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Design of the Rule Out Myocardial Ischemia/Infarction Using Computer Assisted Tomography: A multicenter randomized comparative effectiveness trial of cardiac computed tomography versus alternative triage strategies in patients with acute chest pain in the emergency department

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Abstract

Although early cardiac computed tomographic angiography (CCTA) might improve the management of emergency department (ED) patients with acute chest pain, it could also result in increased testing, costs, and radiation exposure. ROMICAT II was a randomized comparative effectiveness trial enrolling patients 40 to 74 years old without known coronary artery disease who presented to the ED with chest pain but without ischemic electrocardiographic (ECG) changes or elevated initial troponin and who required further risk stratification. Overall, 1000 patients at 9 sites within the United States were randomized to either CCTA as the first diagnostic test following serial biomarkers or to standard of care, which included no testing or functional testing such as exercise ECG, stress radionuclide imaging, or stress echocardiography. Test results were provided to ED physicians, yet patient management was not driven by a study protocol in either arm. Data were collected on diagnostic testing, cardiac events, and cost of medical care for the index hospitalization and during the following 28 days. The primary end point was length of hospital stay. Secondary end points were cumulative radiation exposure, resource utilization, and costs of competing strategies. Tertiary end points were institutional, physician, and patient

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characteristics associated with primary and secondary outcomes. Rate of missed acute coronary syndrome within 28 days was the safety end point. The ROMICAT II will provide rigorous data on whether CCTA is more efficient than standard of care in the management of patients with acute chest pain at intermediate risk for acute coronary syndrome.

More than 8 million patients present annually to the emergency department (ED) in the United States with acute chest pain.¹ However, only a minority (2%–10%) of such patients are diagnosed with acute coronary syndrome (ACS), at a cost in excess of \$8 billion, due to unnecessary hospitalization and testing.^{1–5} Current evaluation strategies typically require hospital admission from 24 to 36 hours in most US hospitals (>90%) and include serial electrocardiograms (ECG) and biomarker (troponin and/or creatine kinase) measurements, observation, and some form of functional testing to exclude myocardial ischemia. This strategy, although safe, is inefficient in patients who present with chest pain suggestive of ACS but without objective signs of myocardial ischemia or necrosis by ECG or biomarkers.

Cardiac computed tomographic (CT) angiography (CCTA) can noninvasively image the entire coronary artery tree and accurately detect the presence and extent of coronary atherosclerotic plaque and significant stenosis.^{6–8} Therefore, CCTA has emerged as an alternative to functional testing to guide the management of patients with acute chest pain. Observational data demonstrate that the absence of coronary atherosclerosis on CCTA has excellent negative predictive values for excluding ACS and that patients with nonobstructive coronary artery disease (CAD) rarely develop ACS.⁹ Both of these findings have excellent prognostic value.^{10,11} These data have been confirmed in several other observational studies in which patients were managed based on CCTA findings.^{12–14} Furthermore, a randomized trial in patients at very low risk for ACS specifically comparing CCTA to nuclear perfusion imaging suggests that, in these patients, CCTA shortens the diagnosis time and lowers the cost of patient care.¹⁵

The recently published ROMICAT I trial demonstrated very good performance characteristics of cardiac CT findings for ACS in the ED setting and defined imaging characteristics associated with the original prognosis.⁹ In this observational cohort study, CCTA was performed in an intermediate risk patient population (ACS rate 8%), but the results were blinded to the physician and patients. Whether clinicians can incorporate the information from CCTA to improve patient management and ED triage can only be established in a comparative effectiveness trial.

Thus, the goals of ROMICAT II were to perform a randomized trial in patients presenting to the ED with acute chest pain who are at intermediate risk for ACS; to determine the effectiveness of CCTA as compared with standard of care (SOC) (as defined by local physicians); and to define institutional, physician, and patient characteristics that influence effectiveness of both strategies.

Study design and methods

ROMICAT II was designed as a randomized, open-labeled multicenter diagnostic comparative effectiveness trial. The trial enrolled 1,000 patients presenting with acute chest pain to the ED at 9 clinical sites between April 2010 and January 2012. We compared 2 evaluation strategies for these patients: (a) cardiac CT imaging as part of the initial ED evaluation and (b) the SOC evaluation used in each hospital, where cardiac CT could not be the first diagnostic test (Figure 1). The patients were randomized immediately after the initial ED evaluation, which included a medical history, physical examination, ECG, serum troponin, and renal function tests. Typically, management included observation with serial cardiac biomarkers and ECGs and other diagnostic tests or interventions as clinically

indicated. All information from diagnostic testing in both arms was reported in real time to physicians to guide patient management. All participating physicians received recommendations for performance and interpretation of diagnostic testing as well as patient management according to published guidelines. As a safety measure, we performed a follow-up telephone call within 48 to 72 hours to assess clinical status if patients were discharged from the ED within 24 hours and a similar follow-up telephone call 28 days after discharge for all patients, irrespective of randomization.

The primary objective of this study is to assess the effectiveness of implementing CCTA as early as possible into the diagnostic workup of patients with acute chest pain, normal initial biomarkers, and normal or nondiagnostic ECGs, as compared with a SOC strategy without early CT. The effectiveness of each strategy will be determined by comparing various indices: (1) the length of hospital stay (LOS) (primary end point); (2) the time to diagnosis; (3) the rates of direct ED discharge; (4) utilization of other diagnostic testing, that is, invasive coronary angiography, and resulting interventions during index hospitalization and within 28 days postdischarge; and (5) cost and cost-effectiveness. In subsequent analyses, we will determine the patient, physician, and institutional factors that influence the effectiveness of patient management. The safety of the 2 strategies will be compared by determining the rates of major adverse cardiovascular events within 48 to 72 hours in patients discharged within 24 hours of ED presentation and within 28 days after the index hospitalization.

Patient population

In ROMICAT II, we included patients between 40 and <75 years of age without known CAD who presented with a chief symptom of acute chest pain lasting at least 5 minutes within the last 24 hours but without objective signs of myocardial ischemia on admission ECG or myocardial necrosis as determined by initial troponin testing. In all patients, health care providers determined that further risk stratification/diagnostic testing was needed after the initial assessment remained inconclusive. We excluded patients with known/documented history of CAD because such patients usually have an abnormal or nondiagnostic cardiac CT and are at higher risk for ACS. The detailed inclusion and exclusion criteria are summarized in Table I. The inclusion criteria were defined with the goal to enroll a patient population at intermediate risk for CAD and ACS, defined as an ACS event rate between 4% and 16%.¹⁶ Although ACS event rate is not a trial end point, it is an important determinant of whether advanced diagnostic imaging tests such as CCTA, which entails iodinated contrast administration, radiation exposure, and costs, may be warranted and render a reasonable risk-benefit ratio. Notably, previous CT trials in the ED were performed in very low- or low-risk populations with 0% to 2% ACS rates.^{15,17}

To identify a population at intermediate risk for ACS, we used data from the ROMICAT I⁹ observational study to assess the utility of adding to the inclusion criteria traditional risk factors (diabetes, hypertension, hyperlipidemia, family history of CAD, and smoking) and clinical presentation (Table II); the ACS rate in that study was 8%. Although patients with 2 risk factors had a 2.75-fold increase risk in having ACS as compared those with <2 risk factors ($P = .0097$), only 41.9% of the ROMICAT I cohort met this criterion. Moreover, presence of 3 risk factors, seen in only 16.6% of patients, did not increase the risk of ACS. In addition, we decided not to use the TIMI unstable angina/non-ST-segment elevation myocardial infarction risk score as an inclusion criterion for several reasons. First, the score was created to predict 14-day outcomes in patients with unstable angina or non-ST-segment elevation myocardial infarction.¹⁸ It remains controversial to use the TIMI risk score in the ED setting.^{19,20} In general, ED health care providers do not typically use the score to assess risk of patients in clinical practice, and >94% of the patients in ROMICAT I were at low

TIMI risk. In fact, one of the reasons to examine the value of CCTA in these low-risk patients is the absence of an effective and feasible risk score for early triage.

We decided to restrict the age of the population to 40 to 74 years for several reasons. We chose the lower limit of 40 years because none of the 38 patients in ROMICAT I who were <40 years old had ACS. In addition, men and women <40 years are more susceptible to future cancer risk from radiation exposure.²¹ We chose an upper age limit of <75 years because the proportion of patients with indeterminate examinations due to calcification in patients ≥75 years was significantly higher as compared with those <75 years old (33.3% vs 7.3%, $P < .0001$).

In ROMICAT I patients, the duration of chest pain did not significantly influence the ACS rate (<5 minutes of chest pain [9.7% ACS], 5–10 minutes (6.3% ACS), and >10 minutes [8.1% ACS], $P = .89$). Given the lack of relationship between ACS rate and chest pain duration, we chose the criterion of >5 minutes of chest pain as a reasonable compromise, which excluded only 12.4% of ROMICAT I patients. Thus, based on ROMICAT I data, neither traditional risk factors nor chest pain duration was used to define the ROMICAT II population because their association with increased risk of ACS was relatively small and was offset by a loss of generalizability.

Patient demographics are listed in Table III. Overall, there was nearly equal representation of gender and significant representation of minorities. As expected, the observed ACS rate was ~7%, indicating that ROMICAT II is indeed a study of an intermediate-risk population.

Criteria for qualification of participating sites or referral laboratories include, for each modality: (1) use of standard equipment for usual care (single photon emission computed tomographic [SPECT] nuclear perfusion imaging, echocardiography, and exercise treadmill testing [ETT] as defined in current practice guidelines^{22–24} and 64-slice cardiac CT scanners); (2) technician expertise as defined by relevant certifying bodies for each test; (3) reader expertise defined as completed at least Core Cardiology Training level II training²⁵; (4) adequate clinical volume performed in the previous 12 months defined as >100 CT scans per year; and (5) adequate compatibility of image data storage and transfer in DICOM format.

The participating sites were Baystate Medical Center, Springfield, MA; Beth Israel Deaconess Medical Center, Boston, MA; Cleveland Clinic, Cleveland, OH; Kaiser Foundation Hospital, Fontana, CA; Massachusetts General Hospital, Boston, MA; Northwestern University Feinberg School of Medicine; Tufts Medical Center, Boston, MA; University of Maryland Medical Center, Baltimore, MD; Washington University, St Louis, MO. These sites are representative of US hospitals in the way they manage patients with acute chest pain.⁵ The sites represent different management settings for patients with acute chest pain, with 7 sites having a chest pain observation unit and 2 sites admitting patients to internal medicine floors. With Siemens Sensation 64 ($n = 2$), GE Lightspeed 64 VCT ($n = 2$), Siemens Definition 64 ($n = 1$), Siemens Definition Flash 128 ($n = 2$), Philips Brilliance 256 ($n = 1$), and Toshiba Aquillion One ($n = 1$). CT imaging equipment of all major vendors as well as several cardiac CT generations from single detector 64 slice CT ($n = 4$) and more advanced scanners ($n = 5$) are represented in ROMICAT II.

Diagnostic testing—Cardiac CT imaging was performed according to published guidelines²⁶ and consisted of a prospective gated low-dose noncontrast CT scan for the detection of coronary artery calcification (CAC) and contrast-enhanced cardiac CT for the detection of CAD. For CT angiography, both retrospective and prospective ECG gating were permitted, tube modulation was strongly encouraged with retrospective CT acquisition,

whereas assessment of left ventricular function and incidental findings is optional. Sites were required not to use the CAC results to influence their decision to proceed with the CT angiogram or their management of patients. The participating clinical sites perform routinely either SPECT nuclear perfusion imaging at rest ($n = 5$) and/or with stress ($n = 3$), and/or stress echocardiography ($n = 3$), and/or ETT ($n = 4$).

CCTA reader case review—All CCTA readers performed a review of 50 cardiac CCTA cases before the trial.

Implementation of measures to guarantee the principles of a comparative effectiveness trial

The ROMICAT II trial was designed to assess the comparative effectiveness of SOC, including functional testing, versus anatomical cardiovascular imaging with CCTA as 2 strategies to evaluate patients with acute chest pain and suspicion of ACS in the ED setting. A key feature of a comparative effectiveness trial is that the patient care in both arms is directed by local physicians according to the principles of good medical practice and not driven by protocol. It is understood that, in such a setting, it may not be possible to separate the influence of test results or test quality from the variability inherent in clinical decision making on the study outcome. However, to ensure generalizability of the study results across a broad range of clinical settings and to address the tension between observation of real-world patient management (effectiveness) and performing good medical practice (efficacy), the following procedures were implemented to ensure high-quality CT data.

The study takes advantage of the fact that CCTA is not a provocative stress test and can be performed even before myocardial ischemia or infarction has been definitively excluded. Enrollment of patients was performed during normal business hours (from 9 AM to 5 PM) on weekdays. Educational grand rounds were given to the participating departments at each site before the first patient enrollment to ensure familiarity with the trial and principles of management in both arms. In order for diagnostic testing and patient management to reflect good medical practice, recommendations for CT imaging and data on the relation of CT findings to outcomes in an ACS clinical setting were provided by the Clinical Coordinating Center (CCC). Thus, the only “intervention” in the trial was the randomization to whether CCTA was performed as the first diagnostic test. All subsequent care was left to the discretion of caregivers, including any downstream testing.

Trial funding and general structure

The ROMICAT trial (ClinicalTrials.gov ID: NCT01084239) was funded by the National Heart, Lung, and Blood Institute (NHLBI) as a Cooperative Agreement with the CCC and the Data Coordinating Center, both based at the Massachusetts General Hospital, but in separate departments. Seven clinical sites were initially funded via subcontracts from the CCC; 2 additional sites were added in the spring of 2011. An independent Data and Safety Monitoring Board was appointed by the NHLBI to monitor the trial. The study committees and imaging core laboratory as well as the participating centers are listed in the online Appendix.

Primary end point

The hypothesis central to ROMICAT II is that adding cardiac CT to the initial ED evaluation of subjects with acute chest pain significantly decreases LOS. Thus, the primary aim is to determine whether LOS is significantly reduced in the CT arm compared with SOC. The primary end point, *LOS*, is defined as the time from ED presentation to the time of discharge note or order. This includes time in the ED, time in any institution-specific specialized chest pain unit, and time as an inpatient. This end point was chosen because it

reflects the summary of actions taken in response to patient factors; test results; and logistic, cost, and medicolegal considerations in the participating hospitals.

Sample size, power determination, and sensitivity analysis

The primary end point of the study is the difference in mean LOS from ED presentation to hospital discharge between cardiac CT and SOC study arms. Based on the results of ROMICAT I, we estimated the mean ($\pm$ SD) hospital LOS of these patients in the SOC arm to be 40.5 ± 43.2 hours. The observed frequency distribution in ROMICAT I appeared to fit well to a log-normal distribution (median was 77 hours, and range was 2.75 to 381.5 hours). We anticipate that the observed distributions of both randomization arms will follow such a pattern. Because the independent-samples *t* test is robust to a departure from the data normality when applied to a large sample size, we will use the *t* test for this inference. We conducted a power evaluation using the estimated mean and SD based on ROMICAT I for the SOC arm and using the estimated mean and SD based on a simulated data for the CCTA arm. We predicted LOS in the CT arm based on the observed CT findings and the prevalence of ACS in each of these categories in ROMICAT I and on the assumed care that the patients would experience in these strata (Figure 2). Thus, LOS in the CT arm represents a mixture of 3 subsets randomly drawn from log-normal distributions: patients with normal left ventricular (LV) function and without CAD (prevalence: 48.6% of the population, LOS: mean $\pm$ SD of 6 ± 1.2 hours), patients with normal LV function and with nonobstructive CAD (prevalence: 28.8% of the population, LOS: mean $\pm$ SD of 10.1 ± 2.0 hours), and all other possible conditions (prevalence: 22.6% of the population, LOS: mean $\pm$ SD of 57.9 ± 60.4 hours) as estimated from ROMICAT I. We also incorporated possible ED triage accuracy rate assumptions. Table IV summarizes for each ED triage accuracy rate assumption, the estimated mean LOS, and the power at a type I error rate of 5% for an independent-samples *t* test using 500 patients in each arm. The proposed sample size provides sufficient power to detect a clinically meaningful difference in mean LOS between the 2 groups even if only 65% of our initial assumptions for LOS were correct; at which point, we still would be able to detect a difference in LOS of 8.7 hours with 86% power.

Secondary and tertiary end points

A major secondary end point was the comparison of health care cost in the 2 arms. To detect differences in the overall costs of CCTA versus standard ED evaluation, we collected actual cost data from the sites' cost-accounting databases. Costs derived in this manner reflect the actual use of resources more accurately than charges or reimbursements. Because these hospital databases do not account for the cost of physician time, the latter was estimated from regional Medicare reimbursement rates for professional charge codes billed. For sites where complete direct and indirect costs were not available, costs were estimated based on a regression analysis that accounted for length of stay, whether or not the patient was hospitalized and the type of tests conducted. Costs for additional testing and treatment within 28 days after initial ED presentation were based on patient self-report. We used the Medicare reimbursement associated with those services. All costs were converted to constant dollars (eg, 2011) using the medical component of the Consumer Price Index.

Other secondary end points were the cumulative radiation exposure, resource utilization, and cost of competing strategies. Tertiary end points included institutional, caregiver, and patient characteristics associated with primary and secondary outcomes. To determine the incremental value of CCTA over a low-radiation, noncontrast CT detecting CAC for early ED triage, the CAC results remained blinded to physicians and patients.

Safety considerations

Missed ACS diagnoses were the primary safety issue in this study. If, as demonstrated in ROMICAT I, none of the patients without CAD has an adverse event, defined as ACS within 48 hours after direct ED discharge, ROMICAT II has 90% power to ensure that the true missed ACS rate is <1%. These assumptions are supported by the results of the ERASE Chest Pain trial, which randomized patients with acute chest pain presenting to the ED to SOC of rest SPECT nuclear perfusion imaging. Missed ACS was a rare event in ERASE; only 2 of 2,475 patients (<0.1%) with a normal SPECT experienced a myocardial infarction.²⁷ Accordingly, in ROMICAT II, we had a very small chance of observing at least 1 inappropriately discharged patient (80% chance if the true rate of missed ACS was 1%). Clinical and serious adverse events were independently adjudicated by a Clinical Events Committee blinded to study arm. The study did not have stopping boundaries because in this trial all patients were managed according to current guidelines, so there was no ethical imperative to stop the trial.

Biomarker collection

In a subset of patients who presented to the ED within 0 to 6 hours after the onset of chest pain to the ED and agreed to partake in the biomarker substudy, we collected blood samples at 3 time points: (1) ED presentation, (2) 90 to 150 minutes after initial blood draw, and (3) 210 to 300 minutes after initial blood draw or at a minimum of 120 minutes between the second and the third blood draws or up until the time of discharge. The primary goal of this substudy is to determine whether initial or serial measurements of high sensitive troponin permits more efficient management of patients presenting with acute chest pain in the ED.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Discussion

ROMICAT II is a randomized, open-labeled comparative effectiveness diagnostic imaging trial designed to assess the effect of implementing CCTA early into the ED evaluation of patients presenting with acute chest pain. The primary end point of the trial was the LOS, which served as a summary measure of the effectiveness to manage patients safely in both arms. Secondary end points included cumulative radiation exposure, resource utilization, and cost of competing strategies. Tertiary end points included institutional, physicians, and patient characteristics associated with primary and secondary outcomes. Rate of missed ACS within 28 days was the safety end point. The framework of “comparative effectiveness” trials is only emerging, but a key difference from typical randomized phase III trials is the uncontrolled nature of patient management. Thus, emphasis in comparative effectiveness trials is to assess and acknowledge the nuances of the entire patient care process for this population, including patient, physician, and institutional characteristics. Thus, although we specified a primary end point, the data collection will permit us to evaluate the overall risks and benefits of these alternative diagnostic strategies within the rigorous setting of a randomized trial, with the sample size supported by power calculations for differences in each of the key effect measures.

Cardiac CT angiography is evolving into a mature imaging modality for assessment of CAD. The growing availability of CCTA in EDs across the United States not only expands the opportunities for its clinical application but also heightens the need to ensure that clinical practice is dictated by evidence-based medicine as repeatedly demanded by the Center for Medicare & Medicaid Services. Two previous randomized trials suggest that CCTA compares favorably to nuclear perfusion imaging in patients at very low risk for ACS

(respective fraction of patients with ACS: 0%¹⁵ and 1.7%¹⁷). However, selective performance of diagnostic testing may be most efficient in those very low-risk patients, given the cost and risks of CCTA. Under those considerations, ROMICAT II will provide novel data necessary to comprehensively assess the efficiency of CCTA including (1) comparing CCTA to all available management strategies including low-cost strategies such as ETT or even no testing; (2) studying a population at intermediate risk for ACS; (3) including sites that have reasonable experience in CCTA but have not used this modality to manage patients in the ED—thus providing a generalized assessment of CCTA in the ED; (4) clarifying whether CCTA is necessary or whether non-contrast assessment of CAC is sufficient; and (5) defining the association of site, physician, and patient characteristics (CCTA technology, CCTA experience, CCTA reader experience, academic vs community setting, predominantly used alternative test strategy, patient presentation and demographics) with primary and secondary outcomes—which is important to formulate recommendations for specific hospital settings or patient populations. In addition, we will be able to determine the value of information from an observational study to predict results of a randomized trial.

Although the descriptive cost comparison between the 2 study arms may indicate that adding cardiac CT to the SOC is associated with substantial cost-savings, a goal of this study is to provide data to health care policymakers and the authors of clinical guidelines regarding the appropriate use of cardiac CT in the ED setting. A formal, model-based cost-effectiveness analysis is planned to estimate costs and benefits from a broader perspective and longer time horizon by combining data from previous studies with the results from this study. Such an analysis will allow us to estimate the incremental cost-effectiveness of adding cardiac CT to the workup of patients presenting to the ED with suspected ACS and to compare cardiac CT not only to a combination of alternative “rule out” strategies, but also to each alternative imaging test separately.

ROMICAT II constitutes the largest randomized multi-center clinical trial using cardiac CT to date and will provide an unbiased assessment of the above stated hypotheses. It will be conducted by a group of experienced clinical researchers consisting of CT imagers, ED physicians and cardiologists with clinical expertise in the management of chest pain syndromes, epidemiologists, and experts in decision and economic analysis. The results from this trial will inform the clinical utility and cost-effectiveness of CCTA over the current available strategies in the ED setting and may lead to a change in the management of these patients on a nationwide level.

Conclusion

ROMICAT II was designed as a randomized, open-labeled comparative effectiveness diagnostic imaging trial. The primary goal of ROMICAT II is to determine whether CCTA is more efficient than SOC in the management of patients at intermediate risk for ACS presenting to the ED with acute chest pain. The trial design was based on ROMICAT I, a blinded observational study that permitted both modeling of the patient population and most end points in ROMICAT II. Results are expected to be available later this year.

References

1. McCaig LF, Nawar EW. National Hospital Ambulatory Medical Care Survey: 2004 emergency department summary. *Adv Data*. 2006; 372:1–29. [PubMed: 16841785]
2. Hollander JE, Sease KL, Sparano DM, et al. Effects of neural network feedback to physicians on admit/discharge decision for emergency department patients with chest pain. *Ann Emerg Med*. 2004; 44:199–205. [PubMed: 15332058]

3. McCaig LF, Burt CW. National Hospital Ambulatory Medical Care Survey: 2002 emergency department summary. *Adv Data*. 2004; 340:1–34. [PubMed: 15068333]
4. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. *JAMA*. 2005; 294:2623–9. [PubMed: 16304077]
5. Zalenski RJ, Rydman RJ, Ting S, et al. A national survey of emergency department chest pain centers in the United States. *Am J Cardiol*. 1998; 81:1305–9. [PubMed: 9631967]
6. 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. [PubMed: 18089704]
7. Leber AW, Johnson T, Becker A, et al. Diagnostic accuracy of dual-source multi-slice CT-coronary angiography in patients with an intermediate pretest likelihood for coronary artery disease. *Eur Heart J*. 2007; 28:2354–60. [PubMed: 17644815]
8. 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. [PubMed: 17084268]
9. Hoffmann U, Bamberg F, Chae CU, et al. Coronary computed tomography angiography for early triage of patients with acute chest pain—the Rule Out Myocardial Infarction Using Computer Assisted Tomography (ROMICAT) trial. *J Am Coll Cardiol*. 2009; 53:1642–50. [PubMed: 19406338]
10. Schlett CL, Banerji D, Siegel E, et al. Prognostic value of CT angiography for major adverse cardiac events in patients with acute chest pain from the emergency department: 2-year outcomes of the ROMICAT trial. *JACC Cardiovasc Imaging*. 2011; 4:481–91. [PubMed: 21565735]
11. Hollander JE, Chang AM, Shofer FS, et al. One-year outcomes following coronary computerized tomographic angiography for evaluation of emergency department patients with potential acute coronary syndrome. *Acad Emerg Med*. 2009; 16:693–8. [PubMed: 19594460]
12. Hollander JE, Chang AM, Shofer FS, et al. Coronary computed tomographic angiography for rapid discharge of low-risk patients with potential acute coronary syndromes. *Ann Emerg Med*. 2009; 53:295–304. [PubMed: 18996620]
13. Hollander JE, Litt HI, Chase M, et al. Computed tomography coronary angiography for rapid disposition of low-risk emergency department patients with chest pain syndromes. *Acad Emerg Med*. 2007; 14:112–6. [PubMed: 17267528]
14. 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. [PubMed: 17372178]
15. Goldstein JA, Gallagher MJ, O'Neill WW, et al. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *J Am Coll Cardiol*. 2007; 49:863–71. [PubMed: 17320744]
16. Goldman L, Cook EF, Johnson PA, et al. Prediction of the need for intensive care in patients who come to the emergency departments with acute chest pain. *N Engl J Med*. 1996; 334:1498–504. [PubMed: 8618604]
17. Goldstein JA, Chinnaiyan KM, Abidov A, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. *J Am Coll Cardiol*. 2011; 58:1414–22. [PubMed: 21939822]
18. 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. [PubMed: 10938172]
19. Pollack CV Jr, Sites FD, Shofer FS, et al. Application of the TIMI risk score for unstable angina and non-ST elevation acute coronary syndrome to an unselected emergency department chest pain population. *Acad Emerg Med*. 2006; 13:13–8. [PubMed: 16365321]
20. Chase M, Robey JL, Zogby KE, et al. Prospective validation of the thrombolysis in myocardial infarction risk score in the emergency department chest pain population. *Ann Emerg Med*. 2006; 48:252–9. [PubMed: 16934646]
21. Einstein AJ, Moser KW, Thompson RC, et al. Radiation dose to patients from cardiac diagnostic imaging. *Circulation*. 2007; 116:1290–305. [PubMed: 17846343]

22. Henzlova MJ, Cerqueira MD, Mahmarian JJ, et al. Stress protocols and tracers. *J Nucl Cardiol.* 2006; 13:e80–90. [PubMed: 17174798]
23. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol.* 2002; 40:1531–40. [PubMed: 12392846]
24. Pellikka PA, Nagueh SF, Elhendy AA, et al. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr.* 2007; 20:1021–41. [PubMed: 17765820]
25. Thomas JD, Zoghbi WA, Beller GA, et al. ACCF 2008 Training Statement on Multimodality Noninvasive Cardiovascular Imaging A Report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training Developed in Collaboration With the American Society of Echocardiography, the American Society of Nuclear Cardiology, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society for Vascular Medicine. *J Am Coll Cardiol.* 2009; 53:125–46. [PubMed: 19118732]
26. Abbara S, Arbab-Zadeh A, Callister TQ, et al. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr.* 2009; 3:190–204. [PubMed: 19409872]
27. 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. [PubMed: 12460092]
28. Seneviratne SK, Truong QA, Bamberg F, et al. Incremental diagnostic value of regional left ventricular function over coronary assessment by cardiac computed tomography for the detection of acute coronary syndrome in patients with acute chest pain: from the ROMICAT trial. *Circ Cardiovasc Imaging.* 2010; 3:375–83. [PubMed: 20484542]

Appendix

ROMICAT II Clinical Investigators

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Figure 1.
ROMICAT II study design.

Figure 2.

Projected LOS for ROMICAT II based on CT findings of CAD and LV function and prevalence of ACS in the ROMICAT I study.⁹ The projections were based on 356 patients with CT coronary and functional data sets from ROMICAT I study (12/368 patients had incomplete LV functional data sets and were excluded in the model).²⁸ ROMICAT I was an observational study in which CT results were used to project the length of stay based on assumptions of patient management related to the CT findings. These data informed sample size and power calculation for the primary end point in the ROMICAT II trial.

Table I**Inclusion and exclusion criteria****Inclusion criteria**

Participant must have at least 5 min of chest pain or equivalent (chest tightness; pain radiating to left, right, or both arms or shoulders, back, neck, epigastrium, jaw/throat; or unexplained shortness of breath, syncope/presyncope, generalized weakness, nausea, or vomiting thought to be of cardiac origin) at rest or during exercise within 24 h of ED presentation, warranting further risk stratification, as determined by an ED attending.

Participant must be able to provide a written informed consent.

Participants must be <75 years old, but ≥40 years old.

Participant must be able to hold breath for at least 10 s.

Participant must be in sinus rhythm.

Exclusion criteria

New diagnostic ischemic ECG changes (ST-segment elevation or depression >1 mm or T-wave inversion >4 mm) in >2 anatomically adjacent leads or left bundle-branch block.

Documented or self-reported history of CAD (MI, PCIs, CABG, known significant coronary stenosis [≥50%]).

>6 h since presentation to ED to time of consent.

Body mass index >40 kg/m².

Impaired renal function as defined by local SOC—eg, measured serum creatinine >1.5 mg/dL.

Markedly elevated troponin as defined by local SOC.

Hemodynamically or clinically unstable condition (BP systolic <80 mm Hg, atrial or ventricular arrhythmias, persistent chest pain despite adequate therapy).

Known allergy to iodinated contrast agent.

Currently symptomatic asthma.

Documented or self-reported cocaine use within the past 48 h (acute).

On Metformin therapy and unable or unwilling to discontinue for 48 h after the CT scan.

Contraindication to β-blockers (taking daily antiasthmatic medication): This exclusion only applies to patients with a heart rate >65 beats/min at sites using a nondual source CT scanner.

Participant with no telephone or cell phone numbers (preventing follow-up).

Participant with positive pregnancy test. Women of childbearing potential, defined as <2 years of menopause in the absence of hysterectomy or tube ligation, must have a pregnancy test performed within 24 h before the CT scan.

Participant unwilling to provide a written informed consent.

BP, Blood pressure; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass graft.

Table II

Usefulness of coronary risk factors and other variables from ROMICAT I to identify a population at intermediate risk for ACS

	No ACS (n = 337)	ACS (n = 31)	P
Diabetes	35 (10.4%)	5 (16.1%)	.33
Hypertension	125 (37.1%)	20 (64.5%)	.003
Hyperlipidemia	117 (34.7%)	18 (58.1%)	.01
Family history of CAD	80 (23.7%)	9 (29.0%)	.13
Current smoking	88 (26.1%)	5 (16.1%)	.28
Summed risk			
1 risk factor	244 (72.4%)	27 (87.1%)	.08
2 risk factor	134 (39.8%)	20 (64.5%)	.01
3 risk factors	51 (15.1%)	10 (32.3%)	.01
4 risk factors	14 (4.2%)	0 (0.0%)	.62
5 risk factors	2 (0.6%)	0 (0.0%)	1.0
Duration of most recent CP [*]	120.0 (20.0, 240.0)	60.0 (20.0, 150.0)	.31
CP on arrival to ED	241 (72.2%)	19 (61.3%)	.22
Time of symptoms to ED [*]	3.23 (1.57, 9.87)	3.00 (1.23, 7.95)	.33

Summed risk includes diabetes, hypertension, hyperlipidemia, family history of CAD, and current smoking. *CP*, Chest pain.

^{*} Median because time is not normally distributed.

Table III

Demographics of the overall ROMICAT II study population

Demographics	N = 1000
Age (y, mean $\pm$ SD)	54.2 $\pm$ 8
Female gender	46.8%
Race	
African American	28.2%
White	66.0%
Asians	3.1%
Others	3.0%
Ethnicity	
Hispanic (n, %)	12.7%
ACS	7.6%

Table IV

Powers to detect estimated differences in mean LOS values at assumed ED triage accuracy rates (type 1 error rate 0.05)

Accuracy rate for assumptions of LOS based on CT results in ROMICAT I	Estimated mean ($\pm$ SD) LOS		Estimated difference in mean (h)	Power
	SOC n = 500	CT evaluation n = 500		
60%	40.5 ($\pm$ 43.2)	34.0 ($\pm$ 47.1)	-6.5	62%
65%	40.5 ($\pm$ 43.2)	32.8 ($\pm$ 46.7)	-8.3	83%
70%	40.5 ($\pm$ 43.2)	30.5 ($\pm$ 45.5)	-10.1	95%
80%	40.5 ($\pm$ 43.2)	26.3 ($\pm$ 41.7)	-14.2	99%
90%	40.5 ($\pm$ 43.2)	22.4 ($\pm$ 37.3)	-18.1	>99%
100%	40.5 ($\pm$ 43.2)	18.8 ($\pm$ 33.5)	-21.7	>99%

Accuracy rates reflect the expected/projected adherence to assumptions made about the LOS in each group of CT findings. Data from ROMICAT I.⁹