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Cardiac risk factors and risk scores vs cardiac computed tomography angiography: a prospective cohort study for triage of ED patients with acute chest pain.

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**Cardiac Risk Factors and Risk Scores versus Cardiac CTA
for Triage of Low and Intermediate Risk Patients with
Acute Chest Pain**

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Abstract

Objective: To evaluate cardiac risk factors and risk scores for prediction of coronary artery disease (CAD) and adverse outcomes in an emergency department (ED) population judged to be at low to intermediate risk for acute coronary syndrome (ACS).

Methods: This prospective study was approved by the institutional review board. Written informed consent was obtained from consecutive ED patients who presented with chest pain and were evaluated with coronary CTA (cCTA). Cardiac risk factors, clinical presentation, ECG and laboratory studies were recorded; TIMI and GRACE scores were tabulated. cCTA findings were rated on a 6 level plaque burden scale and classified for significant CAD (stenosis \geq 50%).

Adverse cardiovascular outcomes were recorded at 30 days.

Results: Among 250 patients evaluated by cCTA, 143 (57%) had no CAD, 64 (26%) demonstrated minimal plaque (<30% stenosis), 26 (10%) demonstrated mild plaque (<50% stenosis), 9 (4%) demonstrated moderate single vessel disease (50-70% stenosis), 2 (1%) demonstrated moderate multivessel disease and 6 (2%) demonstrated severe disease (>70%

stenosis). Six patients developed adverse cardiovascular outcomes. Among traditional cardiac risk factors, only age (older) and sex (male) were significant independent predictors of CAD. Correlation with CAD was poor for TIMI ($r=0.12$) and GRACE ($r=0.09-0.23$) scores. cCTA identified severe CAD in all subjects with adverse outcomes.

Conclusion: Among ED patients who present with chest pain judged to be at low to intermediate risk of ACS, traditional risk factors are not useful to stratify risk for CAD and adverse outcomes. cCTA is an excellent predictor of CAD and outcome.

Introduction

The National Ambulatory Medical Care Survey demonstrates an increasing number of patients presenting annually to the emergency department (ED) with acute chest pain.¹ Chest pain was the principal reason for over 7 million ED visits in 2009.² As admission of chest pain patients to a coronary care unit is not cost effective,³ observation units have been created to improve care and to reduce hospital admissions.⁴ The current practice of observation and diagnostic testing of ED chest pain patients results in billions of dollars in annual medical costs.

Initial assessment of the ED patient with chest pain begins with the medical history, evaluation of cardiac risk factors and assessment of symptoms. The electrocardiogram (ECG), physical examination and cardiac biomarkers may identify higher risk patients. Risk scoring systems – including the Thrombolysis in Myocardial Infarction (TIMI)⁵ and Global Registry of Acute Coronary Events (GRACE)⁶ scores – have been validated to confer additional important prognostic value.⁷ Triage is often based upon myocardial perfusion imaging⁸ or other forms of stress testing.⁹ A scientific statement of the American Heart Association (AHA) supports expedited management of low-risk chest pain patients by combining clinical and laboratory assessments with a confirmatory stress test as “safe, accurate and cost-effective”.¹⁰

Conventional standard of care for ED chest pain patients results in a documented miss rate of 2-5% for acute coronary syndrome (ACS).^{11,12} Missed ACS and subsequent heart attacks account for 20-39% of all ED malpractice judgments.¹³ Several randomized trials have suggested that coronary CT angiography (cCTA) may be more effective than stress testing for evaluation of low-risk chest pain in the ED.^{14,15} Three randomized multicenter trials have recently confirmed cCTA as a safe and cost-effective diagnostic test to discharge low-risk chest pain patients.^{16,17,18}

These randomized multicenter studies have opened the possibility of widespread cCTA testing for low risk ED patients presenting with chest pain, though the utility of such testing depends upon the pre-test probability of disease.¹⁹ Many practicing physicians remain convinced that accurate evaluation of traditional risk factors and clinical presentation can be used for triage of the low risk ED patient and to limit the number of ED patients who should be referred for cCTA. The purpose of the current study was to evaluate individual conventional cardiac risk factors, as well two widely accepted risk scores - TIMI and GRACE - for prediction of coronary artery disease (CAD) and adverse outcomes in an ED population judged to be at low to intermediate risk for ACS.

Materials and Methods

This HIPPA compliant clinical protocol was approved by the university institutional review board. Written informed consent was obtained from each participant prior to enrollment in the study. The study was conducted over a 36 month period from August 2009 through July 2012 on consecutive patients who presented to the ED with chest pain or similar symptoms that might represent an anginal equivalent, and who were admitted to the observation unit and evaluated with coronary CTA (cCTA).

Study Population

The study population included patients presenting to the ED with a chief complaint of chest pain, shortness of breath, syncope or near syncope, or pain radiating to the neck, shoulder, back, or arm and not appearing to be musculoskeletal in nature. Each patient underwent electrocardiography and initial myoglobin and troponin I levels. By agreement with the ED physicians, cCTA was only obtained on patients who they deemed to be at low to intermediate risk of ACS after initial clinical and ECG assessment, and who would otherwise be evaluated with a stress echocardiogram or nuclear perfusion stress test. Patients who were considered high risk for ACS based upon clinical presentation, ECG changes (with clear ST segment elevation or depression) or biomarkers (elevated troponins) were admitted to the hospital or sent directly for cardiac catheterization. Patients with a history of a prior revascularization procedure (bypass surgery or angioplasty \pm stent) were excluded. Patients whose pain was deemed non-cardiac or whose estimated GFR was below 60ml/min were excluded. The remaining low to intermediate risk patients were included in the study whenever dedicated cardiac time on the CT scanner was available within 12 hours of presentation.

History & Laboratory Data Collection

In order to prospectively collect information on study participant risk factors, a co-investigator who was not involved in performance of the cCTA and who was not involved in the care of the patient interviewed each patient with a standard structured questionnaire. This questionnaire was developed in consultation with our cardiologists and ED chest pain division to provide a complete, succinct description of the presenting complaint and cardiac risk factors that could be used for statistical analysis. Chest pain was described by location, character (sharp, aching, burning, tearing, crushing or pressure), radiation (to left arm, jaw/neck, back, right arm, or other), severity (1-10 scale), number of episodes and duration of pain. Patients were asked if pain was exacerbated by exertion or emotional stress. Associated symptoms were recorded. Risk factor evaluation included history of hypertension, hyperlipidemia, diabetes, smoking, prior myocardial infarct, history of known coronary disease, and family history of coronary disease. Medications were recorded and patients were specifically asked about aspirin usage in the previous 7 days. Patient laboratory studies obtained in the ED were reviewed for hyperlipidemia and elevation of troponins. The 12-lead ECG obtained during ED presentation was reinterpreted for study purposes by a cardiology co-investigator. The ED physical examination record was reviewed for body mass index, blood pressure and Killip classification.

Cardiovascular Risk Scores

The TIMI and GRACE risk scores are commonly used for risk assessment among symptomatic patients with ACS or suspected ACS. For the purpose of this study, an excel spreadsheet was constructed to compute both the TIMI and GRACE scores of our study patients based upon their history and risk factors.

The TIMI score consists of seven clinical variables with one point given for each condition met. The seven parameters include: age 65 years or older, the presence of at least 3 risk factors for coronary artery disease, a history of prior coronary stenosis greater than or equal to 50%, use of aspirin in the previous 7 days, severe angina defined as experiencing at least 2 episodes of angina within the past 24 hours, ST-segment deviation of at least 0.5mm on ECG, and the presence of elevated serum cardiac markers. A patient's TIMI score can easily be calculated during routine clinical evaluation and often serves as the basis for making future medical decisions and obtaining additional medical studies. Details of the TIMI scoring system and a TIMI risk score calculator are available on-line at www.timi.org.

The GRACE score is an alternative risk score to predict outcomes among patients presenting with ACS. The GRACE model utilizes various parameters including a patient's age, Killip class, systolic blood pressure, heart rate, creatinine level, the presence of cardiac arrest on admission, ECG changes (definition is different than the TIMI criteria; ST-segment deviation must be at least 1mm), and elevated serum cardiac markers to generate four probabilities: the probability of death in the hospital and at 6 months from the time of hospital admission, as well as the probability of death or MI in the hospital and at 6 months from the time of hospital admission. In contrast to the TIMI scores, the GRACE score is more complicated to compute and requires use of a calculator. Details of the GRACE scoring system and a GRACE risk score calculator are available on-line at www.outcomes-umassmed.org/grace.

TIMI and GRACE scores were computed based upon the collected data. For the purpose of TIMI and GRACE scores, the ECG recorded in the ED at the time of presentation was reinterpreted by a co-investigator (who is a third year cardiology fellow) using TIMI and GRACE criteria. As many of our patients complained of atypical chest pain or continuous chest

pain for an extended duration, we contacted the TIMI study group for clarification regarding the definition of severe anginal symptoms. The presence of continuous chest pain over a long interval was tabulated as multiple episodes for the purpose of the TIMI score (personal communication with Dr. Elliott Antman). Four sets of GRACE scores were calculated, including in-hospital and 6 month scores for death and for death/infarction. These research questionnaires, as well as the TIMI and GRACE scores, were not viewed by the ED physicians caring for the patients or by the physician who interpreted the cCTA.

CT Scan Protocol

Imaging was performed with a 256-MDCT scanner (Brilliance iCT, Philips Medical Systems). Patients with initial heart rates greater than 60 beats/minute were treated with intravenous metoprolol (5-20 mg) to a target heart rate of 50-60 beats/minute. Sublingual nitroglycerin spray (800 µg) was administered 2-3 minutes before scanning. Metoprolol was not given to patients with a history of active asthma within the past 30 days or to those with a history of recent cocaine use. The dose of metoprolol was limited to 10mg for any patients with a history of asthma. Blood pressure was monitored continuously during premedication, and no further premedication was administered when systolic pressure fell below 100mmHg.

A biphasic injection protocol was used with 60 ml of ioversol (Optiray 350, Mallinckrodt Imaging) followed by 30ml of ioversol mixed with 30ml of 0.9% saline solution, injected at a 5-6 ml/s. Prospective ECG-triggering with axial imaging was used in patients with a stable cardiac rhythm and heart rate \leq 60 beats per minute. Retrospective gating with helical imaging and tube current modulation was used in the remaining patients. Tube voltage was set to 120 kVp. For prospective axial scans, tube current was set at 60-100mAs based upon patient size. Estimated effective biological dose for patients scanned with prospective ECG-triggering was 4mSv,

assuming a 12cm scan length and a normalization factor of $0.017\text{mSv} \times \text{mGy}^{-1} \times \text{cm}^{-1}$ for the adult chest.²⁰ For helical scans tube current was generally set at 600 mAs/slice, but was increased to 800 or 1000mAs/slice for obese patients. Estimated mean biological dose for patients scanned at 600mAs/slice was 6mSv, assuming a 12cm scan length. Imaging was initiated by a dynamic bolus monitoring program which was triggered by contrast enhancement in the left atrium. The CTA was performed during a single breath hold.

CT Image Analysis

Reconstructed images of the coronary arteries were evaluated by two experienced cardiac radiologists with experience interpreting over 3000 cCTA cases. Disagreements between the two radiologists were resolved by consensus discussion. Slab maximum intensity projection (MIP) images were obtained with 5mm slice thickness and rotated in various planes to best visualize any area of stenosis in all coronary segments. For any patient with evidence of stenosis, a tracked reconstruction of the coronary arteries was performed to allow evaluation with a curved multiplanar image and a straightened lumen view (comprehensive cardiac package software; Philips Brilliance workstation. See Figure 1). Each coronary artery segment was rated as normal, minimal disease (<30% stenosis), mild disease (<50% stenosis), moderate disease (50-70% stenosis), or severe disease (>70% stenosis). Based upon these ratings, each cCTA study was classified on a 6 level plaque burden scale (0 = no plaque, 1 = minimal disease with <30% stenosis, 2 = mild disease with <50% stenosis, 3 = moderate single vessel disease with 50-70% stenosis, 4 = moderate multivessel disease, and 5 = severe disease with >70% stenosis).

Outcomes & Clinical Follow-up

For the purpose of this study, a positive cardiac outcome was defined as confirmed ACS or myocardial infarction, coronary revascularization or cardiac related death within 30 days. A co-investigator attempted to obtain a telephone follow-up on each patient at 30 days following the cCTA. If there was no answer or the patient was unavailable, additional follow-up calls were made in an attempt to reach the patient for up to one year after the cCTA. For those patients who could not be reached by telephone, hospital medical records were searched for follow-up information including subsequent admissions to the hospital, cardiac events, or revascularization. Although the primary endpoint was to identify adverse outcomes at 30 days, in a minority of patients this follow-up data was obtained from telephone conversations or medical records that were recorded up to 1 year after the cCTA.

Statistical Analysis

Based upon prior experience with cCTA at our institution, we expected to define significant CAD with $\geq 50\%$ stenosis in approximately 10% of our low to intermediate risk ED patients, with adverse outcomes in no more than 2%. As the number of expected adverse outcomes was very small, the study was powered to identify risk factors that might improve the prediction of CAD and allow direct triage of these patients without cCTA. Based upon cost-effectiveness considerations, further non-invasive testing for CAD is unlikely to be cost effective when the probability of significant CAD drops below 1% or rises close to 50%.¹⁹ Power calculations were performed assuming a two sample comparison of proportions using a two-sided test with an alpha of 0.05. For a risk factor present in 50% of the study population, a sample size of 250 is calculated to provide 80% power to detect a reduction in CAD rate from

10% to 1%, and 85% power to detect an increase in CAD rate above 25%. For a risk factor that is present in only 20% of the study population, a sample size of 250 is calculated to provide a power of 70% to detect an increase in CAD rate above 25%, and 88% power to detect an increase in CAD rate above 30%.

Statistical analysis was performed by using Stata software (version 12.0, StatCorp). Two sets of dependent variables were used in the analysis, the presence of coronary disease on cCTA and the clinical follow-up outcome data. For the purpose of evaluating the predictive value of risk factors on the presence of coronary disease, significant coronary disease was defined as $\geq 50\%$ stenosis in at least one vessel (a score ≥ 3 in our grading system). In order to determine whether cCTA was predictive of adverse cardiac outcomes, we cross-tabulated the outcome data with the presence of disease on cCTA.

Univariate analysis: Pearson's correlation coefficients were computed to evaluate correlation of TIMI and GRACE scores with the presence of CAD as demonstrated by cCTA. A chi square test was performed to test the association of binary risk factors (sex, hypertension, hyperlipidemia, diabetes, smoking, etc) with the presence of coronary disease or an adverse cardiac outcome. Logistic regression was used to calculate the odds ratio for the association of binary and continuous risk factors (age, body mass index, severity of pain, TIMI score, GRACE score) with the presence of significant CAD. When multiple categories of a single risk factor were present, as is the case for character of chest pain and radiation of chest pain, an odds ratio was computed for each individual category (ie chest pressure, tightness, etc).

Multivariate analysis: For those risk factors which were found to be significant in the univariate analysis, multivariate logistic regression was performed to determine which of these

risk factors provided independent significant predictive power for CAD. TIMI and GRACE scores were included in a further multivariate analysis to determine whether they provided additional predictive information. A value of $p < 0.05$ was considered statistically significant for all statistical analyses.

Results

cCTA studies were obtained on 250 patients evaluated during the study. Demographics of the study population, tabulation of risk factors and odds ratios for prediction of CAD are reported in Table 1. Over half the patients sent for cCTA had no visible coronary plaque (n=143; 57% of subjects). Minimal plaque was present in 64 patients (26%), mild plaque in 26 patients (10%), moderate single vessel disease was present in 9 patients (4%), moderate multivessel disease was present in 2 patients (1%) and severe plaque in 6 patients (2%). For the purposes of our analysis, 17 patients were classified as having significant CAD (stenosis \geq 50%).

Among traditional risk factors, only age (older), sex (male) and hypercholesterolemia were significant predictors of CAD in the univariate analysis (Table 1). The mean age of patients with significant CAD (58.7 years) was significantly greater than the mean age of patients without significant CAD (50.4 years). Other factors including diabetes, hypertension, hypertension on medication, family history, smoking history, history of prior infarction, character of chest pain, radiation of chest pain (to the arm, neck/jaw or back), and severity of chest pain were not significant predictors of CAD. On multivariate analysis, hypercholesterolemia was correlated with age, but was not a significant independent predictor of CAD. Age and sex continued to be significant predictors on multivariate analysis. Of note, 5 of the 7 patients who claimed to have a history of prior myocardial infarction demonstrated no evidence of CAD, and the other 2 had CAD with less than 50% stenosis on cCTA. Although reinterpretation of the presenting ECG studies by our cardiology co-investigator demonstrated an abnormal result in 17 patients based upon TIMI criteria and 7 patients based upon GRACE criteria (Table 1), only 1 patient with an abnormal ECG result demonstrated significant CAD.

Table 2 tabulates the association of TIMI scores, which varied from 0-5, with the presence of significant CAD on cCTA. Of note, 15/16 patients with coronary stenosis \geq 50% had a TIMI score \leq 2, while 30/31 patients with a TIMI score \geq 3 had no significant coronary stenosis. Table 3 presents the

Pearson correlation coefficients between risk scores (TIMI and GRACE) and the cCTA grade of CAD, demonstrating only a weak correlation between risk score and plaque burden. Although TIMI and GRACE scores were significantly correlated with each other, the r-values for the correlation of TIMI with the various GRACE scores were in the range of 0.24-0.31 ($p < 0.001$).

The data in tables 1, 2 and 3 demonstrate that many patients in our study with significant coronary disease on cCTA are missed by traditional risk factor and/or risk score assessment. Furthermore, a majority of patients with the more elevated TIMI and GRACE scores in this study were, in fact, free of coronary disease. Logistic regression of TIMI scores for prediction of significant CAD with stenosis $\geq 50\%$ failed to demonstrate a significant association. Logistic regression of GRACE scores for prediction of CAD with stenosis $\geq 50\%$ did demonstrate a significant association, but the odds ratio was in the range of 1.01-1.03, suggesting weak predictive ability. Furthermore, when any of the GRACE scores was combined with patient age and sex in a multivariate logistic analysis, the GRACE score did not provide additional predictive power for significant CAD (odds ratios = 0.98-0.99; $p \geq 0.4$).

Follow-up clinical data were obtained in 221/250 patients, demonstrating 6 adverse cardiovascular events within 30 days. The 6 events included 2 patients with confirmed ACS, 2 patients with myocardial infarction, and 2 patients who required revascularization (1 with coronary bypass surgery and 1 with a stent). All 6 adverse cardiovascular events occurred in patients with severe CAD identified by cCTA (cCTA grade = 5). Although 5/6 patients with adverse events were either hypertensive or diabetic and 2/6 did complain of exacerbation of chest pain with exertion, all 6 adverse cardiovascular events occurred in patients with a TIMI score ≤ 2 (Table 4). Among the 31 patients with TIMI scores ≥ 3 , none experienced an adverse cardiovascular event on 30 day follow-up. Although all patients who experienced adverse cardiovascular events did have at least one cardiac risk factor, these risk factors were commonly found among patients who did not suffer adverse events, and were not sufficiently specific to triage patients for discharge versus further observation/evaluation.

Discussion

Our study confirms the ability of cCTA to predict which patients are at risk for adverse cardiovascular events, as all patients who had an adverse event by 30 days demonstrated the presence of severe CAD on cCTA. Our data also support the conclusion that it is safe to discharge a patient with a normal cCTA or a cCTA showing less than 50% stenosis, as no adverse outcomes were documented in the 233 patients with less than 50% coronary stenosis. Furthermore, among conventional criteria used to risk stratify coronary disease, only increasing age and male sex were independent predictors of significant CAD. This finding is concordant with the landmark publication on the probability of CAD by Diamond and Forrester which defined the pre-test likelihood of disease based upon age, sex and presentation of symptoms.²¹ Finally, our data suggest that other commonly employed risk factors are poor predictors for the presence of CAD in ED patients, and should not be used to triage low to intermediate risk patients away from cCTA. These findings are concordant with those of the ROMICAT trial subanalyses that demonstrate only “modest” discriminatory capacity of the Goldman, Sanchis and TIMI risk scores for the diagnosis of ACS, as compared with “good” discriminatory capacity for plaque burden on cCTA.^{22,23}

Why were the remaining traditional risk factors for CAD and risk scores for adverse outcomes not useful in this low to intermediate risk chest pain population? Numerous studies have validated the application of TIMI and GRACE risk scores to predict patient outcome in the setting of ACS.²⁴ For patients presenting to the ED with potential ACS, TIMI and GRACE are the most commonly used scores for risk stratification, with receiver operating characteristic curve (ROC) areas of 0.757 and 0.728 respectively for the prediction of 30-day event rates.²⁵ A comparison of TIMI, GRACE and PURSUIT scores concluded that all three risk scores

demonstrated “good predictive accuracy for death or myocardial infarction at 1 year, and enabled the identification of high-risk subsets of patients who will benefit most from myocardial revascularization performed during initial hospital stay.”²⁶

So why did these risk scores fare poorly in our study of patients who presented to the ED with potential ACS? Firstly, we should note that the ROC areas of 0.757 and 0.728 cited above do not suggest excellent predictive value. Furthermore, the comparison of TIMI, GRACE and PURSUIT cited above with “good predictive accuracy” reports ROC areas of 0.551-0.585 for TIMI and 0.672-0.715 for GRACE.

An additional explanation for the poor performance of TIMI and GRACE scores in our study is likely related to the patient population. For patients with confirmed ACS, TIMI and GRACE scores have been validated to predict outcome and distinguish patients who may benefit most from therapy, but no risk score has been validated for identification of ACS in the ED setting.²⁷ The low to intermediate risk ED chest pain population is very different from the clinical trial and registry settings of ACS patients in which the TIMI and GRACE scores were developed. Furthermore, although three vessel and left main disease are more common in ACS patients with TIMI scores of 3-4 as compared to patients with TIMI scores of 0-2, significantly more single vessel disease may be present in ACS patients with TIMI scores of 0-2 as compared with those of scores 5-7.²⁸ It is likely that the ACS patients who are most commonly seen in the ED are those with single vessel disease and lower risk scores rather than those with extensive CAD and higher risk scores. Our data underscore the importance of risk model validation in an appropriate target population rather than a clinical trial population to establish its generalizability before integration into clinical practice.²⁹

So how can we best expedite management of the low to intermediate risk patient who presents to the ED with chest pain? Patients who present with chest pain that can be attributed to a non-cardiac cause should require no further cardiac testing. Patients who appear to be at high risk for ACS based upon typical anginal symptoms, ECG findings and biomarkers should be referred for cardiac catheterization. However, the remaining large group of low to intermediate risk patients with atypical chest pain cannot be easily stratified by risk factors and scores. As noted in the introduction, randomized trials have demonstrated excellent negative predictive value for cCTA in evaluation of patients presenting to the ED with chest pain, and have suggested that cCTA may be more cost-effective than traditional stress testing for rapid discharge of these ED chest pain patients.¹⁴⁻¹⁸ Another significant advantage of cCTA over stress testing is the ability to assess simultaneously for non-cardiac etiologies of chest pain in the mediastinum, lungs and chest wall. In appropriate clinical situations where both cardiac and non-cardiac vascular causes of chest pain are suspected, a “triple rule-out” CTA study can evaluate the aorta, coronary arteries and pulmonary arteries and expedite discharge of up to 75% of patients presenting to the ED with atypical chest pain.^{30,31}

A recent editorial in the New England Journal of Medicine critiqued the use of cCTA for low risk ED patients citing the “Choosing Wisely” campaign for diagnostic testing, and declared: “The underlying assumption ... is that some diagnostic test must be performed before discharging these low-to-intermediate-risk patients from the emergency department. This assumption is unproven and probably unwarranted”.³² This editorial appears to oppose the recommendations of the 2010 AHA scientific statement that supports expedited management of low-risk ED chest pain patients by combining clinical assessment with a confirmatory diagnostic test to exclude ischemia as “safe, accurate and cost-effective”.¹⁰ Our study suggests that it would

be unwise to discharge low to intermediate risk ED patients on the basis of risk factors and scores without confirmatory testing, as cCTA did identify a small percentage of patients with significant CAD ($17/250 = 6.8\%$) and 30 day adverse events ($6/221 = 2.7\%$) who might not otherwise be detected based upon clinical presentation to the ED. It is also unlikely that our ED physicians would be willing to discharge low to intermediate risk patients when missed CAD/ACS and subsequent heart attacks account for 20-39% of all ED malpractice judgments.¹³ A recent analysis by the Physician Insurers Association of America states "Between 1985 and 2012, the third most common patient condition for which claims were filed against emergency physicians were Acute Myocardial Infarctions (AMIs) . . . Claims involving AMIs resulted with an indemnity payment 52% of the time with an average payment of \$261,856".³³

Several limitations of our study design should be noted. The accuracy of risk factor assessment depends upon accurate recording of risk factors, and patients are often uncertain of their own history or unable to adequately explain their symptoms. This uncertainty is illustrated by the 7 patients who claimed to have had a prior myocardial infarction, but who had no significant coronary disease on cCTA. Furthermore, clinical history and risk factor assessment is often quite variable in the ED setting. For the current study, we attempted to address this issue by prospectively interviewing all patients with a standardized history and risk factor questionnaire that included all standard risk factors as well as all data needed to compute TIMI and GRACE risk scores. This questionnaire was based upon an existing chest pain assessment form which was modified after discussions with our cardiologists and ED observation unit physicians, and expanded to incorporate additional information required for TIMI and GRACE scores. When there was uncertainty regarding a risk factor, we checked back with the medical records and ED chart. With respect to the follow-up data, we initially wanted to collect all follow-up data at 30

days. However, because we were unable to contact many patients within this time interval, the telephone follow-up period was expanded to increase the follow-up rate, and additional follow-up was obtained from medical records. Nonetheless, 30 day follow-up data could not be obtained for 29 patients, representing 11.6% of the patients involved in the study. Furthermore, although 30 day follow-up data should be sufficient to demonstrate the safety of ED discharge, this short term follow-up is not sufficient to demonstrate the long-term prognostic utility of cCTA. Finally, as the focus of this study was upon CAD and cardiovascular outcomes, the 30 day follow-up was focused upon cardiac events but we did not tabulate the non-cardiac pathology detected by cCTA, nor did we obtain follow-up for non-cardiac adverse events.

The low rate of adverse outcomes among ED patients is a limitation for statistical analysis of the risk factors, and might interfere with detection of statistically significant risk factors. Considering those variables with odds ratios > 1.5 in table 1, it is possible that a larger study population would have found statistical significance in the risk factors of hypertension, diabetes, a description of tearing chest pain, and exacerbation of chest pain with exertion. Nonetheless, our outcome results demonstrate that these risk factors did not have good discriminating ability for the limited number of adverse cardiovascular outcomes in our study population. In order to improve our statistical power to demonstrate significant risk factors, we chose to analyze the predictive value of traditional cardiac risk factors and risk scores for both CAD and clinical outcomes. Some degree of CAD was present in 43% of the study population, and significant CAD with greater than 50% stenosis was present in 7% of the study population. Since the development of ACS requires the presence of underlying coronary disease, CAD is reasonable as a proxy marker for potential future development of an adverse cardiovascular event.

Despite these limitations, our data demonstrate that among patients who present to the ED with chest pain and are assessed to be at low to intermediate risk of ACS, traditional risk factors, TIMI and GRACE scores do not predict plaque burden on cCTA or adverse cardiovascular outcomes. cCTA is an effective strategy to triage these patients, but risk factors cannot be used to decide which patients should have cCTA in the low to intermediate risk group seen in our ED. Specifically, cCTA identified patients with significant CAD who would be missed by evaluation of risk factors, TIMI and GRACE scores. cCTA expedited the discharge of over 75% of patients – even those with higher risk scores - based upon normal or minimal disease in the coronary arteries. In conclusion, for a patient who presents to the ED with chest pain and is assessed to be at low to intermediate risk of ACS, cCTA is an appropriate diagnostic study and is superior to clinical assessment by risk factors and risk scores for patient triage.

Figure caption:

Figure 1. Coronary artery grading system for stenosis, demonstrating curved multiplanar and straightened lumen views of the left anterior descending artery (LAD) in 6 patients.

- A. Normal LAD
- B. Minimal disease (arrow) with <30% stenosis.
- C. Mild disease (arrow) with <50% stenosis.
- D. Moderate disease (arrow) with 50-70% stenosis.
- E. Severe disease (arrow) with >70% stenosis. Follow-up: treated with stent, symptoms resolved.
- F. Severe disease (arrow) with >70% stenosis, and more proximal disease with moderate 50-70% stenosis (arrowhead). Follow-up: Sent to cath lab for recurrent symptoms, and diagnosed with ACS.

Figures:

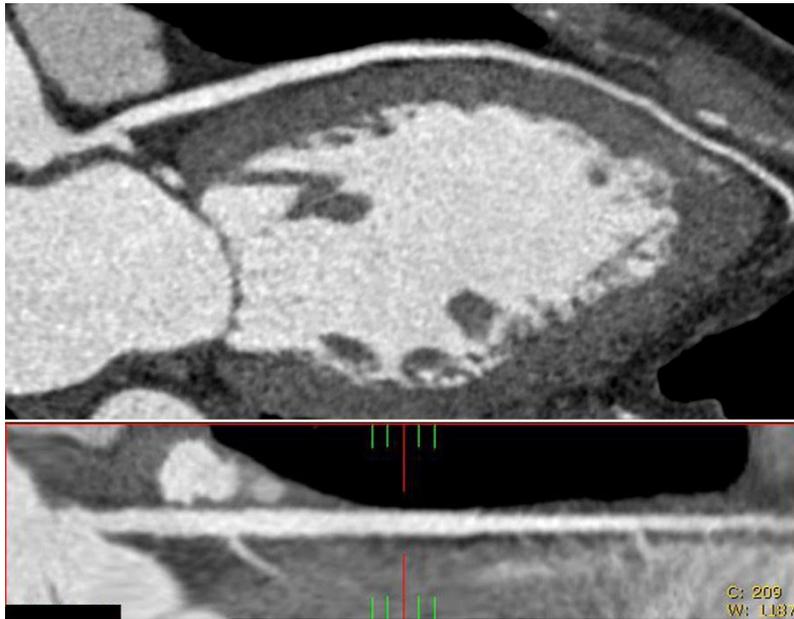


Figure 1. Coronary artery grading system for stenosis, demonstrating curved multiplanar and straightened lumen views of the left anterior descending artery (LAD) in 6 patients.

A. Normal LAD

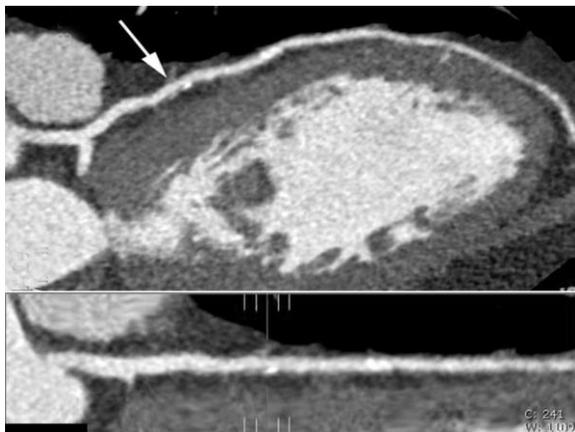


Figure 1. Coronary artery grading system for stenosis, demonstrating curved multiplanar and straightened lumen views of the left anterior descending artery (LAD) in 6 patients.

B. Minimal disease (arrow) with <30% stenosis.

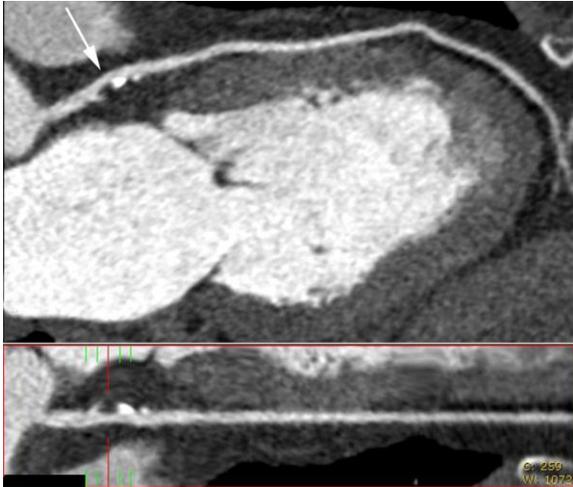


Figure 1. Coronary artery grading system for stenosis, demonstrating curved multiplanar and straightened lumen views of the left anterior descending artery (LAD) in 6 patients.

C. Mild disease (arrow) with <50% stenosis.

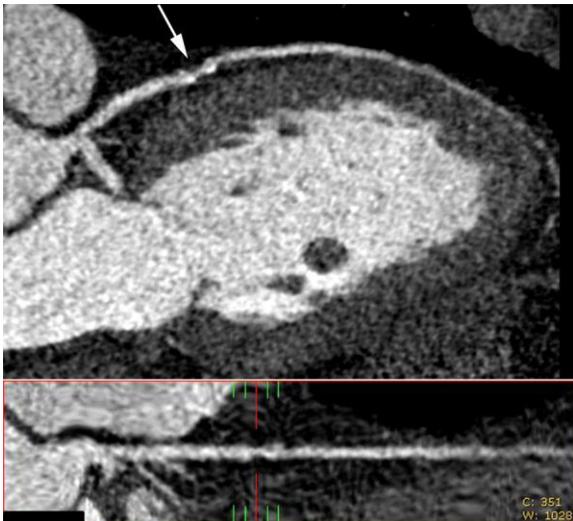


Figure 1. Coronary artery grading system for stenosis, demonstrating curved multiplanar and straightened lumen views of the left anterior descending artery (LAD) in 6 patients.

D. Moderate disease (arrow) with 50-70% stenosis.

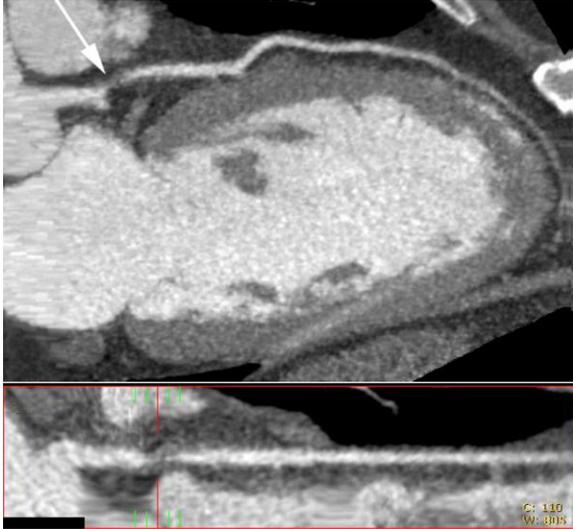


Figure 1. Coronary artery grading system for stenosis, demonstrating curved multiplanar and straightened lumen views of the left anterior descending artery (LAD) in 6 patients.

E. Severe disease (arrow) with $>70\%$ stenosis. Follow-up: treated with stent, symptoms resolved.

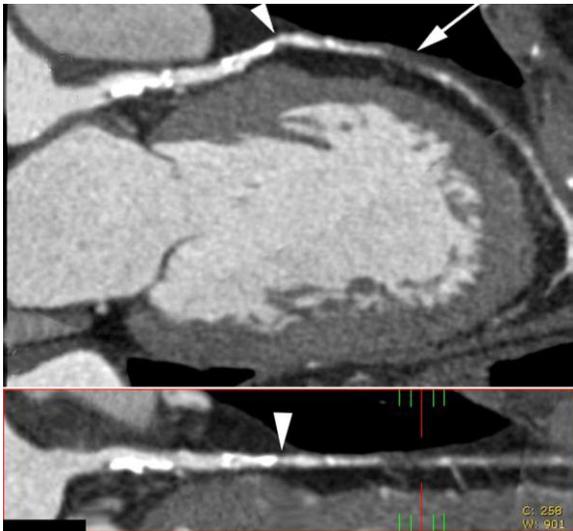


Figure 1. Coronary artery grading system for stenosis, demonstrating curved multiplanar and straightened lumen views of the left anterior descending artery (LAD) in 6 patients.

F. Severe disease (arrow) with $>70\%$ stenosis, and more proximal disease with moderate 50-70% stenosis (arrowhead). Follow-up: Sent to cath lab for recurrent symptoms, and diagnosed with ACS.

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