



COMPUTED TOMOGRAPHIC ANGIOGRAPHY IN THE DIAGNOSIS OF CORONARY ARTERY STENOSIS AND FOR THE EVALUATION OF ACUTE CHEST PAIN

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum was requested to review the scientific evidence for the use of cardiac computed tomographic angiography in the diagnosis of coronary artery stenosis and for the evaluation of acute chest pain. This review was prompted by reports that there may be new information about cardiac computed tomography published since this topic was evaluated by the Blue Cross Blue Shield Association Technology Evaluation Center (BCBSA TEC) in August, 2006¹.

BACKGROUND

Coronary artery disease (CAD) is the number one cause of death in men and women. CAD is caused by atherosclerotic plaques developing in the coronary arteries. Many therapies have been shown to decrease CAD mortality, therefore early detection and treatment is critical.

The gold standard for defining coronary artery anatomy is angiography. During coronary angiography, a catheter is introduced into the femoral, brachial or radial artery and is then passed up to the aorta. Iodinated contrast dye is then directly injected into the coronary arteries, while digital X-ray images are taken. Although the risks are generally considered low, there are some risks to the procedure. These include bleeding and other complications at the catheter insertion site, catheter manipulation causing embolization of plaque leading to stroke or myocardial infarction, dye related complications, including allergic reactions and renal toxicity, and exposure to radiation, which may be associated with an increased risk of cancer^{2, 3}.

Coronary artery computed tomography (CT) angiography (CTA) is a non-invasive technology that can directly image coronary artery anatomy, while decreasing some of the risks associated with an invasive procedure. It has been proposed as an alternative to coronary angiography. CTA requires the use of contrast material (administered intravenously) and high speed high resolution CT machinery to take detailed volumetric pictures of blood vessels.



There are several technical challenges involved in getting good images with CTA. First, the image must be obtained in a short period of time to avoid blurring. Sometimes beta blockers are given before the procedure to slow the heart down; therefore pictures can then be taken during diastole when motion is reduced. Second, rapid scanning is best so that the images can be taken while the patient is holding his/her breath. Third, thin sections enable higher quality images. Volumetric imaging is then performed and enables multiple images to be reconstructed to fully demonstrate the coronary arteries.

Multidetector row CT (MDCT) scanning uses helical CT (rotating a tube around the patient to get continuous spiral images). They have multiple detectors – 4, 8, 16, 32, 40 or 64. Limitations of MDCT include: 1) it is harder to obtain good images with a fast heart rate, and 2) the distal portions of the coronary arteries are more difficult to see due to more motion artifact. Many of the earlier studies were done with 16 row MDCT, but MDCT with at least 32 rows is soon likely to become standard.

Important negative consequences of CTA are radiation exposure, which is significantly higher than conventional angiography³, and nephrotoxicity from the dye. An additional potential complication is the identification of incidental non-coronary lesions, which then require additional evaluation to determine their significance.

Two potential uses of CTA are addressed in this report; 1) Use of CTA to diagnose coronary artery stenosis, and 2) use of CTA in the evaluation of acute chest pain.

Use of CTA to diagnose coronary artery stenosis has the goal of determining whether or not patients have significant stenoses of the coronary arteries, while avoiding an invasive procedure. CTA could be used as an alternative to invasive angiography or as an additional noninvasive cardiac test that may be complementary to other noninvasive tests routinely used (e.g. exercise stress tests). An important issue to consider is whether or not it replaces other diagnostic tests or becomes an additional or additive test.

For patients with acute chest pain being evaluated in the emergency room, an important goal would be to exclude clinically significant CAD, so as to avoid unnecessary hospitalization. It would thus potentially be most useful in a low risk chest pain population.



TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from appropriate government regulatory bodies.

Several manufacturers (including GE Healthcare, Philips Medical, Toshiba Medical and Siemens Medical) have received clearance to market MDCT machines equipped with at least 16 detector rows through the FDA 510 (k) process. The intravenous iodinated contrast agents used for cardiac CTA have also received FDA approval.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

Search Methods: The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words 'X-ray computed tomography', 'coronary computed tomography or coronary tomographic angiography' and cross-referenced with the keywords 'heart disease' and 'coronary artery disease'. The search was performed for the period from 1966 through July 2007. We also included the following search limits: English language reports, human subjects, and publication type (randomized controlled trials, controlled trials, review, meta-analysis, editorial). The bibliographies of systematic reviews and key articles were manually searched for additional references. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

Diagnosis of Coronary Artery Stenosis-Criteria: We used similar criteria to that used for the TEC report in August, 2006 to define study inclusion criteria. For studies of CTA as an alternative to coronary angiography for diagnosing coronary artery stenosis, studies had to meet the following criteria:

- Used contrast enhanced electron beam computed tomography (EBCT) with slice thickness no greater than 1.5 mm or contrast enhanced MDCT with at least 32 rows. Many of the earlier studies were done with 16 row MDCT, but MDCT with at least 32 rows will soon become the standard so these are the focus of this review.
- Applied reference standard of invasive angiography to all patients

- Reported sensitivity and specificity for per patient analyses and/or provided enough data to calculate them
- Included only humans
- Published in English as a peer reviewed article

Evaluation of Chest Pain Criteria: To evaluate the use of CTA in managing patients in the emergency room, we also used similar criteria to the TEC reviews. We selected prospective studies where patients who met specific chest pain and clinical criteria were chosen to have the test. Typically, the criteria included factors associated with having “low risk” chest pain. For example, no prior CHD, no clear ischemic EKG changes and no elevation of cardiac enzymes, all of which would suggest a higher pre-test likelihood of disease.

Search Results: A total of 14 articles met the criteria for diagnosis of coronary artery stenosis and a total of five articles met the criteria for the evaluation of chest pain.

CTA in the Diagnosis of Coronary Artery Disease

Summary of Prior Studies: Six earlier studies of 16 row CTA performed per patient analyses (as opposed to per segment analyses) and compared CTA with invasive angiography. In most of these studies, CTA was interpreted without knowledge of the angiography results. Only one study ⁴ was a multicenter study and only one study ⁵ focused on a low risk population [Table 1].

Table 1: Results of Per-Patient Analyses of 16 Row CTA

Adapted with permission from Blue Cross and Blue Shield Association TEC Assessments, vol.21, no. 5, Table 3, p.9. ©2006¹

Study	N (patients)	Prevalence of Stenosis (%)	Sensitivity (%)	Specificity (%)
Ropers, 2003 ⁶	77	53	85	78
Hoffmann, 2005 ¹⁸	33	67	90	75
Mollett, 2004 ⁷	128	83	100	86
Mollet, 2005 ⁸	51	61	100	85
Garcia, 2006 ⁴	187	32	98	54
Nikoloau, 2006 ⁵	60	8	80	94.5

Several of the studies also reported “per-segment analyses” which are less clinically relevant. Often the non-evaluable segments were excluded, which led to exaggerated sensitivities and specificities. Additional limitations of all of these studies are their relatively small sizes and a high proportion of non-evaluable segments. In general, the sensitivity was quite high, resulting in a high negative predictive value. But, the specificity was more variable, which resulted in a lot of false positives, especially in a low-risk population.

Studies of CTA with 32 rows or greater. Resolution improves with a greater number of rows, thus, the newer studies have focused on CTA with 32 rows or more. Eight studies met the inclusion criteria, included per patient outcomes and are described below. All but one were 64 slice CTA.

Table 2: Per Patient Diagnostic Test Characteristics of >32 slice CTA to Detect Patients with one or more lesions >50%

Adapted with permission from Blue Cross and Blue Shield Association TEC Assessments, vol.21, no. 5, Table 5, p.12 ©2006¹

Study	Excluded Patients	N (patients)	Number of Slices	Prevalence of Stenosis	Sensitivity	Specificity
Leber, 2005 ⁹	4	45*	64	56	88	86**
Mollet, 2005 ⁸	1	51	64	75	100	92
Raff, 2005 ¹⁰	0	70	64	57	95	90
Ropers, 2006 ¹¹	3	81	64	32	96	91
Pugliese, 2006 ¹²	0	35	64	71	100	90
Leschka, 2005 ¹³	0	67	64	70	100	100***
Grosse, 2007 ¹⁴	0	40	40	75	97	100
Shabestari, 2007 ¹⁵	5	138	64	78	96	67

*per patient results reported only on patients without stents

** specificity calculated based on threshold of 75% stenosis, different from 50% threshold for sensitivity

***numbers not cited in the paper but stated in words, “in all patients with CAD, at least one lesion was appropriately classified; all patients without CAD could be correctly determined”.

Study size was generally small, ranging from 35 to 138 patients. In general, participants were individuals who were scheduled to undergo angiography anyway, and who were considered at least at intermediate risk, and therefore the prevalence of CAD was high: from 32-78%. All participants underwent angiography as the gold standard diagnostic test. With the exception of the study by Leber,⁹ test sensitivity was quite

high, ranging from 95-100%. Test specificity, although not perfect is significantly improved from earlier studies and ranges from 67-100%. With the exception of the study by Ropers, the prevalence of CAD is high (>50%) in these study populations. Thus, the utility of CTA in low risk populations, who are the individuals most likely to benefit from avoiding angiography, is not known.

An important question is whether or not CTA can include or exclude proximal disease that should be treated with coronary revascularization? Another related question is what is the accuracy of CTA in assessing one vessel versus two-vessel versus three-vessel disease? Given its high negative predictive value, a totally normal CTA can exclude significant disease that would require revascularization, and can thus obviate the need for angiography. However, an important limitation of CTA would be the challenges in determining the hemodynamic significance of intermediate lesions, which limits its ability to assess the significance of disease in individual vessels.

In summary, 32-slice or greater scanners are more accurate in CAD diagnosis than scanners with fewer slices. In contrast to 16 row scanners, 64 row scanners are more sensitive and also more specific. However, radiation exposure is higher in higher row scanners. All of the studies of the 64 row scanners included a population with a high prevalence of CAD. Thus, the utility of CTA in a lower risk population, who are more likely to have false positive tests, is not known.

CTA in the Evaluation of Patients with Chest Pain in the Emergency Department

Four studies have studied the use of MDCT in the evaluation of chest pain in the emergency room. Only one was a trial comparing the use of CTA to an alternative standard. Estimates of sensitivity and specificity were calculated based on a mixed "gold standard" which included angiographic and clinical data. The studies are listed in the Table below:

Table 3: Performance of CTA in Chest Pain Patients in the ER

Study	Excluded patients	N (patients)	CT # rows	Prevalence of stenosis	Sensitivity (%)	Specificity (%)
Sato, 2005 ¹⁶	3	31	4 or 16	71	96%	89%
White, 2005 ¹⁷	0	69	16	17	83	96
Rubinshtein, 2007 ¹⁸	0	58	64	40	92	76
Hoffman, 2005 ¹⁹	3	103	64	14%	1.00	0.82
Goldstein, 2007 ¹⁹	0	99 (197 in overall study; 99 in CTA arm)	64	12%	Unable to calculate	Unable to calculate *



- MSCT was not considered adequate for diagnosis in 24 of 99 patients due to intermediate severity lesions or non-diagnostic scans and not all patients underwent catheterization.

In two early studies^{16, 17}, 4 or 16 row CT was performed on individuals presenting to the ER with chest pain. One study¹⁶ included patients that had non-diagnostic EKG changes and normal cardiac enzymes. In the other study¹⁷, patients received CTA to evaluate causes of chest pain, including angina and pulmonary embolism. Twenty-four of the 89 patients enrolled in the study would have received CTA for other indications. Neither study compared CTA with other evaluation modalities. Each study had less than 100 patients, and both used a mixed reference standard for determining the presence or absence of CAD. In neither of these studies was the result of CTA available in the ER, so it was not used to make discharge decisions. Thus, the results of these studies could not be compared to an alternative strategy that does not use CTA.

A more recent study used the same design but a 64 row scanner. Rubinshtein et al performed 64-slice CT on 58 intermediate risk patients with chest pain¹⁸. Patients were deemed to be intermediate risk if they had chest pain, a normal baseline EKG and no clinical suspicion of alternative diagnoses such as pulmonary embolism, aortic dissection or pericarditis. The reference standard included angiography and clinical findings. In this group, where the prevalence of stenosis was 40%, the sensitivity was 92% and the specificity was 76%. During 15-month follow-up, no deaths or myocardial infarctions occurred in the 35 patients discharged from the ED after triage and based on CTA findings.

In all three of these studies, the result of CTA were not used to make discharge decisions and CTA was not compared to an alternative strategy; therefore the role and efficacy of CTA in the evaluation of patients with acute chest pain could not be determined. The finding that individuals discharged from the ER after CTA results did not have any adverse outcomes is promising, but not conclusive as the absolute numbers are small.

Hoffman and colleagues conducted a blinded prospective study using 64 row CTA¹⁹. Participants were patients with chest pain, but had normal or indeterminate EKGs and normal initial cardiac biomarkers, admitted to rule out acute coronary syndrome (ACS). One hundred and three individuals underwent CTA on admission. An expert panel blinded to CTA determined the presence of ACS based on all available data gathered during hospitalization and five month follow-up. For detecting coronary stenosis, MDCT has a 100% sensitivity and a specificity of 82%. The absence of significant coronary artery stenosis and nonsignificant coronary atherosclerotic plaque accurately predicted the absence of ACS, the most important



clinical outcome (negative predictive value 100%). Again, since there was no comparison evaluation approach, we cannot determine how CTA performs compared with other diagnostic strategies.

The study by Goldstein et al was the only randomized controlled trial of multi-slice coronary computed tomography for the evaluation of acute chest pain²⁰. Patients with “low-risk” chest pain at a single site were randomized to CTA (n=99) versus standard of care (n=98). Exclusion criteria included known CAD, EKG changes suggestive of ischemia/infarction, elevated serum biomarkers, known cardiomyopathy, atrial fibrillation, obesity and renal insufficiency. CTA was performed with a 64 slice scanner, and results were evaluated by an investigator blinded to other information. Patients in the standard of care group got serial EKGs, cardiac biomarkers and same day nuclear stress testing. Decisions about further testing and treatment were defined by prespecified clinical algorithms, so that not all patients underwent angiography. CTA immediately identified or excluded disease in 75% of patients (eight had severe CAD and 67 had normal coronary arteries). The remaining 25% of patients required additional stress testing because of intermediate severity lesions or intermediate diagnostic scans. Six-month clinical outcomes including rehospitalization and the number of patients requiring subsequent cardiovascular evaluation were not significantly different between the two groups, but the numbers were small. The high proportion of indeterminate scans limits the utility of CTA in the ED, where the goal would be to identify patients who do not need further testing and can be safely discharged.

In summary, especially with the 64 row scanners, MDCT sensitivity is quite good, which ensures that most patients with significant coronary artery disease will not be missed. However, specificity is not ideal, which means that some people will be subjected to unnecessary additional testing. In the one study where MDCT was evaluated in comparison with the standard of care in evaluating individuals with chest pain, it was useful and accurate in many patients, but about 25% of patients had tests that could not be interpreted and therefore required additional testing, thus limiting its utility in the ED setting. Finally, since MDCT cannot provide physiologic blood flow data, the significance of some intermediate lesions is unclear and therefore angiography may still be required to evaluate blood flow.

Level of Evidence: 2, 3 and 5

TA Criterion 2 is not met



TA Criterion 3: The technology must improve net health outcomes

For a diagnostic test, ideally there should be evidence that use of the test would result in improved medical management in a way that would benefit the patient. Ideally, the consequences of missed diagnoses by CTA would need to be compared to the consequences of avoided negative angiography to determine overall health outcomes and this has not yet occurred.

CTA in the Diagnosis of CAD

Studies of CTA as a diagnostic test have assessed its test characteristics, but have not compared it with conventional non-invasive diagnostic strategies. Therefore, there is no current evidence that CTA improves net health outcomes compared with conventional diagnostic strategies.

TA Criterion 3 is not met

CTA in the Evaluation of Chest Pain

One randomized controlled trial has evaluated CTA compared with another standard in the evaluation of chest pain. The study by Goldstein et al was the only randomized controlled trial of multi-slice coronary computed tomography for the evaluation of acute chest pain. As described above, patients with low-risk chest pain at a single site were randomized to multi-slice CT (n=99) versus standard of care (n=98). CTA was performed with a 64 slice scanner and results were evaluated by an investigator blinded to other information. Patients in the standard of care group got serial EKGs, cardiac biomarkers and same day nuclear stress testing. Decisions about further testing and treatment were defined by prespecified clinical algorithms. CTA immediately identified or excluded disease in 75% of patients (eight had severe CAD and 67 had normal coronary arteries). The remaining 25% of patients required additional stress testing because of intermediate severity lesions or intermediate diagnostic scans. Thus, CTA can definitely include or exclude CAD as the cause of chest pain in some patients, but there are many patients in whom CTA is indeterminate (lesions of intermediate severity or those that were not adequately imaged), who then require additional testing to clarify the diagnosis. In addition, clinically important outcomes such as number of patients admitted to the hospital, length of stay in the hospital or ED were not reported, although the number of individuals requiring late cardiovascular evaluation after the test was similar in both groups. Whether or not CTA improves long-term outcomes compared with conventional strategies is not known.



TA Criterion 3 is not met

Harms

Although MDCT is non-invasive, the main potential harms are radiation exposure and renal damage from the dye. An increase in the number of rows in the scanner increases the sensitivity and specificity of the test, but also increases the radiation exposure. Radiation exposure is three to four times greater than that with conventional angiography^{3, 21}. It has been estimated that a 10 MSv CT study may be associated with an increase in the probability of fatal cancer by about 1/2000²². Recent estimates suggest that the use of 64 slice CTA is indeed associated with an increased lifetime attributable risk of cancer, and that this risk is greater for women, younger patients and for combined cardiac and aortic scans².

The other major harm comes from inaccuracy of the CTA leading to additional testing. For example, in the clinical trial of MTA in the emergency room by Goldstein, approximately 25% of patients needed additional testing to clarify the results of the CTA. Finally, a potential harm is renal damage from the contrast used in the test. Thus, given the clear evidence of harms and the fact that there is no clear evidence of benefit, currently there is inadequate evidence to conclude that the technology improves health outcomes.

TA Criterion 3 is not met

TA Criterion 4: The technology must be as beneficial as any of the established alternatives

Diagnosis of CAD

CTA has generally not been compared with the established alternatives. As described above, CTA has a relatively high sensitivity, especially with the 32 or greater row scanners, but a lower specificity. Thus, the negative predictive value is high, but there is a high false positive rate, which then leads to additional testing. In addition, in several studies a high proportion of studies are unevaluable, which further limits the utility of CTA. A precise estimate of the proportion of tests that are unevaluable is difficult to ascertain, because the absolute numbers of patients in each of the studies is small.



Evaluation of Chest Pain

In only one study was CTA compared with the standard of care for the evaluation of chest pain²⁰. In that study, although CTA was accurate for ruling in or ruling out significant CAD in about 75% of people, about 25% of individuals required additional diagnostic testing to clarify the diagnosis. In addition, the important clinical outcomes that should be evaluated, such as the number of patients with acute coronary syndrome and the number of patients safely discharged from the emergency room, have not been evaluated in most of the studies.

Based on this, there is not current evidence that CTA is as beneficial as any of the established alternatives. Ideally, we would like to see that CTA reduced the need for invasive procedures, accurately identified patients with ACS and correctly identified patients who could safely be sent home from the emergency room.

TA Criterion 4 is not met:

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Whether the use of CTA improves health outcomes when used to diagnose individuals with CAD or to evaluate patients with acute chest pain has not been demonstrated in the investigational setting and therefore it cannot be considered attainable outside this setting.

TA Criterion 5 is not met.

SUMMARY

In conclusion, cardiac CTA is being evaluated for use in the diagnosis of coronary artery stenosis or for the evaluation of acute chest pain. Although several studies have assessed diagnostic accuracy of CTA (e.g. sensitivity and specificity), fewer have assessed clinical outcomes or compared CTA to conventional diagnostic strategies. Additional limitations include the inability of CTA to accurately assess all the coronary arteries (a certain percentage of the arteries are read as indeterminate which then leads to additional diagnostic testing), and the risks of radiation exposure and nephrotoxicity. Although TA Criteria 1 is met (several CTA manufacturers have FDA approval), TA criteria 2, 3, 4 and 5 are not met.



RECOMMENDATION

- CTA as a substitute for coronary angiography for the diagnosis of coronary artery stenosis does not meet the CTAF TA criteria 2 through 5 for safety, efficacy and improvement in health outcomes..
- CTA in the evaluation of acute chest pain in the ER does not meet CTAF TA criteria 2 through 5 for safety, efficacy and improvement in health outcomes.

The California Technology Assessment Forum voted unanimously in favor of the recommendation.

October 17, 2007



RECOMMENDATIONS OF OTHERS

BLUE CROSS BLUE SHIELD ASSOCIATION (BCBSA)

Summary of prior TEC evaluations

Two prior TEC evaluations have addressed this topic (May 2005 and August 2006). The Medical Advisory Panel concluded that the evidence was inadequate to determine whether or not CTA improves net health outcomes or was as beneficial as other alternatives in the diagnosis or coronary artery stenosis or in the evaluation of chest pain in the ER, therefore, it was concluded that CTA did not meet TEC criteria.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

CMS has issued a National Coverage Analysis and requested public comments. The expected NCA completion date is March 12, 2008. Several organizations have responded to the call for comment. Comments are noted on the CMS web site.

CALIFORNIA CHAPTER OF THE AMERICAN COLLEGE OF CARDIOLOGY (CA ACC)

A CA ACC representative attended the meeting and participated in the discussion on this technology.

CALIFORNIA RADIOLOGICAL SOCIETY (CRS)

A CRS representative attended the meeting and participated in the discussion.

AMERICAN HEART ASSOCIATION (AHA)

The AHA and ACC have recently updated the AHA/ACC Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction. This guideline was released on August 6, 2007.

ABBREVIATIONS USED IN THIS REPORT

TEC: Technology Evaluation Center

CAD: Coronary artery disease

CT: Computed tomography

CTA: Computed Tomography Angiography

MDCT: Multi Detector Computed Tomography

EBCT: Electron Beam Computed Tomography

CHD: Coronary Heart Disease

EKG: Electrocardiogram

ACS: Acute Coronary Syndrome

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