Coronary Computed Tomographic Angiography in the Evaluation of Patients with Acute Chest Pain

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Executive Summary

Background

Emergency room visits for evaluation of acute chest pain are common. Among those patients without known coronary artery disease, after acute coronary syndromes are excluded but disease is still suspected, further patient evaluation is generally indicated. Noninvasive testing prior to discharge, or soon after, is an approach often used to exclude the presence of clinically significant disease. Given its high negative prognostic value and ability to be quickly obtained, coronary CTA has been proposed as an approach in this setting.

Objective

The objective of this Assessment is to compare the net health outcomes following a coronary CTA diagnostic strategy to outcomes in other commonly used strategies for evaluating patients with acute chest pain and no known coronary artery disease presenting to the emergency room and found not to have evidence of acute coronary syndromes.

Search Strategy

Randomized controlled trials and prospective observational studies reporting prognosis of coronary CTA in the emergency room setting were identified by searching the MEDLINE® (via PubMed) database through September 2011. A separate search was performed to identify studies reporting follow-up of incidental findings in any setting.

Selection Criteria

Randomized controlled trials conducted in the samples of the target population were included. Prospective observational studies including more than 100 patients reporting prognostic value of coronary CTA were also reviewed.

Main Results

Two randomized, controlled trials and 2 prognostic studies were identified. The first trial evaluated 197 patients from a single center without evidence of acute coronary syndromes to coronary CTA (n=99) or usual care (n=98). Over 6 months' follow-up, no cardiac events occurred in either arm. Invasive coronary angiography rates were somewhat higher in the coronary CTA arm (12.1% versus 7.1%). Diagnosis was achieved more quickly following coronary CTA. The second trial (CT-STAT) evaluated a similarly selected sample of 699 randomized patients from 16 centers—361 undergoing coronary CTA and 338 undergoing myocardial perfusion imaging. Over 6 months' follow-up, there were no deaths in either arm, 2 cardiac events in the coronary CTA arm, and 1 in the perfusion imaging arm. Invasive coronary angiography rates were similar in both arms (7.2% after coronary CTA; 6.5% after perfusion imaging). A second noninvasive test was obtained more often following coronary CTA (10.2% versus 2.1%), but cumulative radiation exposure in the coronary CTA arm

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(using retrospective gating) was significantly lower—mean 11.5 versus 12.8 mSv. Time to diagnosis was shorter (mean 3.3 hours) and estimated emergency room costs were lower with coronary CTA.

Two studies of patients from the target population reported no cardiac events following a negative coronary CTA after 12 months' (n=481) and 24 months' (n=368) follow-up.

Author's Conclusions and Comments

Owing to the negative prognostic value of coronary CTA in this population, the test offers an alternative for patients and providers. Evidence obtained in the emergency setting, similar to more extensive results among ambulatory patients, indicates a normal coronary CTA appears to provide a prognosis as good as other noninvasive tests. Other important outcomes that need be considered in comparing technologies include invasive coronary angiography rates, use of a second noninvasive test, radiation exposure, and follow-up of any incidental lung findings. While there is uncertainty accompanying the limited trial evidence, it is reasonable to conclude that the invasive angiography rate following coronary CTA is similar to that following perfusion imaging. Evidence regarding comparative differences in obtaining a second noninvasive test is limited to CT-STAT and was greater following coronary CTA. Despite that difference, cumulative radiation exposure remained lower in the coronary CTA arm utilizing retrospective gating techniques. Given radiation reduction realized with prospective gating and spiral acquisition, radiation exposure accompanying coronary CTA will continue to decrease. Incidental findings following coronary CTA are common and lead to further testing without evidence for benefit.

While uncertainties exist and should be further studied, considering important outcomes in the patient population, the net health outcome following coronary CTA appears to be as good as that following other strategies.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) made the following judgments about coronary CTA for patients with acute chest pain presenting to the emergency room with no known history of coronary artery disease, and found not to have evidence of acute coronary syndromes.

1. **The technology must have final approval from the appropriate governmental regulatory bodies.**

Coronary CTA is performed using multidetector-row CT (MDCT), and multiple manufacturers have received U.S. Food and Drug Administration (FDA) 510(k) clearance to market machines. Current machines are equipped with at least 64 detector rows. Intravenous iodinated contrast agents used for coronary CTA have also received FDA approval.

2. **The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

For patients with acute chest pain presenting to the emergency room with no known history of coronary artery disease, and found not to have evidence of acute coronary syndromes, there is sufficient evidence to permit conclusions concerning the effect of coronary CTA on relevant health outcomes.

3. **The technology must improve the net health outcome.**
4. **The technology must be as beneficial as any established alternatives.**

By avoiding adverse cardiac events, use of coronary CTA in the target population will improve the net health outcome, as well as other strategies currently used in practice.

5. The improvement must be attainable outside the investigational settings.

Coronary CTA is widely available and used outside the investigational setting. The main clinical trial evaluating its use was primarily performed in real-world settings.

Based on the above, for patients with acute chest pain presenting to the emergency room with no known history of coronary artery disease, and found not to have evidence of acute coronary syndromes, coronary CTA meets the TEC criteria.

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Assessment Objective

The objective of this Assessment is to compare the net health outcome following a coronary CTA diagnostic strategy to outcomes in other commonly used strategies for evaluating patients with acute chest pain and no prior history of coronary artery disease presenting to the emergency room and found not to have evidence of acute coronary syndromes.

Background

In 2007, there were 6.4 million annual patient visits to U.S. emergency rooms for evaluation of chest pain (Niska et al. 2010). Approximately 25% of patients present with an acute coronary syndrome (Weaver et al. 1993; Selker et al. 1998; Lee and Goldman 2000; Farkouh et al. 2009), evidenced by an abnormal electrocardiogram or elevated biomarkers (e.g., troponin). Evaluating patients without evidence of acute coronary syndromes can pose challenges because disease probability is low, yet without accurate identification of clinically significant coronary artery disease, potential adverse outcomes can occur (Pope et al. 2000).

Emergent Evaluation of Patients with Chest Pain

The goals of emergency evaluation of patients with chest pain include: 1) identify those without disease appropriate for discharge, and 2) refer patients with probable disease for evaluation and treatment. An effective testing strategy should identify patients who can be safely discharged—a desirable test or strategy will have a high negative prognostic value or low negative likelihood ratio. In practice, a number of different approaches can be used, among them hospitalization and observation, short-stay chest pain units, or a noninvasive test followed by discharge if normal—exercise treadmill testing (ETT), stress echocardiography (SECHO), myocardial perfusion imaging (MPI), magnetic resonance imaging (MRI), or coronary CTA. Given the low pretest disease probability in the patient population, a reasonably sensitive and specific (e.g., both ≥85%) test's negative likelihood ratio will lower post-test disease probability sufficiently to have a high negative prognostic value for subsequent cardiac events.[1] While sensitivities and specificities differ among the noninvasive tests used, the differences are not substantial. Furthermore, because events after a negative test are uncommon, comparing cardiac outcomes following different strategies would require large samples and nearly complete follow-up (see example in review of evidence).

Prognostic Value of Testing Strategies in the Emergency Setting

We identified just 6 published direct comparisons between testing strategies in the emergency setting—rapid rule-out compared to usual care (Gomez et al. 1996); chest-pain unit compared to hospitalization (Farkouh et al. 1998); pre-discharge coronary angiography and exercise treadmill testing (deFilippi et al. 2001); usual care and resting MPI (Udelson et al. 2002); and coronary CTA compared to MPI (Goldstein et al. 2007; Goldstein et al. 2011). Given a paucity of direct comparative evidence, particularly for specific noninvasive testing strategies, the prognostic value of a negative noninvasive test result is of interest.

The recent scientific statement, "Testing of low-risk patients presenting to the emergency department with chest pain" from the American Heart Association (Amsterdam et al. 2010) identified observational studies reporting outcomes after evaluation using exercise treadmill testing, MPI, and stress echocardiography (Tsakonis et al. 1991; Kerns et al. 1993; Varetto et al. 1993; Hilton et al. 1994; Gibler et al. 1995; Gomez et al. 1996; Kontos et al. 1997; Tatum et al. 1997; Trippi et al. 1997; Zalenski et al. 1997; Heller et al. 1998; Kirk et al. 1998; Polanczyk et al. 1998; Kontos et al. 1999; Diercks et al. 2000; Geleijnse et al. 2000; Sarullo et al. 2000; Amsterdam et al. 2002; Udelson et al. 2002; Bholasingh et al. 2003; Ramakrishna et al. 2005; Nucifora et al. 2007; Schaeffer et al. 2007). Following a negative exercise treadmill test and MPI adverse cardiac events were infrequent (Tables 1 and 2; sample descriptions in Appendix C, Tables C1 and C2) while angiography use varied overall and was conditional on test result.[2] In the four studies of stress

[1] For example using a pretest probability of 5%, sensitivity and specificities of 85% (LR- of 0.18) would result in a post-test disease probability under 1%. While cardiac events will occur in a population with a 1% disease prevalence, they will not be common.
[2] The results are also consistent with the prognostic value of negative test obtained among patients evaluated for stable angina—annual cardiac death rates of 0.6% after normal perfusion imaging and 0.8% after a negative stress echocardiogram (Metz LD, Beattie M, Hom R et al. (2007). The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. *J Am Coll Cardiol*, 49(2):227-37.).

Table 1. Studies of Exercise Treadmill Testing in Emergency Department Patients with Acute Chest Pain According to Duration of Follow-up—after (Amsterdam et al. 2010)

Study	n	F/U, mo	Test Results: Positive n (%)	Test Results: Negative n (%)	MACE after Negative Test, n (%)	Angiography n (%)	Angiography after Positive Test, n (%)	Angiography after Negative Test, n (%)
Zalenski 1997	224	0	17 (7.6)	148 (66.0)	—	—	—	—
Gibler 1995[a]	791	1	9 (1.1)	782[b] (98.9)	1 (0.1)	—	—	—
Gomez 1996	50[c]	1	2 (4.0)	41 (82.0)	0 (0)	2 (4.0)	2 (100)	0 (0)
Kirk 1998	212	1	28 (13.2)	125 (59.0)	0 (0)	17 (8.0)	12 (42.8)	2 (1.6)
Amsterdam 2002	1000	1	125 (12.5)	640 (64.0)	2 (1.6)	71 (7.1)	52 (41.6)	0 (0)
Kerns 1993	32	6	0 (0)	32 (100)	0 (0)	0 (0)	—	—
Polanczyk 1998	276	6	81b (23.3)	195 (70.7)	4 (2.1)	14 (5.1)	12 (14.8)	2 (1.0)
Ramakrishna 2005[a]	125	6	32 (25.6)	91 (72.8)	0 (0)	—	—	—
Tsakonis 1991	28	6	5 (17.9)	23 (82.1)	0 (0)	0 (0)	—	—
Diercks 2000[b]	958	12	27 (2.8)	605 (63.2)	5 (0.8)	0 (0)	0 (0)	0 (0)
Sarullo 2000	190	17	57 (30.0)	111 (58.4)	8 (7.2)	45 (23.7)	44 (77.2)	0 (0)

[a] Angiography rates not reported
[b] Includes inconclusive results
[c] 50 of the 100 were randomized to receive ETT, but only 44 underwent ETT

Table 2. Studies of Perfusion Imaging Testing in Emergency Department Patients with Acute Chest Pain—after (Amsterdam et al. 2010)

Study	n	F/U, mo	Test Results		MACE after Negative Test, n (%)	Angiography n (%)	Angiography after Positive Test, n (%)	Angiography after Negative Test, n (%)
			Positive n (%)	Negative n (%)				
Kontos 1997	532	0	171 (32.1)	361[b] (67.9)	2 (1.2)	162 (30.5)	92 (25.5)	70 (19.4)
Heller 1998	357	1	153 (42.9)	204 (57.1)	6 (2.9)	49 (13.7)	35 (22.9)	14 (6.9)
Kontos 1999	216	1	5 (2.3)	211 (97.7)	0 (0)	16 (7.4)	5 (100.0)	2 (0.9)
Schaeffer 2007	479	1	45 (9.4)	434 (90.6)	3 (0.7)	5 (1.0)	3 (6.7)	2 (0.5)
Hilton 1994	102	3	17 (16.7)	70 (68.6)	1 (1.4)	1 (1.0)	0 (0)	1 (1.4)
Tatum 1997[a]	438	12	100 (22.8)	338 (77.2)	3 (0.9)	—	—	—
Varetto 1993	64	18	30 (46.9)	34 (53.1)	0 (0)	52 (81.3)	30 (100.0)	22 (64.7)

[a] Angiography rates not reported
[b] Includes inconclusive results

echocardiography (Table 3 sample description Appendix C Table C3), events were more frequent following a negative test in comparison. Rates of positive results reflecting disease prevalence suggest heterogeneous patient samples and follow-up durations varied. Limited by the lack of a comparator for exercise treadmill testing and MPI, the studies suggest cardiac events following a negative result are infrequent, while the few studies of stress echocardiography are not consistent.

Net Health Outcome

Although adverse cardiac events (myocardial infarction [MI], cardiac death, angina) are most relevant here, noncardiac consequences of testing require consideration to compare net health outcomes—particularly for coronary CTA and MPI. Table 4 summarizes outcomes and relevance to strategies; Figure 1 depicts their place in the diagnostic pathway.

While strategies including the different noninvasive tests, as well as chest pain units, hospitalization and observation, and invasive coronary angiography could be compared, as mentioned, direct comparative evidence is limited or lacking.

Coronary CTA to Evaluate Low-Risk Patients in the Emergency Department

From a diagnostic and prognostic perspective, coronary CTA is a practicable alternative given its generally similar performance characteristics to other noninvasive tests for identifying anatomic obstruction. The ability to obtain results quickly without exercise is also a desirable test attribute. Potential negative aspects of coronary CTA include: inability to assess functional consequences of a stenosis and therefore possible need to obtain a subsequent functional test for moderate stenoses, radiation exposure, and incidental noncardiac findings needing follow-up. Given its sensitivity to detect nonobstructive disease, there is also justifiable concern over a potential for increased subsequent angiography rates. Comparing a coronary CTA diagnostic strategy to others then entails assessing relevant cardiac and noncardiac outcomes of different diagnostic strategies.

Prior TEC Assessments

A previous Technology Evaluation Center (TEC) Assessment (2006; Vol. 21, No. 5) evaluated evidence concerning coronary CTA for evaluating acute chest pain and concluded that the technology did not meet TEC criteria. Only diagnostic accuracy data were available using angiography as the reference standard.

FDA Status. Coronary CTA is performed using multidetector-row CT (MDCT) and multiple manufacturers have received U.S. Food and Drug Administration (FDA) 510(k) clearance to market machines. Current machines are equipped with at least 64 detector rows. Radiation exposure is minimized using either retrospective (Raff et al. 2009) or more recently prospective (Duarte et al. 2011) gating techniques (imaging only during diastole). Intravenous iodinated contrast agents used for coronary CTA have also received FDA approval.

Methods

Search Methods

Randomized controlled trials, prospective observational studies reporting prognosis, and studies evaluating incidental findings were identified by searching the MEDLINE® (via PubMed) database through September 2011. Search strategies detailed in Appendix B.

Study Selection

For cardiac outcomes, randomized controlled trials conducted in the samples of the target population were included. For prognosis, prospective observational studies including more than 100 patients reporting prognostic value of coronary CTA were included. For incidental findings, studies utilizing 64-slice or greater scanners and including 100 or more patients were reviewed.

Data Abstraction, Calculations, Quality Assessment

Relevant data were abstracted describing patient populations, interventions, comparators, and outcomes. The approach to trial quality assessment was based on the framework outlined by the U.S. Preventive Services Task Force (USPSTF) for assessing randomized, controlled trials (Harris et al. 2001).

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on June 30, 2011. In order to maintain the timeliness of the scientific information in this Assessment, literature searches were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies

Table 3. Studies of Stress Echocardiography Testing in Emergency Department Patients with Acute Chest Pain—after (Amsterdam et al. 2010)

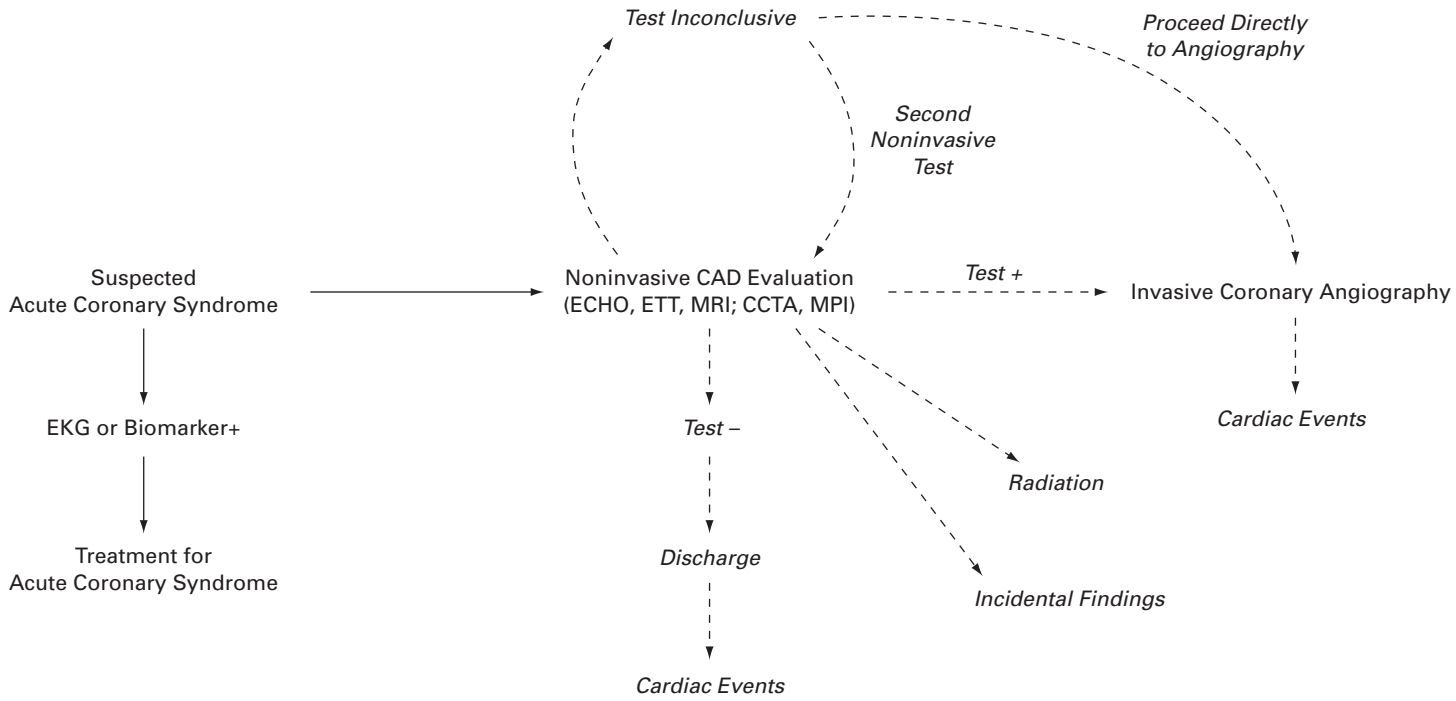
Study	n	F/U, mo	Test Results: Positive n (%)	Test Results: Negative n (%)	MACE after Negative Test, n (%)	Angiography n (%)	Angiography after Positive Test, n (%)	Angiography after Negative Test, n (%)
Nucifora 2007	97	2	20 (18.7)	87 (81.3)	8 (9.2)	0 (0)	—	—
Trippi 1997[a]	139	3	7 (5.0)	130 (93.5)	0 (0)	—	—	—
Geleijnse 2000	89	6	36 (40.5)	44 (49.4)	4 (9.1)	18 (20.2)	12 (33.3)	2 (4.5)
Bholasingh 2003	377	6	26 (6.9)	351 (93.1)	14 (4.0)	—	—	—

[a] Angiography rates not reported

Table 4. Cardiac and Non Cardiac Outcomes Relevant When Comparing Net Health Outcomes Following Noninvasive Testing Strategies

	ETT	ECHO	MPI	Coronary CTA	MRI
Outcome					
Adverse cardiac events	■	■	■	■	■
Angiography rates	■	■	■	■	■
Radiation			■	■	
Duplicate testing	■	■	■	■	■
Incidental findings				■	?
Costs and efficiency	■	■	■	■	■

Figure 1. Depiction of Important Parameters/Outcomes *(in italics)* Following Testing for Evaluation of Patients Without Acute Coronary Syndromes and Acute Chest Pain Suspected of Cardiac Origin



that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusions of this Assessment.

Formulation of the Assessment

Patient Indications

The target population includes patients with acute chest pain presenting to the emergency room with no known history of coronary artery disease, and found not to have evidence of acute coronary syndromes.

Technologies to be Evaluated and Compared

Coronary CTA would be ideally compared to all noninvasive diagnostic strategies used to detect the presence of coronary artery disease. However, because myocardial perfusion imaging is most often the noninvasive test used in practice, it is the comparator of primary interest.

Health Outcomes

All relevant outcomes are adverse and include:

- Adverse cardiac events following a negative test—e.g., cardiac death, MI, angina, revascularization
- Angiography rates
- Radiation exposure
- Duplicate/subsequent noninvasive testing (e.g., outcome of inconclusive test results)
- Follow-up for incidental findings

Specific Assessment Questions

What is the net health outcome of a coronary CTA-first diagnostic strategy compared to other commonly used diagnostic strategies (primarily perfusion imaging) for evaluating patients with acute chest pain presenting to the emergency room found not to have evidence of acute coronary syndromes? A "diagnostic strategy" is one where the noninvasive test is the initial test in any sequence.

Review of Evidence

Randomized, Controlled Trials

Characteristics of the two identified randomized controlled trials are summarized in (Table 5). Goldstein et al. (2007) screened 461 patients and randomized 203 presenting to the emergency department with low-risk acute chest pain, normal biomarkers, and negative ECGs obtained 4 hours apart. Six patients did not complete testing, leaving 197 allocated to 64-slice coronary CTA (n=99) or standard-of-care MPI (n=98). In the coronary CTA arm, patients with stenoses 25% or less and calcium score less than 100 Agatston units were eligible for discharge; those with stenoses greater than 70% were referred to invasive coronary angiography; those with stenoses 26–70% or calcium score greater than 100 Agatston units underwent MPI. In the standard-of-care arm, angiography was performed during the initial visit after MPI in 3 patients with abnormal results; in 4 others, angiography was performed following discharge home. In the coronary CTA arm (n=99), invasive coronary angiography was performed during the initial visit in 8 patients with abnormal results; in 1 patient following discharge. Twenty-four patients in the coronary CTA arm underwent MPI due to intermediate or nondiagnostic scans, with 3 subsequently undergoing angiography.

Trial quality was rated as good (Appendix C, Table C5). There were no major adverse cardiac events or mortality in either arm over a 6-month follow-up (Table 5). Angiography was more common following coronary CTA (12.1% versus 7.1%). Diagnosis was achieved more quickly following coronary CTA (Table 6).

The Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment (CT-STAT) trial screened 6,640 patients presenting to 16 emergency departments and randomized 749 without initial evidence of acute coronary syndromes by ECG or biomarkers (low to intermediate risk patients) to a coronary CTA (n=375) or MPI (n=374) diagnostic strategy (Goldstein et al. 2011). Randomization was performed using sealed envelopes, stratified by site, with an unspecified block size. Coronary CTA was performed with 64- to 320-slice scanners, "read immediately," and results conveyed to emergency room physicians. In the MPI arm, rest images were obtained immediately after enrollment; stress imaging (pharmacologic or exercise) was performed when resting results were normal. Interpretation using the standard 17-segment model was "performed immediately" and results conveyed to emergency room physicians. Patients with normal or "probably normal" MPI were eligible for discharge. In patients undergoing coronary CTA, those with stenosis 25% or less and calcium score less than 100 Agatston units were eligible for discharge; those with stenoses greater than 70%

Table 5. Randomized Trials Comparing Coronary CTA to Other Diagnostic Strategies in Evaluating Patients With Acute Chest Pain Presenting to the Emergency Room Found Not to Have Evidence of Acute Coronary Syndromes

Study	Goldstein 2007	Goldstein 2011
Acronym		CT-STAT
Sponsor/funding	William Beaumont Hospitals and Minestrelli Advanced Cardiac Research Imaging Center, Royal Oak, Michigan	Bayer HealthCare®, Berlin, Germany
n Randomized	203	701
Centers	1	11 university, 5 community hospitals
Dates	3/2005–9/2005	6/2007–11/2008
n Coronary CTA	99	361
n Comparator	98 (standard of care)	338 (rest-stress MPI)
Inclusion Criteria	1. chest pain or angina equivalent symptoms compatible with ischemia during the past 12 hours; 2. age >25 years; and 3. a prediction of a low risk of infarction and/or complications.	1. chest pain suspicious for angina based on an ED physician's history and physical; 2. age ≥25 years; 3. time from onset of chest pain to presentation ≤12 hours; 4. time from ED presentation to randomization ≤12 hours; 5. normal or non-diagnostic rest ECG at the time of enrollment, without ECG evidence of ischemia; 6. Thrombolysis in Myocardial Infarction risk score ≤4 for unstable angina or non-ST elevation myocardial infarction.

Table 5. Randomized Trials Comparing Coronary CTA to Other Diagnostic Strategies in Evaluating Patients With Acute Chest Pain Presenting to the Emergency Room Found Not to Have Evidence of Acute Coronary Syndromes (cont'd)

Study	Goldstein 2007	Goldstein 2011
Exclusion Criteria	1. known CAD; 2. EKG diagnostic of cardiac ischemia and/or infarction; 3. elevated serum biomarkers including creatine kinase-MB, myoglobin, and/or cardiac troponin I on initial and 4-h testing; 4. cardiomyopathy, with EF <45%; 5. contraindication to iodinated contrast and/or beta-blocking drugs; 6. atrial fibrillation; BMI >39 kg/m^2; and 7. creatinine >1.5 mg/dL; CT or contrast <48 hours.	1. known coronary artery disease; 2. elevated serum biomarkers including creatine kinase-MB, myoglobin and/or troponin I (e.g., Advia Centaur assay, Bayer Healthcare, Tarrytown, N.Y.); 3. ischemic ECG changes, as denoted above; 4. previously known cardiomyopathy, with an estimated ejection fraction ≤45%; 5. contraindication to iodinated contrast and/or beta blocking drugs; 6. atrial fibrillation or markedly irregular rhythm; 7. body mass index equal to or greater than 39 kg/m^2; 8. elevated serum creatinine levels (creatinine ≥1.5 milligrams/deciliter [mg/dL]); and 9. CT imaging or contrast administration within the past 48 hours.
Endpoints	6-month MACE (cardiac death, acute MI, unstable angina); time to diagnosis; cost of care	Primary: time-to-diagnosis from randomization. Secondary: cost of care and safety (6-month MACE--MI, unstable angina, cardiac death, revascularization)
Power to detect 50% relative risk reduction with 2% event rate	0.03	0.12

Table 6. Outcomes of Randomized Controlled Trials

	Goldstein 2007		Goldstein 2011	
	Coronary CTA n=99	Standard of Care n=98	Coronary CTA n=361	MPI n=338
Minimal or no CAD	67 (67.7%)	93 (94.9%)	297 (76.0%)	334 (89.9%)
6-month MACE following normal test	0 (0%)	0 (0%)	2 (0.8%)	1 (0.4%)
6-month mortality	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Second noninvasive test	24 (24.2%)[d]	0 (0%)[d]	37 (10.2%)[e]	7 (2.1%)[f]
Angiography	12 (12.1%)	7 (7.1%)	26 (7.2%)[a]	22 (6.5%)[a]
Time to diagnosis (hours)[b]	3.4 (2.3, 14.8)	15.0 (7.3, 20.2)	2.9 (2.1, 4.0)	6.2 (4.2, 19.0)
Cost[b]	$1,586 (1,413, 2,059)	$1,872 (1,727, 2,069)	$2,137 (1,660, 3,077)	$3,458 (2,900, 4,297)
Procedure Radiation mSv (mean 95% CI)	men-13, women-18[c]	NR	11.5 (6.8, 16.8)[c]	12.8 (11.6, 13.9)[c]

NR: Not Reported
[a] Includes invasive coronary angiography during index visit and subsequent 6 month follow-up using randomized patient as denominator
[b] Median (lower, upper quartiles)
[c] Used retrospectively gated; current prospective gating accompanied by lower radiation exposure (Earls et al. 2008)
[d] Not relevant comparison as protocol mandated MPI in the coronary CTA arm for indeterminate
[e] MPI
[f] Coronary CTA

were referred to invasive coronary angiography; those with stenoses 26–70% or calcium score greater than 100 Agatston units or uninterruptable scans had MPI recommended. Radiation dose during each procedure was also estimated.

Trial quality was rated fair (Appendix C, Table C5) due to unclear allocation concealment and greater loss to follow-up in the MPI arm. Of the 749 patients enrolled, 50 failed to complete the protocol or withdrew consent (14 [3.7%] and 36 [9.6%] in the coronary CTA and MPI arms, respectively); 72 patients were subsequently lost to follow-up (31 [8.2%] and 41 [11.0%] in the coronary CTA and MPI arms, respectively). Follow-up was complete in 330 of 375 (88%) in the coronary CTA arm and 297 of 374 in the MPI arm (79%), and all-cause mortality was ascertained by Social Security Death Index for all but one patient. In the coronary CTA arm, 297/361 (82.2%) had stenosis 25% or less with 262 discharged in under 6 hours; in the MPI arm 304/338 studies were interpreted as normal or probably normal and 271 discharged in less than 6 hours. In the coronary CTA arm 37 patients (10.2%) had "intermediate/non-diagnostic" coronary CTA results which were followed by MPI; 7 patients (2.1%) in the MPI arm underwent coronary CTA after an abnormal or equivocal test result. Angiography rates in the coronary CTA and MPI arms were similar. Over 6 months, there were 2 (0.8%) major adverse cardiac events following a normal coronary CTA result and 1 (0.4%) after a negative MPI. Time to diagnosis was shorter and estimated emergency room costs[5] were lower in the coronary CTA arm (Table 6).

In a small sample, Goldstein et al. (2007) found a coronary CTA strategy achieved a diagnosis more quickly than with usual care (MPI). Angiography rates were somewhat higher following coronary CTA (12.1% versus 7.1%; p=0.34). Over 6 months' follow-up, no cardiac events occurred following negative coronary CTA or MPI. The trial protocol precluded comparing second noninvasive testing rates following coronary CTA. Comparative radiation exposure was not reported.

CT-STAT enrolled a sample size powered to evaluate a primary endpoint of diagnostic efficiency (Goldstein et al. 2011). As in the prior trial, diagnosis was achieved more efficiently following coronary CTA. Angiography rates following coronary CTA and MPI were similar (7.2% versus 6.5%, respectively; p=0.77). Over 6 months' follow-up, cardiac events were uncommon and similar—coronary CTA 0.8% and after MPI, 0.4%. A second noninvasive test was more common following coronary CTA than MPI (10.2% versus 2.1%; p<0.001). Cumulative radiation exposure was lower following coronary CTA.

Owing to the rarity of events following negative tests, both trials lacked power to examine cardiac endpoints (see power estimates in Table 5). Comparison would necessitate rather large samples—to examine noninferiority with a 1% event rate and a 0.5% noninferiority margin would require 10,000 patients; to demonstrate equivalence with a similar rate and margin, a sample of 12,500 would be needed. Angiography rates were somewhat higher following coronary CTA in both trials, although in CT-STAT, just slightly. Radiation exposure in CT-STAT was lower following coronary CTA than MPI. With contemporary prospective gating for coronary CTA, radiation exposure is often reduced to less than 5 mSv (Earls et al. 2008). Neither report discussed follow-up of incidental findings.

Prognosis After Negative Coronary CTA

Two prospective observational studies reporting prognosis in the target patient population were identified (Hollander et al. 2009; Schlett et al. 2011) (Table 7; sample characteristics in Appendix C Table C4). Over 12- and 24-months' follow-up, no cardiac events were observed following a negative result.

Incidental Findings

Nine studies using 64+ slice scanners were identified (Table 8) (Kawano et al. 2007; Kirsch et al. 2007; Husmann et al. 2009; Koonce et al. 2009; Lehman et al. 2009; Machaalany et al. 2009; Aglan et al. 2010; Lazoura et al. 2010; Yorgun et al. 2010). Incidental findings were frequent (26.6% to 68.7%) with pulmonary nodules typically the most common and cancers rare (Table 9). Guidance for follow-up of detected lung nodules has been established (MacMahon et al. 2005). Aglan et al. (2010) compared the prevalence of incidental findings when the field of view was confined narrowly to the cardiac structures to those seen when the entire thorax was imaged. As expected, incidental findings

[5] Determined from cost to charge ratio as only charges were recorded.

Table 7. Studies Reporting Prognosis Following Coronary CTA in Emergency Department Patients with Acute Chest Pain

Study	n	F/U, mo	Test Results: Positive n (%)	Test Results: Negative n (%)	MACE after Negative Test, n (%)	Angiographies n (%)	Angiography after Positive Test, n (%)	Angiography after Negative Test, n (%)
Schlett 2011	368	24	68 (18.5)	300 (81.5)	0 (0)	368 (100)	—	—
Hollander 2009	481	12	0 (0)[a]	481 (100)	0 (0)[b]	481 (100)	—	—

[a] patients with stenosis of 50% or greater were excluded from the study (n=57)
[b] No MACE were recorded, but 51 patients received further testing and 53 patients were rehospitalized

Table 8. Studies of Incidental Findings Using 64+ Slice Scanners in Patients Evaluated for Coronary Artery Disease

Study	Scanner	Patients	Participants	% Male	Mean Age (SD or Range)
Kawano et al. 2007	64 slice	617	Suspected CAD	56%	66±12
Kirsch et al. 2007	64 slice	100	Suspected CAD	68%	63±14
Husmann et al. 2009	64 slice w/SPECT	582	Known or Suspected CAD	64%	64±11
Koonce et al. 2009	64 slice	737	NR	52%	57.2 (17–91)
Lehman et al. 2009	64 slice	395	ER Chest Pain	63%	53±12
Machaalany et al. 2009	64 slice	966	Registry (98% outpatients)	55%	58±16
Lazoura et al. 2010	128-slice	1,044	Suspected CAD	74%	≈60.7
Yorgun et al. 2010	64 slice	1,206	Known or Suspected CAD	58%	59±11
Aglan et al. 2010	64 slice	542 (Full Field) 542 (Cardiac Field)	Low-Intermediate Risk CAD	56%	≈58

NR: Not Reported

Table 9. Prevalence of Incidental Findings in Included Studies

Study	Patients w/Incidental Findings n (%)	Significant Findings n (%)	Incidental Cancers n (%)	Pulmonary Nodules n (%)	Smoking Current/Former n (%)
Kawano et al. 2007	149 (24.1)	NR	7 (1.1)	58 (9.4)	NR
Kirsch et al. 2007	67 (67.0)	16 (11.0)	0	NR	NR
Husmann et al. 2009	400 (68.7)	196 (33.7)	3 (0.5)[a]	156 (26.8)	235 (40)
Koonce et al. 2009	196 (26.6)	149 (20.2)	NR	87 (11.8)	NR
Lehman et al. 2009	177 (44.8)	81 (20.5)	2 (0.5)	100 (25.3)	190 (48.1)
Machaalany et al. 2009	401 (41.5)	80 (8.3)	6 (0.6)	63 (6.5)	245 (25.4)
Lazoura et al. 2010	588 (56.3)	174 (16.7)	2 (0.2)	52 (4.9)	751 (72.0)
Yorgun et al. 2010	NR	NR	3 (0.2)	90 (48.4)	469 (38.9)
Aglan et al. 2010 (Full field)	234 (43.2)	132 (24.4)	1 (0.2)	22[b]	NR
Aglan et al. 2010 (Cardiac field)	182 (33.6)	78 (14.4)	1 (0.2)	12[b]	NR

NR: Not Reported
[a] Detected with follow-up
[b] Total, not per patient

were less frequent in the restricted field. In the emergency setting Lehman et al. (2009) reported clinical significant findings in approximately 5% of 395 patients, but 21% of the cohort received recommendations for further evaluation of some incidental finding. Despite detecting an occasional remediable condition, there is no evidence or reason to suspect that detection of incidental findings will lead to any clinical benefit.

Discussion

Strategies for evaluating patients with chest pain in the emergency setting without evidence of acute coronary syndromes have evolved. A variety of approaches can be used—hospitalization, chest pain units, exercise treadmill testing, stress echocardiography, MPI, and more recently coronary CTA (and MRI). Yet there are only a handful of published direct comparisons between strategies. In current practice, MPI is the most common noninvasive testing strategy used to avoid hospitalization. Support for this practice derives from a single trial comparing MPI to usual care that included 2,146 patients without acute ischemia (Udelson et al. 2002) together with evidence for a high negative prognostic value of MPI. Whether MPI is the superior noninvasive strategy is unclear.

Coronary CTA offers an alternative owing to its ability to identify coronary stenoses and to provide results quickly. A normal test obtained in a patient without acute ischemia arguably provides sufficient prognostic certainty that cardiac events are unlikely, so hospitalization is safely avoided. But when evidence for all relevant outcomes is considered, is a coronary CTA strategy as good as alternatives?

The qualitative model or framework outlined (Figure 1) for relevant outcomes accompanying noninvasive strategies (including coronary CTA) requires evidence on cardiac events, angiography rates, radiation exposure, duplicate testing, and incidental findings. While spending less time in the emergency room is relevant and of interest, it is not as important as adverse cardiac events. Costs and efficiencies are therefore not to be neglected—but more relevant to resource utilization—are aspects of decision making of lesser interest here.

Adverse Cardiac Events

As expected in a low-risk population, cardiac events following a negative coronary CTA occur infrequently. Results from identified trials and observational studies are consistent. While evidence does not demonstrate lower adverse cardiac event rates following coronary CTA than MPI or other noninvasive testing strategies, exceedingly large samples would be required to show plausible differences. Similarly, indirect evidence indicates coronary CTA has as good, and possibly better, prognostic value than other noninvasive strategies (Tables 1 through 3 and Table 7). Borrowing evidence from a higher-risk population, patients with stable angina, a recent meta-analysis of 18 studies estimated the pooled annual adverse cardiac event rate (cardiac death, MI, or revascularization) following a negative test to be 0.17% (Hulten et al. 2011). For comparison in this population, annual cardiac death and MI rates following a negative MPI are estimated to be 0.6% and 0.8%, respectively after negative stress echocardiography (Metz et al. 2007).

Invasive Coronary Angiography Rates

Because a goal of noninvasive testing is to obviate a need for invasive coronary angiography, angiography rates are of interest. In both trials, angiography rates following coronary CTA were somewhat higher than after an MPI strategy, but differences were small and likely attributable to chance. In a previous trial comparing MPI to usual care (Udelson et al. 2002), following MPI, the angiography rate (7.1%) was similar to rates following coronary CTA or MPI in CT-STAT. Angiography rates following a negative MPI varied considerably in the observational studies reporting prognosis (Table 2). Given limited data for coronary CTA and MPI, there is uncertainty whether a difference exists.

Radiation

Radiation with the current generation coronary CTA scanners is lower than radiation exposure accompanying MPI. In CT-STAT utilizing retrospective gating techniques, cumulative exposure was significantly less following coronary CTA. Given the reduction realized with prospective gating, radiation exposure with coronary CTA will continue to decrease.

Duplicate Testing

Lack of a definitive result with any noninvasive test can lead to angiography, or alternatively, a second noninvasive test. Because coronary CTA defines coronary artery anatomy and not ischemia, an inconclusive result is often logically followed by a functional test. Evidence regarding comparative differences in obtaining a second noninvasive test is limited to CT-STAT and was greater following coronary CTA. Despite the difference, cumulative radiation exposure was lower in the coronary CTA arm.

Incidental Findings

Incidental findings following coronary CTA are common and lead to further testing without evidence suggesting benefit. Their identification prompts additional testing and costs; the average per patient cost incurred was reported by Machaalany et al. (2009) to be $86, and by Lee et al. (2010) $17.

Costs and Efficiency

Results from the two trials support concluding that a coronary CTA strategy is quicker and less costly than a MPI strategy.

Potential Biases and Uncertainties

There are few direct comparisons of diagnostic strategies used in the emergency setting for evaluation of patients with acute chest pain. However, a negative exercise treadmill test, MPI, or coronary CTA confer a favorable prognosis. Studies suggest a normal coronary CTA could have a better prognosis than following other tests but given the low event rates, existing evidence is insufficient to allow a conclusion. Angiography rates were similar following coronary CTA and MPI in the 2 trials, but deserve further study. Use of a second noninvasive test following coronary CTA is likely more common, but not at the expense of radiation exposure, costs, or efficiency of diagnosis. Incidental findings accompany only coronary CTA, can be minimized by limiting images to cardiac structures, and result in further testing without evidence for benefit.

Conclusion

There are uncertainties that future research should address. Observational studies or well-designed registries could inform many of these uncertainties—particularly prognosis, angiography rates, and use of a second noninvasive test. Given the lower radiation exposure and negative prognostic value, evidence supports concluding that the net health outcome following a coronary CTA strategy is as good as those following the dominant strategies currently used in practice.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) made the following judgments about coronary CTA for patients with acute chest pain presenting to the emergency room with no known history of coronary artery disease, and found not to have evidence of acute coronary syndromes.

1. **The technology must have final approval from the appropriate governmental regulatory bodies.**

Coronary CTA is performed using multidetector-row CT (MDCT) and multiple manufacturers have received U.S. Food and Drug Administration (FDA) 510(k) clearance to market machines. Current machines are equipped with at least 64 detector rows. Intravenous iodinated contrast agents used for coronary CTA have also received FDA approval.

2. **The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

For patients with acute chest pain presenting to the emergency room with no known history of coronary artery disease, and found not to have evidence of acute coronary syndromes, there is sufficient evidence to permit conclusions concerning the effect of coronary CTA on relevant health outcomes.

3. **The technology must improve the net health outcome.**
4. **The technology must be as beneficial as any established alternatives.**

By avoiding adverse cardiac events, use of coronary CTA in the target population will improve the net health outcome, as well as other strategies currently used in practice.

5. **The improvement must be attainable outside the investigational settings.**

Coronary CTA is widely available and used outside the investigational setting. The main clinical trial evaluating its use was primarily performed in real-world settings.

Based on the above, for patients with acute chest pain presenting to the emergency room with no known history of coronary artery disease, and found not to have evidence of acute coronary syndromes, coronary CTA meets the TEC criteria.

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Appendices

Appendix A. Abbreviations/Definitions

ACS	acute coronary syndromes
ECG	electrocardiogram
MACE	major adverse cardiac events; although can have many definitions (Kip et al. 2008)
ETT	exercise treadmill testing
SECHO	stress echocardiogram
MPI	myocardial perfusion imaging (inclusive of all variations, e.g., single-photon computed tomography [SPECT], positron emission tomography [PET])
Coronary CTA	coronary computed tomographic angiography (recommended usage by Society of Cardiovascular and Computed Tomography) (Weigold et al. 2011)

Appendix B. Search Strategies and Modified PRISMA Diagrams

Randomized Controlled Trials

(Myocardial ischemia [MH] OR Myocardial [TIAB] OR Coronary [TIAB] OR Ischemic heart [TIAB] OR Angina [TIAB] OR Acute Coronary Syndrome[MH] OR Chest Pain[MH])
AND (Multidetector* [TIAB] OR Multislice* [TIAB] OR Multi slice* [TIAB] OR Msct* [TIAB] OR Mdct* [TIAB] OR Multi detector [TIAB] OR Computed tomograph* [TIAB] OR Spiral ct [TIAB] OR Helical ct [TIAB] OR Spiral computed [TIAB] OR Helical computed[TIAB] OR Tomography, spiral computed [MH] OR Tomography, X-Ray Computed [MH])
NOT (Case reports [PT] OR Comment [PT] OR Editorial [PT] OR Letter [PT] OR News [PT] OR Newspaper article [PT] OR Review [PT] OR Scientific integrity review [PT])
AND English [LA]
AND ((((“Randomized Controlled Trial “[Publication Type] OR “Randomized Controlled Trials as Topic”[Mesh])) OR “Controlled Clinical Trial “[Publication Type]) OR “Random Allocation”[Mesh]) OR “Double-Blind Method”[Mesh] OR (“Clinical Trial “[Publication Type] OR “Clinical Trials as Topic”[Mesh]) OR “clinical trial”

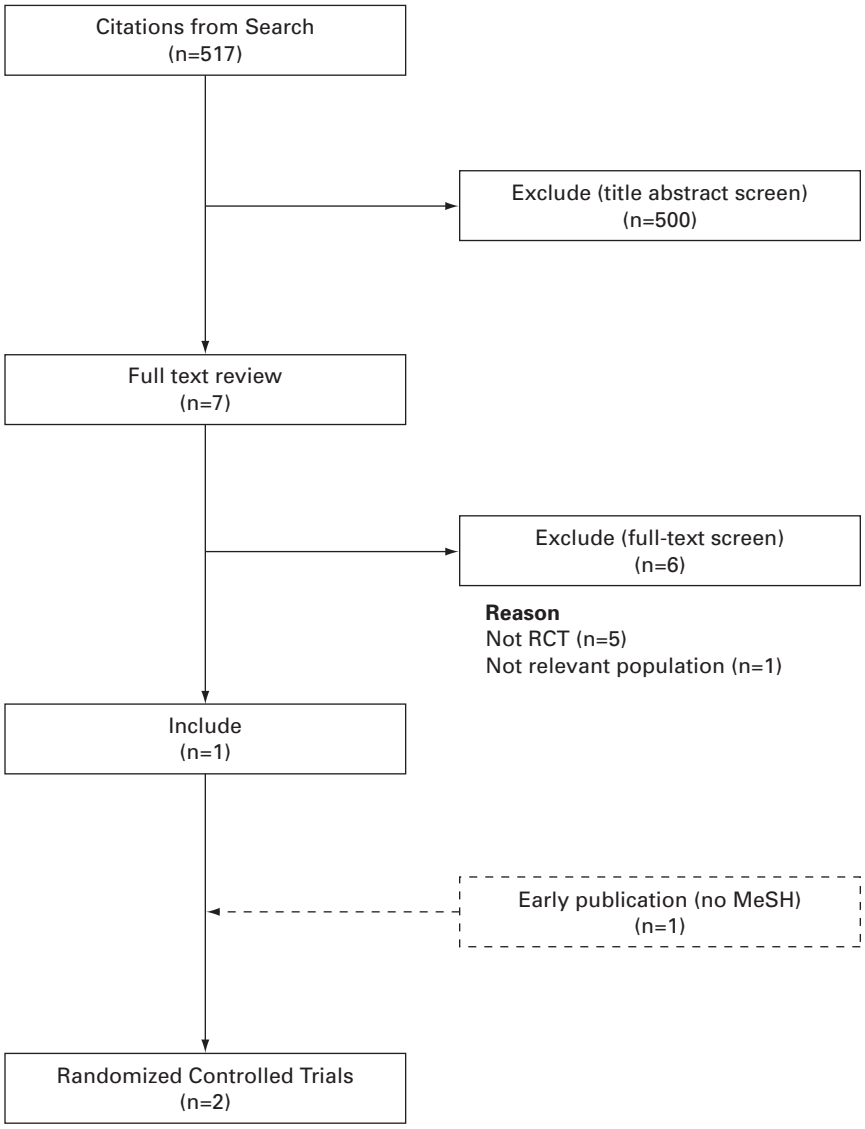
Prognosis

(Myocardial ischemia [MH] OR Myocardial [TIAB] OR Coronary [TIAB] OR Ischemic heart [TIAB] OR Angina [TIAB] OR Acute Coronary Syndrome[MH] OR Chest Pain[MH])
AND (Multidetector* [TIAB] OR Multislice* [TIAB] OR Multi slice* [TIAB] OR Msct* [TIAB] OR Mdct* [TIAB] OR Multi detector [TIAB] OR Computed tomograph* [TIAB] OR Spiral ct [TIAB] OR Helical ct [TIAB] OR Spiral computed [TIAB] OR Helical computed[TIAB] OR Tomography, spiral computed [MH] OR Tomography, X-Ray Computed [MH])
NOT (Case reports [PT] OR Comment [PT] OR Editorial [PT] OR Letter [PT] OR News [PT] OR Newspaper article [PT] OR Review [PT] OR Scientific integrity review [PT])
AND English [LA]
AND Emergency Service, Hospital [MH] AND Predictive Value of Tests[MH]

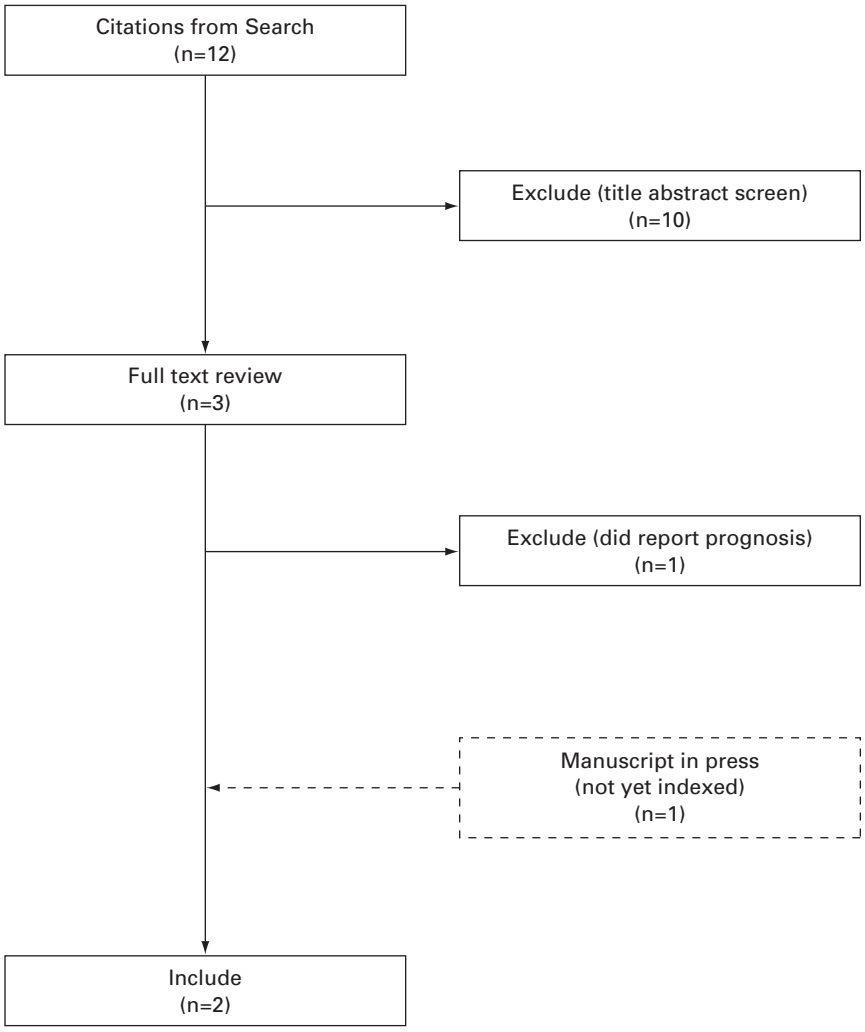
Incidental Findings

(Myocardial ischemia [MH] OR Myocardial [TIAB] OR Coronary [TIAB] OR Ischemic heart [TIAB] OR Angina [TIAB] OR Acute Coronary Syndrome[MH] OR Chest Pain[MH])
AND (Multidetector* [TIAB] OR Multislice* [TIAB] OR Multi slice* [TIAB] OR Msct* [TIAB] OR Mdct* [TIAB] OR Multi detector [TIAB] OR Computed tomograph* [TIAB] OR Spiral ct [TIAB] OR Helical ct [TIAB] OR Spiral computed [TIAB] OR Helical computed[TIAB] OR Tomography, spiral computed [MH] OR Tomography, X-Ray Computed [MH])
NOT (Case reports [PT] OR Comment [PT] OR Editorial [PT] OR Letter [PT] OR News [PT] OR Newspaper article [PT] OR Review [PT] OR Scientific integrity review [PT])
AND English [LA]
AND Incidental [ALL]

Appendix Figure B1. Modified PRISMA Diagram Randomized Controlled Trials



Appendix Figure B2. Modified PRISMA Diagram Prognostic Studies



Appendix C. Supplemental Tables

Table C1. Patients Included in Studies of Exercise Treadmill Testing in Emergency Department Patients with Acute Chest Pain—after (Amsterdam et al. 2010)

Study	Mean Age	Men (%)	White (%)	Smoking (%)	History of CAD (%)	Prior MI (%)	DM (%)
Zalenski 1997	46.6	53.5	7.6	—	—	—	—
Gibler 1995	45.0	50.7	38.7	—	—	—	—
Gomez 1996	50.0	62.0	—	22.0	2.0	—	—
Kirk 1998	49.0	57.1	—	—	6.0	—	—
Amsterdam 2002	50.5	52.0	—	—	7.5	—	—
Kerns 1993	35.0	62.5	—	—	—	—	—
Polanczyk 1998	56.5	47.1	—	—	—	13.8	
Ramakrishna 2005	57.6	56.0	—	17.0	23.0	14.0	8.0
Tsakonis 1991	44.8	82.1	—	—	—	—	—
Diercks 2000	47.0	54.5	—	55.7	4.1	4.1	10.0
Sarullo 2000	57.0	66.8	—	42.6	—	—	18.4

Table C2. Patients Included in Studies of Perfusion Imaging Testing in Emergency Department Patients with Acute Chest Pain—after (Amsterdam et al. 2010)

Study	Mean Age	Men (%)	White (%)	Smoking (%)	History of CAD (%)	Prior MI (%)	DM (%)
Kontos 1997	56	39.3	—	40.2	—	21.4	25.2
Heller 1998	—	57	—	58	—	—	17
Kontos 1999	36	67	—	63	—	—	6
Udelson 2002	53	53	62	28	13	—	13
Schaeffer 2007	44.8	50.7	37.7	59.2	—	—	12.8
Hilton 1994	—	—	—	—	—	—	
Tatum 1997	52	48	—	48.5	26	—	22.5
Varetto 1993	58.5	54.7	—	39.1	—	—	9.4

Table C3. Patients Included in Studies of Stress Echocardiography Testing in Emergency Department Patients with Acute Chest Pain—after (Amsterdam et al. 2010)

Study	Mean Age	Men (%)	White (%)	Smoking (%)	History of CAD (%)	Prior MI (%)	DM (%)
Nucifora 2007	52.0	52.0	—	44.0	7.0	3.0	8.0
Trippi 1997	49.8	52.1	—	30.7	—	—	4.9
Geleijnse 2000	58.0	66.0	—	46.0	58.0	—	14.0
Bholasingh 2003	56.0	58.0	—	37.0	20.0	—	10.0

Table C4. Patients Included in Prognostic Studies of Coronary CTA Testing in Emergency Department Patients with Acute Chest Pain

Study	Mean Age	Men (%)	White (%)	Smoking (%)	History of CAD (%)	Prior MI (%)	DM (%)
Schlett 2011	52.8	61.4	—	48.9	24.2	—	10.9
Hollander 2009	46.1	40.0	23	30.0	17.0	0.4	

Table C5. Quality Assessment of Randomized Controlled Trials

	Goldstein 2007	CT-STAT 2011
Groups/randomization		
Adequate randomization	Yes	Yes
Initial assembly comparable groups (covariates appropriately distributed)	Yes	Yes
Adequate allocation concealment	Yes	Unclear[a]
Follow-up and maintenance comparable groups		
Maintenance of comparable groups	Yes	Unclear[b]
Approximately 20% loss to follow-up in each arm	Yes	No for MACE[b]
Equal measurements		
Measurements equal reliable valid	Yes	Yes
Comparable interventions		
Interventions comparable and clearly defined	Yes	Yes
Appropriate analyses		
Intention to treat analysis	Yes	Yes
Other aspects of analyses appropriate (e.g., missing data, sensitivity analyses)	Yes	Yes
Overall Quality	Good	Fair

[a] Envelopes used; 1:1 allocation and unspecified block size.
[b] Differential loss to follow-up for MACE (major adverse cardiac events) over 1 to 6 months; overall mortality ascertained for similar groups.

Technology
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