Usefulness of Age and Gender in the Early Triage of Patients With Acute Chest Pain Having Cardiac Computed Tomographic Angiography

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To identify the age- and gender-specific subpopulations of patients with acute chest pain in whom coronary computed tomographic angiography (CTA) will yield the greatest diagnostic benefit. Subjects with acute chest pain and an inconclusive initial evaluation (nondiagnostic electrocardiograhic findings, negative cardiac biomarkers) underwent contrast-enhanced 64-slice coronary CTA as a part of an observational cohort study. Independent investigators determined the presence of significant coronary stenosis (>50% luminal narrowing) and the occurrence of acute coronary syndrome (ACS) during the index hospitalization. We determined the diagnostic accuracy and effect on pretest probability of ACS using Bayes' theorem by age and gender. Of 368 patients (age 52.7 ± 12 years, 61% men), 8% had ACS. The presence of significant coronary stenosis on CTA and the occurrence of ACS increased with age for both men and women (p <0.001). Cardiac CTA was highly sensitive and specific in women <65 years of age (sensitivity 100% and specificity >87%) and men <55 years of age (sensitivity 100% for men <45 years and 80% for men 45 to 54 years old; specificity >88.2%). Moreover, in these patients, coronary CTA led to restratification from low to high risk (for positive findings on CTA) or from low to very low risk (for negative findings on CTA). In contrast, a negative result on CTA did not result in restratification to a low-risk category in women >65 years and men >55 years old. In conclusion, the present analysis provides initial evidence that men <55 years and women <65 years might benefit more from cardiac CTA than older patients. Thus, age and gender might serve as simple criteria to appropriately select patients who would derive the greatest diagnostic benefit from coronary CTA in the setting of acute chest pain. **(Am J Cardiol 2009;104:1165–1170)**

Although evidence demonstrating that cardiac computed tomographic angiography (CTA) might enhance the current workup of patients with acute chest pain is growing, it remains unclear in which subpopulation cardiac CTA yields the highest diagnostic benefit.[1–4] To establish a usefulness classification for patients with suspected acute coronary syndrome (ACS) undergoing cardiac CTA, we determined the pretest probability of ACS using the ACS event rates, the diagnostic accuracy of coronary CTA, and the post-test probability in age- and gender-specific patient strata in a large observational cohort study. Our hypothesis was that younger men and women would benefit the most from coronary CTA.

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Methods

The study sample was drawn from the Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT) trial, which enrolled patients who had a chief complaint of acute chest pain for >5 minutes during the past 24 hours, normal initial troponin, an initial electrocardiographic without evidence of myocardial ischemia, and normal sinus rhythm. Subjects were excluded if their serum creatinine was >1.3 mg/dl and they had a history of coronary artery disease (CAD), defined as stent implantation or coronary artery bypass grafting. Detailed inclusion and exclusion criteria have been reported previously.[4] All patients had sufficient clinical suspicion of ACS by the emergency department physicians to be admitted to the hospital for the assessment of ACS. Data on demographics, cardiovascular risk factors, Thrombolysis In Myocardial Infarction (TIMI) risk score, medication history, and clinical course of the study participants were prospectively collected during the hospitalization. All study participants underwent contrast-enhanced coronary CTA before admission to the hospital floor where they received the standard of care. Importantly, all caregivers and the study participants were kept unaware of the results of coronary CTA. The institutional review

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doi:10.1016/j.amjcard.2009.06.029

board approved the study protocol, and all patients provided written informed consent.

Coronary CTA was performed using a 64-slice CT scanner (Sensation 64, Siemens Medical Solutions, Forchheim, Germany). Per standard protocol, the subjects received an intravenous β blocker (if the heart rate was >60 beats/min; metoprolol 5 to 20 mg) and sublingual nitroglycerin before the scan unless contraindicated. The detailed protocol has been previously described.[4] Axial images were reconstructed (slice thickness 0.75 mm; increment 0.4 mm) at different intervals of the cardiac cycle to minimize motion artifacts. The best phase was selected for analysis and transferred to an off-line workstation for analysis (Leonardo, Siemens Medical Solutions, Forchheim, Germany). The presence of significant coronary stenosis (>50% luminal narrowing) was determined in a consensus reading by 2 experienced investigators, with a third expert reader adjudicating any disagreement and previously described. If image quality did not permit definite exclusion of the presence of a significant stenosis (because of the presence of motion artifacts, calcification, or a low contrast/noise ratio), the segment was classified as inconclusive. For clinical applicability of the analysis, inconclusive segments were counted as positive for the determination of the test characteristics of cardiac CTA.

The outcome of interest was ACS, defined as either an acute myocardial infarction with positive troponin during serial testing (6 or 9 hours after emergency department presentation) or unstable angina pectoris according to the American Heart Association/American College of Cardiology/European Society of Cardiology guidelines.[5–7] Unstable angina pectoris was defined as clinical symptoms suggestive of ACS (unstable pattern of chest pain—at rest, new onset, or crescendo angina), optimally with objective evidence of myocardial ischemia, such as a positive stress test, as previously defined.[4] The occurrence of ACS was determined by an independent outcome panel of 2 experienced physicians with >10 years of experience (1 emergency department physician and 1 cardiologist), who reviewed all patient data pertaining to the index hospitalization, including other test results. Disagreement was resolved by consensus, which included an additional cardiologist.[8]

The demographics, traditional risk factors, and clinical events, as well as the prevalence of coronary stenosis as detected by coronary CTA, are presented as the mean ± SD or median and interquartile range for continuous variables and as percentages for categorical variables. Because age and gender are the most easily obtainable independent strong predictors for both ACS and CAD,[9–11] the analysis was performed using age- (per 10-year increments) and gender-specific strata (women ≤45, >45 to ≤55, >55 to ≤65, and >65 years of age; men ≤45, >45 to ≤55, >55 to ≤65, and >65 years of age). For each strata, we determined the prevalence of ACS and the diagnostic accuracy of detecting ACS using coronary CTA (sensitivity and specificity, including 95% confidence intervals, using the exact binominal distribution and positive and negative likelihood ratio). The chi-square trend test was used to test for differences in the prevalence of significant coronary stenosis and ACS across the subgroups. The pretest probability of ACS was defined as the prevalence of ACS within the strata. The change in probability of ACS given as positive and negative coronary CTA (defined as the presence of >50% significant coronary artery stenosis or an inconclusive coronary segment) was subsequently determined using Baye's theorem (for a negative test result: pretest odds × negative likelihood ratio = post-test odds for ACS; for a positive test result: pretest odds × positive likelihood ratio = post-test odds for ACS). To translate the nominal change of probability of ACS into clinically relevant restratification of the risk of ACS, we used the classification suggested by Goldman et al[12] and defined very low risk as a ≤1% ACS event rate, low risk as a 1% to ≤4% ACS event rate, intermediate risk as a 4% to ≤16% ACS event rate, and high risk as a >16% ACS event rate.

A 2-sided p value of <0.05 was considered statistically significant. All analyses were performed using Statistical Analysis Systems, version 9.1 (SAS Institute, Cary, North Carolina).

Table 1
Patient demographics and clinical outcomes

Variable	Value
Age (years)	52.7 ± 12
Men	223 (61%)
Body mass index (kg/m^2)	29.0 ± 6
Diabetes mellitus	40 (11%)
Hypertension	145 (39%)
Hyperlipidemia or statin use	135 (37%)
Current or former smoker	180 (49%)
TIMI score	
Low	94.3%
Intermediate	5.4%
High	0.3%
Index hospitalization	
Acute coronary syndrome	31 (8%)
Unstable angina pectoris	23 (74%)
Myocardial infarction	8 (26%)

Results

A total of 368 patients, who were predominantly middle-age, relatively young men at low TIMI risk (61% men, mean age 52.7 ± 12 years, 95% low TIMI risk) were included in the present analysis (Table 1). The prevalence of ACS, significant coronary stenosis, and examinations with inconclusive coronary segments increased significantly across the age strata for both women and men (all p <0.001, Table 2).

In women <65 years of age, coronary CTA correctly identified 2 women with ACS (sensitivity 100% for women age 45 to 65 years; Table 2) and correctly excluded ACS in all but 4 patients (specificity 90.7% and 87.0% for women aged 45 to 54 years and 55 to 64 years, respectively). In contrast, coronary CTA had low sensitivity and moderate specificity for ACS in women aged ≥65 years (sensitivity 66.7% and specificity 72.7%).

In men <45 years old, cardiac CTA correctly identified all men with ACS (sensitivity 100%) and correctly identified 4 of 5 men with ACS aged 45 to 54 years (sensitivity 80%; Table 2). Similarly, cardiac CTA correctly excluded ACS in a significant fraction of men aged <45 years and 45

Table 2
Diagnostic accuracy of cardiac computed tomographic angiography (CTA) for detection of acute coronary syndrome (ACS) stratified by age

Variable	Age (years)				
	All Ages	<45	45–54	55–64	≥65
Women	142	28	48	47	28
ACS	8 (6%)	0	1 (2%)	1 (2%)	6 (21%)
Coronary stenosis	20 (14%)	0	3 (6%)	7 (15%)	10 (35%)
Inconclusive segments	15 (11%)	0	1 (2%)	6 (13%)	8 (29%)
Sensitivity	75.0% (6/8)	—	100% (1/1)	100% (1/1)	66.7% (4/6)
95% Confidence interval	0.35–0.96%	—	0.03–1.00%	0.03–1.00%	0.22–0.96%
Specificity	89.6% (120/134)	—	95.7% (45/47)	87.0% (40/46)	72.7% (16/22)
95% Confidence interval	0.83–0.94%	—	0.85–0.99%	0.74–0.95%	0.50–0.89%
Men	226	65	98	35	28
ACS	23 (10%)	3 (5%)	5 (5%)	8 (23%)	7 (25%)
Coronary stenosis	48 (21%)	7 (6%)	13 (15%)	11 (31%)	18 (64%)
Inconclusive segments	19 (8%)	1 (2%)	6 (6%)	3 (9%)	9 (32%)
Sensitivity	78.3% (18/23)	100% (3/3)	80.0% (4/5)	62.5% (5/8)	85.7% (6/7)
95% Confidence interval	0.56–0.93%	0.29–1.00%	0.28–0.99%	0.24–0.91%	0.42–0.99%
Specificity	85.2% (173/178)	98.4% (61/62)	88.2% (82/93)	77.8% (21/27)	42.9% (9/21)
95% Confidence interval	0.94–0.99%	0.91–1.00%	0.80–0.94%	0.58–0.91%	0.23–0.66%

Table 3
Pre- and post-test probability of acute coronary syndrome (ACS), contingent on positive or negative findings* on cardiac CTA stratified by gender and age

Age Group (years)	Pretest Probability	Risk Category	Probability Given Negative Test Result (Diagnostic Gain)	Risk Category	Probability Given Positive Test Result (Diagnostic Gain)	Risk Category
Women						
<45	0%	Very low	—	—	—	—
45–54	2%	Low	0% (2%)	Very low	33% (31%)	High
55–64	2%	Low	0% (4%)	Very low	16% (14%)	High
≥65	21%	High	11% (10%)	Intermediate	40% (19%)	High
Men						
<45	5%	Low	0% (5%)	Very low	75% (70%)	High
45–54	5%	Low	1% (4%)	Very low	27% (22%)	High
55–64	23%	High	13% (10%)	Intermediate	45% (22%)	High
≥65	25%	High	10% (15%)	Intermediate	33% (8%)	High

Pretest probability equals observed prevalence of ACS in each subgroup; risk classified according to Goldman et al.[12]
* Presence of significant coronary stenosis or indeterminate findings.

to 54 years (specificity 98.4% and 88.2%, respectively). In contrast, cardiac CTA had moderate sensitivity and low specificity for ACS in men aged ≥55 years (Table 2).

Because of the low prevalence of ACS, the absolute change in pretest probability was greater after positive coronary CTA than after negative coronary CTA in all strata, except for men ≥65 years of age (Table 3). In women aged 45 to 54 years and 55 to 64 years (prevalence of ACS 2%), negative findings on coronary CTA resulted in a post-test probability of 0%, and positive findings were associated with a post-test probability of 33% and 14%, respectively. In men <45 years and men 45 to 54 years of age, positive findings on coronary CTA resulted in a dramatic increase in post-test probability of 75% and 27%, respectively, and negative findings resulted in a 0% and 1% post-test probability for men aged <45 and 45 to 54 years, respectively.

Figure 1 demonstrates the change in the probability of ACS given negative or positive findings on coronary CTA within the risk classification suggested by Goldman et al.[12] Both resulted in a change in the risk category, except for a positive test in women >65 years of age and men 55 to 64 years of age. For women aged 45 to 54 and 55 to 64 years and men aged <45 and 45 to 54 years, positive and negative findings both resulted in a change in the risk estimate into the very low- or high-risk category. Positive findings on coronary CTA restratified men and women into high risk, except for men >65 years of age.

Discussion

In the present study, we demonstrate that coronary CTA in patients with acute chest pain substantially changes the probability of ACS for both negative and positive test results (as determined by the presence of 50% stenosis or inconclusive findings) in men <55 years of age and women <65 years of age. Moreover, applying these results to a risk classification scheme demonstrated that coronary CTA leads to a restratification from low risk to high (for positive findings) or to very low risk (for negative findings). Thus,

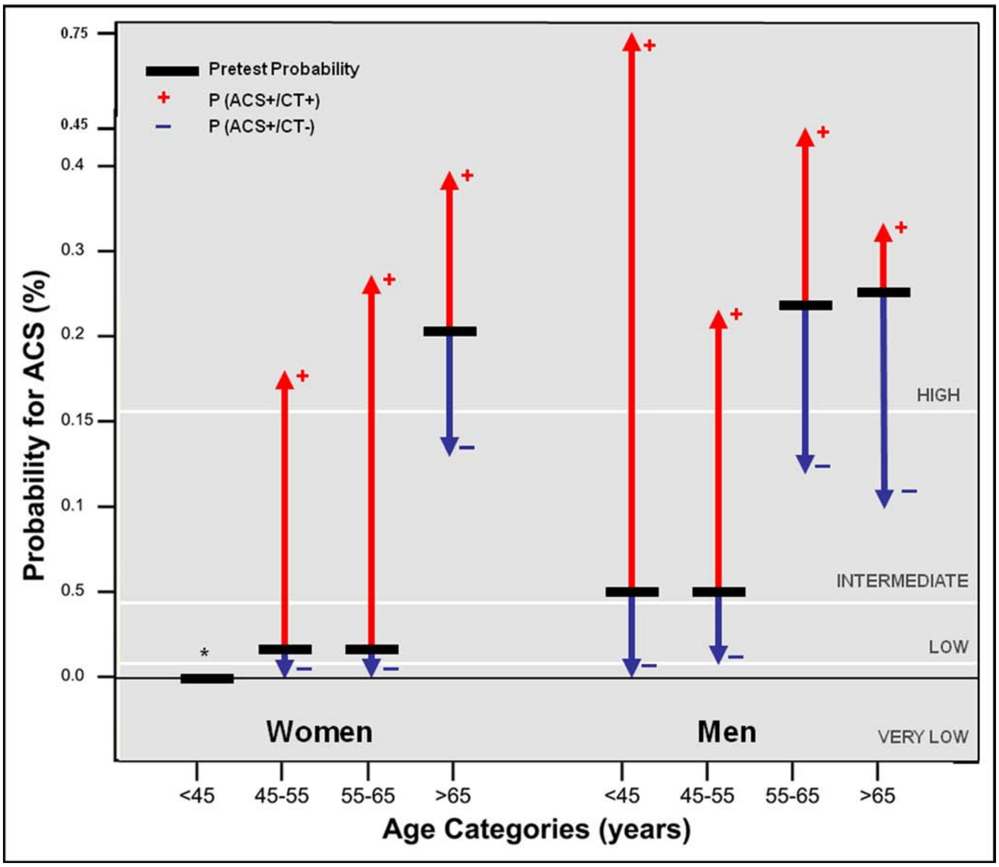

Figure 1. Effect of positive and negative findings using cardiac CTA on pretest probability *(horizontal black bar)* of ACS according to age group and gender. Either positive *(red arrow, +)* or negative *(blue arrow, −)* findings on CTA revised the probability for ACS upward or downward, respectively, and could result in restratification of risk categories (very low [≤1%], low risk [<4%], intermediate [<16%], and high risk [>16%], according to Goldman et al[12]).

coronary CTA might have the greatest clinical utility in women <65 and men <55 years of age.

Several recent studies have demonstrated that coronary CTA might be helpful to guide the treatment of patients presenting with acute chest pain in the emergency department, especially in the early triage of patients with a low to intermediate likelihood of ACS, for whom CTA might facilitate early discharge. However, these studies reported a wide range of ACS rates (0% to 34%),[1,2,4] suggesting heterogeneity of the populations studied. In the present analysis, we have demonstrated that the clinical utility of coronary CTA in the setting of acute chest pain appears to vary with age and gender, even within a population of patients overwhelmingly classified as having low risk according to the TIMI risk score (95%). This observation was determined by differences in the prevalence of ACS, the prevalence of significant stenosis on coronary CTA, and the accuracy of this finding for identifying patients with ACS in age- and gender-specific strata.

Age and gender are well-known as strong predictors of CAD, myocardial infarction, and ACS.[9–11] Consequently, we observed a significant increase in the prevalence of ACS and significant CAD from 0% to 21% and 0% to 35% in women and 5% to 25% and 6% to 64% in men across the age strata, respectively. The diagnostic accuracy of CTA for ACS was related to the prevalence of CAD (sensitivity range 66.7% to 100% and 62.5% to 100% for women and men, respectively). The observed 10-year difference between women and men mirrored exactly the gender difference previously described with respect to intima media thickness and coronary artery calcification.[13,14] Thus, our findings are consistent with the high accuracy for the detection of stenosis in populations with a low prevalence of CAD and the close association of CAD and ACS.[15]

Although the ultimate assessment of the clinical efficiency of a diagnostic test should be performed within the framework of a cost-effectiveness analysis, the changes in pretest probability within clinically accepted risk categories according to basic clinical and demographic variables are often used. Examples include the TIMI risk score for patients with unstable angina and non–ST elevation myocardial infarction acute chest pain and suspicion for ACS,[16] the Diamond and Forrester classification for patients with suspected CAD,[17,18] and the Framingham Risk Score for asymptomatic patients.[19] The definition of high, low, or intermediate risk is usually arbitrary but reflects the severity and consequences of an event. For example, low risk is considered as <4% ACS in patients with acute chest pain,[12] <30% significant CAD (>50%) in patients with suspected CAD,[20] and <10% (death or myocardial infarction) during a 10-year period (1% annually) in asymptomatic patients.[21]

In contrast to previous work by Meijboom et al,[22] who based the pretest probability for CAD on the Duke score, we based the pretest probability for ACS on the observed prevalence of ACS in each subgroup. This was necessary, because 95% of our patient population had a low TIMI risk score, and thus further stratification was not feasible. However, our results are consistent with those of Meijboom et al[22] in that coronary CTA was not useful in patients with a high pretest probability.

In women <65 years of age and men <55 years of age, both a positive and negative test resulted in a change in the risk estimate to either very low (<1%) or high (≥16%), indicating the greatest clinical utility. Most remarkable was that a finding of significant stenosis in men <45 years of age resulted in an absolute increase of 70% in the probability of ACS. The cost-effectiveness of coronary CTA, at least the cost saving in younger patients, has been suggested by recent cost-effectiveness analyses[23,24] and a small, randomized, computed tomography trial of patients with acute chest pain ($1,586 vs $1,872, p <0.001).[1] Overall, this is consistent with the notion that the clinical value of coronary CTA is mostly derived from its ability to safely exclude significant coronary artery disease.[25] Although our results have indicated that a large portion of women <65 and men <55 years of age with negative findings on CTA can be safely discharged without additional testing, it remains to be determined whether restratification to very low risk or high risk will consistently result in immediate and significant management decisions such as discharge (as suggested by Goldman et al[12]) or referral for invasive angiography, respectively. Such determinations are typically done within registries or randomized trials.

The clinical utility of cardiac CTA for women >65 years and men >55 years of age might be low, because the observed prevalence of significant stenosis (>30%), ACS (>20%), and inconclusive coronary segments (>9%) by CTA is already high, and coronary CTA only results in restratification to intermediate/high risk. One explanation for this finding is that coronary calcification (CAC), a known reason for the low positive predictive value of coronary CTA, becomes highly prevalent in this age group.[26] Thus, alternative testing modalities might be superior in the triage of these patients.[27]

Our finding that women <45 years of age did not have any stenosis detectable by CTA and did not develop any event deserves additional comment. Primarily, this finding can be attributed to our limited sample size, because it is known that ACS can occur in women <45 years old. Moreover, these women were all admitted to the hospital as the standard of care, and 28% underwent myocardial perfusion imaging (data not shown). Thus, cardiac CTA might prove beneficial in these subjects. However, the associated radiation exposure with an increased risk in younger women warrants additional research of the feasibility of low-dose protocols (<5 mSv) and a subsequent risk-benefit analysis of computed tomography in these younger women.

The major limitation of our study was the low number of events within the subgroups, resulting in wide 95% confidence intervals. However, ROMICAT currently is the largest observational cohort study of patients with low to intermediate likelihood undergoing coronary CTA in the emergency department. Also, at this point, it might be impossible to repeat a study in which the caregivers remain unaware of the results of coronary CTA, given the proven high negative predictive value of coronary CTA and that randomized trials are already underway. Also, optimally, our probability revision would have included a clinical risk stratification algorithm such as the TIMI score, to demonstrate the incremental value. However, 95% of the patients in our population had a low TIMI risk score, and stratification was not possible. This might emphasize the limitations of the TIMI score in the large population of low-risk patients. This was a single center trial, and the population, because of institutional review board recommendations (i.e., conservative creatinine threshold <1.3 mmol/ml), might have resulted in a slightly healthier population than the population with chest pain in whom CTA would be used in clinical practice. However, the observed event rate of 8% was consistent with a low to intermediate risk of ACS.[28]

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