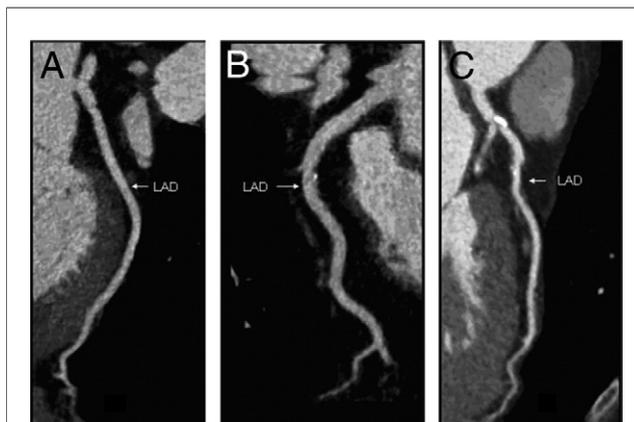


Figure 2 Coronary Lesions

(A) A 47-year-old man with substernal chest pain and dyspnea with normal coronary arteries (arrow). (B) A 58-year-old man with accelerating chest discomfort with mild coronary disease (arrow). (C) A 60-year-old woman with progressive dyspnea and atypical chest discomfort with significant mixed plaque (arrow). LAD = left anterior descending artery.

cases had significant stenoses and underwent revascularization (9 by percutaneous coronary intervention [PCI], 4 by coronary artery bypass graft surgery). As adjudicated by the clinical events committee, 1 revascularized patient also had

Table 1 Clinical Variables

	CCTA Group (n = 361)	MPI Group (n = 338)	p Value
Age, yrs	50 ± 10 (49)	50 ± 10 (49)	0.40
Male	163 (45.2%)	159 (47.0%)	0.62
Weight, lbs	182 ± 38 (180)	186 ± 40 (183)	0.19
BMI, kg/m ²	28.1 ± 4.7 (28.0)	28.7 ± 5.1 (29.0)	0.13
Hypertension	128 (35.5%)	131 (38.8%)	0.37
Dyslipidemia	112 (31.0%)	122 (36.1%)	0.16
Diabetes mellitus	20 (5.5%)	28 (8.3%)	0.15
Family history of CAD	111 (30.8%)	101 (30.0%)	0.82
Current smoker	91 (25.2%)	66 (19.5%)	0.07
ASA within past 7 days	90 (24.9%)	103 (30.5%)	0.10
Chest pain in last 24 h	177 (49.0%)	176 (52.1%)	0.42
TIMI risk score	0.99 ± 0.84 (1.0)	1.04 ± 0.87 (1.0)	0.38

Values are mean ± SD (median) or n (%).

ASA = acetylsalicylic acid (aspirin); BMI = body mass index; CAD = coronary artery disease; CCTA = coronary computed tomographic angiography; MPI = myocardial perfusion imaging; TIMI = Thrombolysis In Myocardial Infarction.

Table 2 Early and Late Clinical Events

Event	CCTA Group (n = 361)	MPI Group (n = 338)	p Value
Early (index visit)			
Index visit ICA	24 (6.7%)	21 (6.2%)	0.80
Index visit PCI	9 (2.5%)	8 (2.4%)	0.90
Index visit CABG	4 (1.1%)	0 (0%)	0.12
MI	1 (0.3%)	5 (1.5%)	0.11
Other unstable angina	3 (0.8%)	3 (0.9%)	1.00
Death	0 (0%)	0 (0%)	NA
Radiation, median, mSv	11.5 (6.8–16.8)	12.8 (11.6–13.9)	0.02
Scanner availability, h	7.1 ± 2.3	8.4 ± 3.2	0.065
Late (6-month follow-up)			
	n = 330	n = 297	
Late ICA	2 (0.6%)	1 (0.3%)	1.00
Late PCI	1 (0.3%)	0	1.00
Late CABG	0	0	NA
Late other unstable angina	0	0	NA
Late MI	0	0	NA
Late death	0/361	0/337	NA
Repeat ED (cardiac)	2 (0.6%)	4 (1.3%)	0.43
Repeat hospitalization (cardiac)	0	0	NA
Cumulative events			
ICA	26 (8.0%)	22 (7.4%)	0.78
PCI	10 (3.1%)	8 (2.7%)	0.78
CABG	4 (1.2%)	0 (0%)	0.13
MI	1 (0.3%)	5 (1.7%)	0.11
Additional unstable angina	3 (0.9%)	3 (1.0%)	1.00
All events	17 (5.2%)	12 (3.7%)	0.36

Values are n (%), median (25th to 75th percentile), mean ± SD, or n/N.

CABG = coronary artery bypass graft surgery; ED = emergency department; ICA = invasive coronary angiography; MI = myocardial infarction; NA = not appropriate; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

a non-ST-segment elevation MI and 7 had unstable angina; an additional 3 patients had unstable angina but did not undergo revascularization.

The 6-month CCTA mortality data are based on 361 patients, whereas other late clinical outcomes in the CCTA group are based on the 327 randomized patients with complete follow-up records (Table 2). Two patients were re-evaluated in the ED for cardiac symptoms: 1 was admitted and had a normal ICA; the other was considered to have benign palpitations without additional workup. One previously catheterized patient who did not undergo early PCI was admitted for an elective staged PCI. Among the cumulative 26 CCTA patients undergoing ICA, CCTA findings were consistent with ICA findings for presence or absence of CAD ($\geq 50\%$ stenosis) in 20 of 26 cases (76.9%). After 6 months, a cumulative 17 of 330 (5.2%) of all CCTA patients had clinical events (14 patients undergoing revascularization, including 1 with AMI and 7 with unstable angina, plus 3 additional patients with adjudicated unstable angina). No patients died or had late ACS.

MPI GROUP. Among 338 MPI patients, index testing was normal or probably normal in 304 of 338 (89.9%), of whom 271 of 304 (89.1%) were discharged home within 6 h; 2 patients with abnormal MPI results were also discharged per physician discretion. ICA was performed in 21 (6.2%) patients (15 for abnormal MPI results, 3 for subsequent abnormal CCTA, and 3 per physician discretion); of these, 8 underwent PCI. As adjudicated by the clinical events committee, among PCI patients, 4 had non-ST-segment elevation MI and 3 had unstable angina, and 3 of 338 (0.9%) patients had unstable angina but were not revascularized.

The 6-month mortality data are from 337 of 338 MPI patients, and the other late clinical outcomes in the MPI arm are from 297 patients with complete follow-up records. Four patients were re-evaluated in the ED for cardiac symptoms; 1 patient underwent ICA and had normal coronary arteries. The 3 other patients were medically treated for pre-syncope and noncardiac chest pain. Among the 22 cumulative MPI patients undergoing ICA, MPI findings were consistent with ICA in 12 of 22 (54.5%). At 6 months, a cumulative 12 of 297 (3.7%) patients had clinical events (8 patients undergoing revascularization, 4 of whom also had AMI and 3 with unstable angina, plus 1 AMI case and 3 unstable angina patients who did not undergo revascularization). No patient died or had post-discharge ACS.

Comparative clinical outcomes in the CCTA versus MPI groups. There were no significant differences in either early or late clinical outcomes between the CCTA and MPI groups. Similar numbers of patients underwent ICA during the index visit (CCTA = 24 of 361 [6.7%], MPI = 21 of 338 [6.2%], $p = 0.80$) and total revascularizations were similar as well (CCTA = 13 of 361 [3.6%], MPI = 8 of 338 [2.4%], $p = 0.34$). There were no differences in AMI (CCTA = 1 of 361 [0.3%] vs. MPI = 5 of 338 [1.5%], $p = 0.11$) or mortality (0 vs. 0). There was no late ACS or death in either arm, and cumulative event rates were comparable (CCTA = 17 of 326 [5.2%], MPI = 12 of 297 [3.7%], $p = 0.36$). The only clinical variable that was significantly different between the 2 groups was a lower median effective radiation dose in the CCTA group (CCTA = 11.5 mSv [25th to 75th percentile: 6.8 to 16.8 mSv], MPI = 12.8 mSv [25th to 75th percentile: 11.6 to 13.9 mSv], $p = 0.02$). Of the 16 sites, 14 used exclusively a single-isotope (^{99m}Tc) protocol, 1 site used dual isotopes (^{99m}Tc and ^{201}Tl), and 1 site used both protocols. All study sites used retrospective ECG-gated CTA; prospective ECG-triggered scanning was not available at any site at the time of the study.

Study endpoints. PRIMARY OUTCOME: DIAGNOSTIC EFFICIENCY. The CCTA diagnostic strategy demonstrated more rapid diagnosis compared with MPI (Table 3). The CCTA strategy was associated with a 54.0% reduction in time to diagnosis (CCTA median 2.9 h [25th to 75th percentile: 2.1 to 4.0 h], MPI median 6.2 h [25th to 75th percentile: 4.2 to 19.0 h], $p < 0.0001$). The average scanner availability per day was similar between modalities (CCTA mean 7.1 ± 2.3 h vs. MPI mean 8.4 ± 3.2 h, $p = 0.065$).

SECONDARY OUTCOME: ED COSTS OF CARE. The total ED costs of care were reduced by 38.2% (CCTA median \$2,137 [25th to 75th percentile: \$1,660 to \$3,077], MPI median \$3,458 [25th to 75th percentile: \$2,900 to \$4,297], $p < 0.0001$). The cost of CCTA and nuclear stress tests per se was similar (\$507 vs. \$538).

SECONDARY OUTCOME: SAFETY. The safety endpoint was calculated based on 268 CCTA patients and 266 MPI patients who had normal or near-normal index testing and completed 6-month follow-up results. Among such patients, both strategies had a similar low number of cases with adjudicated MACE events (CCTA = 2 of 268 [0.8%]; MPI = 1 of 266 [0.4%]; $p = 0.29$). The 2 CCTA cases had significant stenoses on ICA and underwent PCI, whereas

Table 3 Study Outcomes: Efficiency, Cost, and Safety

Outcomes	CCTA Group (n = 361)	MPI Group (n = 338)	p Value
Time to diagnosis, h	2.9 (2.1–4.0)	6.2 (4.2–19.0)	<0.0001
Total ED costs, \$	2,137 (1,660–3,077)	3,458 (2,900–4,297)	<0.0001
MACE in patients with normal index test	2/268 (0.8%)	1/266 (0.4%)	0.29

Values are median (25th to 75th percentiles) or n/N (%).

MACE = major adverse cardiac events; other abbreviations as in Tables 1 and 2.

the MPI patient had a total occlusion by ICA and was treated medically. Mortality data were available for 698 of 669 patients (CCTA = 361; MPI = 337); there were no deaths in either group.

Discussion

Observations from this randomized multicenter trial involving low-risk acute chest pain patients demonstrate that a diagnostic approach employing CCTA as the primary noninvasive imaging modality in appropriately selected patients is safe, facilitates more rapid evaluation compared with a strategy utilizing rest-stress MPI, and is associated with lower total ED costs (21).

The present findings are consistent with and extend those of previous single-center observational and randomized studies employing CCTA for evaluation of acute chest pain in this patient group (16,17). These findings demonstrated that CCTA facilitated safe early discharge of patients from the ED, and showed that the presence and severity of atherosclerotic plaque on CCTA was predictive of ACS. The enhanced diagnostic efficiency of utilizing CCTA was first demonstrated in a single institution randomized trial, which showed reduced diagnostic times and lower ED costs compared to MPI (16).

This study validates those results and documents that CCTA reduced time to diagnosis by one-half and lowered costs of the index ED visit by one-third, even though this test alone was not definitive in 14% of patients. Importantly, the present findings confirm that CCTA and rest-stress MPI are both safe diagnostic methods that permit early discharge in most low-risk patients.

Clinical implications. At a time when economic resources are constrained while healthcare demand is increasing, it is important to assess the comparative effectiveness of diagnostic methodologies not only in terms of safety and accuracy, but also for efficiency and cost. Over the last 2 decades, studies of acute chest pain triage employing diagnostic imaging have demonstrated significant improvements in efficiency and cost over alternative strategies without imaging, with significant reductions in hospital admission rates (30–33).

The present study demonstrates that a CCTA-based strategy, when specifically compared to rest-stress MPI, provides ED cost benefits and a reduction in the time required for diagnosis, with similar safety and a lower radiation burden. These benefits could potentially reduce the onerous healthcare resource burden of this common, expensive clinical scenario in appropriately selected patients. However, there are important caveats to be considered. This study did not compare CCTA to other less costly alternatives or to those with no or lower radiation risk (9). In many EDs and chest pain centers, rest-stress MPI is not the standard of care for low-risk patients without prior history of CAD and a normal ECG and cardiac enzymes. In future

studies, the “CCTA-first” strategy should be compared to other expeditious protocols such as electrocardiographic stress alone, rest-only or stress-only MPI, stress echocardiography, and imaging only in patients with positive electrocardiographic stress (2,5,9,10,34–39). Before the present results can be extrapolated to generalized recommendations, CCTA should also be evaluated in comprehensive comparative effectiveness studies that include a broader patient risk profile (40,41).

The findings of this study should be applied only to the subset of patients who met eligibility criteria and are suitable for CCTA. These data provide evidence about the proportion of patients who might be suitable for CCTA among the general ED acute chest pain population. Because patients with known CAD are likely to show multiple lesions on CCTA, the investigators believe these patients benefit more from physiologic testing with MPI or stress echocardiography; such cases constituted 22% of the screened population. Patients with creatinine levels ≥ 1.5 mg/dl, contraindications to beta-blockers, contrast allergy, or irregular rhythms totaled 15.1% of cases. High-risk patients and patients with positive biomarkers or ECG signs compatible with ischemia may need invasive angiography without delay; these patients totaled 5.4% of screened cases. On the basis of these considerations, approximately 58% of all screened acute chest pain patients could be triaged by CCTA; it is apparent that a “one size fits all” approach does not provide optimal management for a diverse ED clinical population.

Study limitations. The present study was not powered to provide a statistically conclusive comparison between the 2 study groups with regard to safety. Powering the study for safety was not feasible, based on the data from 2 previous studies in which the number of CCTA and/or rest-stress MPI patients with misdiagnoses were 0 of 200 and 7 of 368 (1.9%), respectively, for a total missed rate of 7 of 568 (1.2%) (12,13). To power a study by a 1.2% missed MACE event rate, using 80% power, equivalence tests for 2 proportions, and accepting a difference of no more than 25% (absolute difference of 0.3%) would require 45,126 cases without adjusting for patients lost to follow-up.

This study is not a formal cost-effectiveness analysis, nor is it an analysis of total downstream healthcare costs. Our methodology tabulated total charges from the time of registration until the time of discharge or inpatient index noninvasive diagnosis, and estimated cost from charges multiplied by the Medicare cost-to-charge ratio; this methodology relies on several assumptions. Direct measurement of costs is advantageous but was not feasible within existing funding and time constraints. Capturing costs related to subsequent hospitalizations, procedures, and interventions are important to ultimately assess the societal cost of each technology. The number of hospitalizations, ED visits, noninvasive and invasive testing, and percutaneous revascularizations were similar between the groups, which is encouraging but insufficient evidence that the cost reduction

from CCTA is sustained. There were more coronary bypass surgeries in the CCTA group; that was not statistically significant but might be in a larger study and would have important cost effects. Comparing long-term downstream resource utilization after CCTA to a broad spectrum of tests will be required to provide definitive information.

The number of patients randomized to each arm of the study was similar (CCTA 375 cases, MPI 374 cases), but excluding patients who withdrew consent or had protocol deviations produced a significant difference (CCTA 361 patients, MPI 338 patients, $p = 0.001$). This was primarily attributable to 1 site at which MPI patients initially received both tests. If this site were excluded, the patients in each group would be similar (CCTA 338 cases, MPI 329 cases) and the study endpoints unchanged (time to diagnosis 4.2 h vs. 4.3 h for CCTA, 11.5 h vs. 11.2 h for MPI; costs \$6,795 vs. \$6,706 for CCTA, \$10,070 vs. \$10,102 for MPI; safety endpoints unchanged).

During the 6-month follow-up period, a total of 72 of 699 (10.3%) cases were lost to follow-up; these patients had no office or hospital visits and could not be contacted by research coordinators. Although mortality information was available for 698 of 699 patients (there were no deaths in either group), in a population with so few safety endpoints (3 cases), it is possible that complete follow-up in all patients might have revealed a difference in other MACE events that could affect the safety outcome.

There are also limitations intrinsic to the CCTA procedure itself, which engenders radiation exposure and theoretically may impose some increased lifetime cancer risk (41–43). Exposure to iodinated contrast must also be considered. Fortunately, recent scanner innovations since the time of this study dramatically reduced exposure levels (to as low as 1 to 4 mSv for many patients) (29,44,45). These scanners can also reduce contrast dose because of subsecond scan times.

Conclusions

Observations from this randomized multicenter trial involving low-risk acute chest pain patients demonstrate that a diagnostic approach employing CCTA as the primary noninvasive imaging modality in appropriately selected patients is safe, facilitates more rapid evaluation compared with a strategy utilizing rest-stress MPI, and is associated with lower total ED costs. More comprehensive trials comparing CCTA to other expedited diagnostic protocols, including stress-ECG, rest-only MPI and stress-only MPI, and stress echocardiography are needed to define the optimal evaluation strategies for specific patient subgroups. In addition, long-term studies of downstream healthcare resource utilization and cost-effectiveness analyses will be required to compare the societal costs of these alternative diagnostic strategies.

Reprint requests and correspondence: Dr. Gilbert L. Raff, Cardiology Division, William Beaumont Hospital, 3601 West 13 Mile Road, Royal Oak, Michigan 48073. E-mail: graff@beaumont.edu.

REFERENCES

1. McCaig LF, Burt CW. The National Hospital Ambulatory Medical Care Survey: 2003 emergency department summary. *Adv Data* 2005; 358:1–38.
2. Amsterdam EA, Kirk JD, Bluemke DA, et al. Testing of low-risk patients presenting to the emergency department with chest pain. A Scientific Statement from the American Heart Association. *Circulation* 2010;122:1756–76.
3. Pitts SR, Niska RW, Xu J, Burt CW. National Hospital Ambulatory Medical Care Survey: 2006 emergency department summary. *Natl Health Stat Report* 2008;7:1–38.
4. 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.
5. Farkouh ME, Smars PA, Reeder GS, et al., for the Chest Pain Evaluation in the Emergency Room (CHEER) Investigators. A clinical trial of a chest-pain observation unit for patients with unstable angina. *N Engl J Med* 1998;339:1882–8.
6. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J Am Coll Cardiol* 2003;42:1318–33.
7. Tatum JL, Jesse RL, Kontos MC, et al. Comprehensive strategy for the evaluation and triage of the chest pain patient. *Ann Emerg Med* 1997;29:116–25.
8. Zalenski RJ, Rydman RJ, Ting S, Kampe L, Selker HP. A national survey of emergency department chest pain centers in the United States. *Am J Cardiol* 1998;81:1305–9.
9. Berman DS, Hachamovitch R, Shaw LJ, Hayes SW, Germano G. Nuclear cardiology. In: Fuster V, Walsh RA, Harrington RA, editors. *Hurst's The Heart*. 13th edition. New York, NY: McGraw-Hill, 2011:562–98.
10. Heller GV, Stowers SA, Hendel RC, et al. Clinical value of acute rest technetium-99m tetrofosmin tomographic myocardial perfusion imaging in patients with acute chest pain and nondiagnostic electrocardiograms. *J Am Coll Cardiol* 1998;31:1011–7.
11. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008;52:1724–32.
12. Meijboom WB, Meijis MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol* 2008;52:2135–44.
13. Meijboom WB, Mollet NR, Van Mieghem CA, et al. 64-Slice CT coronary angiography in patients with non-ST elevation acute coronary syndrome. *Heart* 2007;93:1386–92.
14. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008;359:2324–36.
15. Mowatt G, Cook JA, Hillis GS, et al. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. *Heart* 2008;94:1386–93.
16. 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.
17. Hoffmann U, Bamberg F, Chae CU, et al. Coronary computed tomography angiography for early triage of patients with acute chest pain: the

- ROMICAT (Rule Out Myocardial Infarction Using Computer Assisted Tomography) trial. *J Am Coll Cardiol* 2009;53:1642-50.
18. Hendel RC, Berman DS, Di Carli MF, et al. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. *J Am Coll Cardiol* 2009;53:2201-29.
 19. Hendel RC, Patel MR, Kramer CM, et al. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol* 2006;48:1475-97.
 20. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835-42.
 21. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 2010;56:1864-94.
 22. Raff GL, Gallagher MJ, O'Neill WW, Goldstein JA. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. *J Am Coll Cardiol* 2005;46:552-7.
 23. Raff GL, Abidov A, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. *J Cardiovasc Comput Tomogr* 2009;3:122-36.
 24. Berman DS, Hachamovitch R, Kiat H, et al. Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: a basis for optimal utilization of exercise technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography. *J Am Coll Cardiol* 1995;26:639-47.
 25. Hansen CL, Goldstein RA, Akinboboye OO, et al. Myocardial perfusion and function: single photon emission computed tomography. *J Nucl Cardiol* 2007;14:e39-60.
 26. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;105:539-42.
 27. Hendel RC, Wackers FJ, Berman DS, et al. American Society of Nuclear Cardiology consensus statement: reporting of radionuclide myocardial perfusion imaging studies. *J Nucl Cardiol* 2003;10:705-8.
 28. Mark DB, Shaw L, Harrell FE Jr., et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med* 1991;325:849-53.
 29. Raff GL, Chinnaiyan KM, Share DA, et al. Radiation dose from cardiac computed tomography before and after implementation of radiation dose-reduction techniques. *JAMA* 2009;301:2340-8.
 30. Radensky PW, Hilton TC, Fulmer H, McLaughlin BA, Stowers SA. Potential cost effectiveness of initial myocardial perfusion imaging for assessment of emergency department patients with chest pain. *Am J Cardiol* 1997;79:595-9.
 31. Weissman IA, Dickinson CZ, Dworkin HJ, O'Neill WW, Juni JE. Cost-effectiveness of myocardial perfusion imaging with SPECT in the emergency department evaluation of patients with unexplained chest pain. *Radiology* 1996;199:353-7.
 32. 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.
 33. Kontos MC, Schmidt KL, McCue M, et al. A comprehensive strategy for the evaluation and triage of the chest pain patient: a cost comparison study. *J Nucl Cardiol* 2003;10:284-90.
 34. Wackers FJ. Can acute rest imaging shorten evaluation in chest pain centers? *J Nucl Cardiol* 1999;6:676-8.
 35. Abbott BG, Abdel-Aziz I, Nagula S, Monico EP, Schriver JA, Wackers FJ. Selective use of single-photon emission computed tomography myocardial perfusion imaging in a chest pain center. *Am J Cardiol* 2001;87:1351-5.
 36. Kontos MC, Wackers FJ. Acute rest myocardial perfusion imaging for chest pain. *J Nucl Cardiol* 2004;11:470-81.
 37. Mattera JA, Arain SA, Sinusas AJ, Finta L, Wackers FJ. Exercise testing with myocardial perfusion imaging in patients with normal baseline electrocardiograms: cost savings with a stepwise diagnostic strategy. *J Nucl Cardiol* 1998;5:498-506.
 38. Duvall WL, Wijetunga MN, Klein TM, et al. The prognosis of a normal stress-only Tc-99m myocardial perfusion imaging study. *J Nucl Cardiol* 2010;17:370-7.
 39. Dakik HA, Hwang WS, Jafar A, Kimball K, Verani MS, Mahmarian JJ. Prognostic value of quantitative stress myocardial perfusion imaging in unstable angina patients with negative cardiac enzymes and no new ischemic ECG changes. *J Nucl Cardiol* 2005;12:32-6.
 40. Hlatky MA. Evaluating use of coronary computed tomography angiography in the emergency department. *J Am Coll Cardiol* 2009;53:1651-2.
 41. Redberg RF, Walsh J. Pay now, benefits may follow—the case of cardiac computed tomographic angiography. *N Engl J Med* 2008;359:2309-11.
 42. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. *JAMA* 2007;298:317-23.
 43. Fazel R, Krumholz HM, Wang Y, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. *N Engl J Med* 2009;361:849-57.
 44. Achenbach S, Marwan M, Schepis T, et al. High-pitch spiral acquisition: a new scan mode for coronary CT angiography. *J Cardiovasc Comput Tomogr* 2009;3:117-21.
 45. Earls JP, Berman EL, Urban BA, et al. Prospectively gated transverse coronary CT angiography versus retrospectively gated helical technique: improved image quality and reduced radiation dose. *Radiology* 2008;246:742-53.

Key Words: acute chest pain ■ coronary computed tomography ■ cost of care ■ diagnostic effectiveness ■ emergency department.

 **APPENDIX**

For a list of the investigators, coordinators, and site locations, please see the online version of this paper.