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Contrast-Enhanced Cardiac Computed Tomographic Angiography in the Diagnosis of Coronary Artery Stenosis or for Evaluation of Acute Chest Pain

Executive Summary

Background

Coronary artery disease is currently diagnosed using angiography, an invasive procedure with risk of complications. Contrast-enhanced computed tomography angiography (CTA) is a noninvasive method of visualizing the coronary arteries, which might be useful in various clinical scenarios in which coronary artery disease is under consideration.

Objective

The objective of this Assessment is to determine the usefulness of CTA as a substitute for coronary angiography for two indications: 1) in the diagnosis of coronary artery stenosis, and 2) in the evaluation of acute chest pain in the emergency room (ER). Uses of CTA for other indications are not addressed in this Assessment.

Search Strategy

MEDLINE[®] was searched (via PubMed) through June 2006 to identify all articles pertaining to use of contrast-enhanced cardiac CT angiography.

Selection Criteria

Studies that evaluated 32- or greater row CTA and compared CTA to angiography for diagnosis of coronary artery stenosis, and any study evaluating CTA for patients with acute chest pain in the ER were selected.

Main Results

Seven studies compared CTA to angiography for diagnosis of coronary artery stenosis, ranging in size from 30 to 84 patients. These studies enrolled essentially convenience samples of consecutive patients scheduled to undergo angiography, and thus may be subject to spectrum bias. No study specifically studied a lower-risk subset of those patients referred for angiography, which is the target population for this procedure. A high prevalence of coronary stenosis was noted in all studies. In 5 studies reporting a per-patient analysis, 3 studies excluded patients with indeterminate test results. The sensitivity of CTA in identifying a 50% stenosis ranged from 88–100%, with 4 of 5 studies reporting sensitivities of at least 95%. Specificity ranged from 86–100%. In a per-segment analysis, sensitivity ranged from 79–99%, and specificity ranged from 95–98%. Four of these studies excluded either patients or segments from the analysis.

Two studies evaluated the use of CTA for patients with acute chest pain in the ER. The sample sizes of the studies were 31 and 69. The studies used a mixed reference standard of angiography, clinical data, and noninvasive testing, which allows a calculation of sensitivity and specificity, but does not allow a comparison of performance to an alternative strategy. No alternative strategies for diagnosis



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were evaluated. Sensitivity of CTA was 83% and 96%, and specificity was 89% and 96%. It is unknown whether this indicates better or worse performance than an alternative strategy.

Author's Conclusion and Comments

The studies evaluating the use of CTA in comparison to angiography are relatively small studies from single centers.¹ Their major failing is that they enrolled convenience samples of patients being referred for angiography. The results from these studies may not generalize to lower-risk populations. In addition, such studies only directly address the question of whether CTA can accurately triage patients already referred for angiography. The use of CTA as part of the initial workup of chest pain or possible angina is not addressed at all in these kinds of studies. However, analyzing the information from these studies solely from the perspective of sensitivity and specificity in identifying a specific amount of coronary stenosis may shortchange the potential utility of CTA. Visualizing the coronary anatomy may provide useful prognostic information for optimally managing patients even if no direct referral to angiography results. However, in order to demonstrate improved patient outcomes, valid prognostication tied to improved management and outcomes must be demonstrated. Clinical trials comparing patients undergoing CTA as part of their diagnostic workup compared to patients not undergoing CTA may be required to demonstrate improved patient outcomes. There is no evidence except in the ER regarding the use of CTA in the early workup of patients in whom CAD is being considered.

Current published studies of CTA in the management of acute chest pain in the ER are clearly inadequate to determine utility. No comparator strategy was specified in any study, and there was no solid reference standard for diagnosis. Clinical trials may be necessary to demonstrate utility in this setting.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether CTA for screening or diagnostic evaluation of the coronary arteries meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

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

Multiple manufacturers have received U.S. Food and Drug Administration (FDA) 510(k) clearance to market MDCT machines equipped with at least 16 detector rows and at least two models of EBCT machines have been cleared through FDA 510(k) clearance. Intravenous iodinated contrast agents used for cardiac CTA have also received FDA approval.

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

Current studies are inadequate to determine the effect of CTA on health outcomes for the diagnosis of coronary artery stenosis in patients referred for angiography or for evaluation of acute chest pain in the ER.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

The available evidence is inadequate to determine whether CTA improves the net health outcome or is as beneficial as established alternatives for diagnosis of coronary artery stenosis or for evaluation of acute chest pain in the ER.

¹ As this Assessment went to press, a multicenter trial of 16-row CTA was published (Garcia et al. 2006). This trial is summarized in the "Review of Evidence" as an addendum to the summary of the 2005 TEC Assessment (which was limited to 16-row technology or greater); however, its results do not change the conclusions of this Assessment.

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

Whether use of CTA improves health outcomes has not been established in the investigational setting.

Based on the above, CTA as a substitute for coronary angiography in the diagnosis of coronary artery stenosis does not meet the TEC criteria. CTA in the evaluation of acute chest pain in the emergency room also does not meet the TEC criteria.

Contents	
Assessment Objective	4
Background	4
Methods	6
Formulation of the Assessment	7
Review of Evidence	9
Discussion	14
Summary of Application of the Technology Evaluation Criteria	14
References	15
Appendix	16

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Assessment Objective

The objective of this Assessment is to evaluate the clinical effectiveness of contrast-enhanced cardiac computed tomographic angiography, hereafter referred to as CTA, for two specific uses—diagnosis of coronary artery stenosis and evaluation of acute chest pain. CTA may be performed using either electron beam computed tomography (EBCT) or multidetector-row computed tomography (MDCT), although most recent technical developments have been focused on MDCT. This report focuses on studies examining 64-row CTA, which provides better resolution than the previous generation of 16-row machines.

CTA has been proposed as a noninvasive alternative to invasive coronary angiography. This is the only indication that has been studied rigorously, as the vast majority of clinical studies simply compare the performance of CTA and invasive angiography. Negative findings on CTA obviate invasive angiography but those with positive CTA findings (i.e., significant stenosis) may still need to be confirmed by invasive coronary angiography. In this case, a high negative predictive value and high sensitivity for detection of coronary artery stenosis would be important. In this indication for CTA, patients have had sufficient prior workup so that the probability of coronary disease is sufficiently high to warrant invasive angiography. Because the principal value of CTA in this indication is the avoidance of angiography, it would be most valuable in the low-risk subset of patients referred for angiography.

CTA has also been proposed as an alternative noninvasive cardiac test which may be useful for managing patients with chest pain in the emergency room (ER). In patients without definitive findings of a cardiac origin of their pain, noninvasive tests and a period of observation are used to rule in or rule out a cardiac origin of pain. CTA may provide a more accurate and more timely diagnosis, improving patient outcomes and speeding up the evaluation of the patient.

The use of CTA to image the coronary arteries could be extended to other scenarios, such as the elective workup of chest pain as a substitute for other noninvasive tests, or for screening asymptomatic persons, but these indications will not be evaluated in this Assessment, because of lack of data in these populations.

Diagnostic performance would need to be specifically assessed in these lower-risk populations, and in comparison to other methods of diagnosis. Up to this point in time, CTA has not been rigorously evaluated as a diagnostic test to be used as an initial or early test in the workup of coronary disease.

Other less-common uses of CTA to evaluate less-common abnormalities of the coronary arteries, such as characterization of plaque, coronary artery aneurysm, and congenital anomalies will not be included in this Assessment. CTA may also be used to evaluate the cardiac chambers, coronary venous anatomy, myocardial wall thickness, and functional evaluation of the heart, including perfusion patterns of enhancement and estimation of ejection fraction; however, these uses are not included in this Assessment. Furthermore, this Assessment does not address the use of unenhanced cardiac computed tomography to quantify coronary calcification, which was addressed in a prior TEC Assessment on Electron Beam Computed Tomography (1994; Vol. 9, No. 16).

Background

Coronary Artery Stenosis

Evaluation of obstructive coronary artery disease (CAD) involves quantifying the presence and extent of arterial stenoses in coronary vessels. Symptomatic lesions with greater than 50–75% diameter stenosis are generally considered significant, and stenotic lesions of more than 70% often result in revascularization procedures when associated with ischemia. Patients with lesser degrees of coronary arterial stenosis may be managed with medical therapies. It has been suggested that computed tomographic angiography may be helpful to rule out the presence of significant CAD and to avoid invasive coronary angiography in patients with a low clinical likelihood of significant CAD.

The current reference standard for diagnosis of CAD is angiography, a procedure that requires specialized equipment and carries some risk of complications. Because of the resource use and risk of angiography, practice guidelines generally limit the indications for the procedure to patients in whom the probability of finding CAD is sufficiently high. In addition, the findings should have an impact on the management of the patient such that the

health outcomes, either symptom or survival outcomes, are improved. In many cases where significant stenoses are found on angiography, patients then receive either percutaneous angioplasty or coronary bypass surgery. In other cases, knowledge of the presence and extent of coronary stenoses could lead to different medical management and may improve health outcomes.

Emergency Room Evaluation of Chest Pain

Chest pain is a common reason for patients to be evaluated in the emergency room (ER). Patients with chest pain present both a diagnostic and management problem, because of the variety of possible diagnoses and the risk of missing, in the acute setting, a potentially lethal illness. A prior study by Pope et al. (2000) estimated that about 5% of patients with chest pain of cardiac etiology were discharged from emergency departments. In patients without immediate test results indicating chest pain of cardiac or other origin, it is common practice that a diagnostic algorithm using serial electrocardiograms, serial cardiac enzymes, and a stress imaging study is performed. Such an approach has been found to be as safe as hospital admission in a clinical trial (Farkouh et al. 1998). Although such an approach uses less medical care resources than hospitalization, it is still resource and time intensive, and the vast majority of patients do not have acute cardiac source of chest pain.

CTA could potentially replace or complement the evaluation of chest pain patients in the ER, reduce the length of stay, and reduce costs. In addition, chest CT is a standard method to diagnose at least 2 other causes of chest pain in which a rapid diagnosis is critical, pulmonary embolism and aortic dissection. CT performed to diagnose these conditions, however, is technically different than coronary CTA, and requires alteration in the technique such that the coronary arteries are not as well visualized compared to a CTA done strictly to examine coronary arteries.

Computed Tomographic Angiography

Computed tomographic angiography or CTA is a noninvasive imaging test that requires the use of intravenously administered contrast material and high-resolution, high-speed CT machinery to obtain detailed volumetric images of blood vessels. CTA can be applied to image blood vessels throughout the body; however, to apply CTA in the coronary arteries, several technical

challenges must be overcome to obtain high-quality diagnostic images. First, very short image acquisition times are necessary to avoid blurring artifacts from the rapid motion of the beating heart. In some cases, premedication with beta-adrenergic-blocking agents is used to slow the heart rate below about 60–65 beats per minute to facilitate adequate scanning, and electrocardiographic triggering or retrospective gating is used to obtain images during diastole when motion is reduced. Second, rapid scanning is also helpful so that the volume of cardiac images can be obtained during breath-holding. Third, very thin sections (e.g., ≤ 1 mm) are important to provide adequate spatial resolution and high-quality 3D reconstruction images.

Volumetric imaging permits multiplanar reconstruction (MPR) of cross-sectional images to display the coronary arteries. Curved MPR and thin-slab maximum intensity projections (MIPs) provide an overview of the coronary arteries, and volume-rendering techniques (VRT) provide a 3D anatomical display of the exterior of the heart. Quantification of coronary artery stenosis may be difficult given current techniques, although improvements in image reconstruction algorithms such as automatic vessel tracking are being developed.

Two different CT technologies can achieve high-speed CT imaging. Electron-beam CT (EBCT, also known as “ultrafast” CT) uses an electron gun rather than a standard X-ray tube to generate X-rays, thus permitting very rapid scanning, on the order of 50–100 milliseconds per image. Helical CT scanning (also referred to as “spiral” CT scanning) also creates images at greater speed than conventional CT by continuously rotating a standard X-ray tube around the patient so that data are gathered in a continuous spiral or helix, rather than individual slices. Multidetector row helical CT scanning (MDCT) or multislice CT (MSCT) is a technological evolution of helical CT, which uses CT machines equipped with an array of multiple X-ray detectors that can simultaneously image multiple sections of the patient during a rapid volumetric image acquisition. Currently available MDCT machines may have 4, 8, 16, 32, 40, or 64 detectors. Diffusion of MDCT machines into the medical community has been occurring over the past several years.

CTA has several important limitations. The presence of dense arterial calcification or an

intracoronary stent can produce significant beam-hardening artifacts and may preclude a satisfactory study. EBCT generally has better temporal resolution and may be able to achieve satisfactory images of the proximal and mid-segment coronary vessels without significant motion artifact, as compared to MDCT. The presence of an uncontrolled rapid heart rate or arrhythmia hinders the ability to obtain diagnostically satisfactory images, particularly with MDCT. However, modifications of MDCT technique are being explored to improve temporal resolution and improve diagnostic quality with higher heart rates (Hoffmann et al. 2005; Dewey et al. 2004). For both EBCT and MDCT techniques, evaluation of the distal coronary arteries is generally more difficult than visualization of the proximal and mid-segment coronary arteries due to greater cardiac motion and the smaller caliber of coronary vessels in distal locations.

MDCT with 4-row technology or EBCT with 3-mm collimation offer lower spatial resolution than current technology for evaluation of the coronary arteries. Budoff et al. (2003) reported that approximately 31% of 4-row MDCT CTA studies were unevaluable, and sensitivity and specificity for detecting significant coronary stenosis was 59% and 89%, respectively.

The ionizing radiation exposure associated with CTA is an important consideration. Radiation dose depends on X-ray tube voltage, current, scan time, and speed of table movement, and with MDCT, dose also depends on the number of overlapping adjacent scans (Bae et al. 2004). Also, radiation dose depends on the manner in which CTA images are synchronized with the cardiac cycle using electrocardiographic (ECG) tracings. Images at one cardiac phase can be obtained with prospective ECG triggering. This technique is frequently used with EBCT and has a lower radiation dose as compared with retrospective ECG gating. The retrospective approach provides a wider range of images during different cardiac phases and permits reconstruction of a cine view of the moving heart; however, dose exposure is greater because exposure occurs throughout the cardiac cycle. Dose-modulation techniques have been developed that reduce exposure during less-important phases of the cardiac cycle.

Bae et al. (2004) have published estimated radiation exposures using selected cardiac

imaging protocols; however, variation would be expected with different protocols used in practice. For comparison, 4-row MDCT with 1-mm sections delivered approximately 7.1 to 11.9 mSv; 16-row MDCT with 0.75-mm sections delivered approximately 8.8 mSv; and EBCT with 3-mm sections delivered approximately 0.7 to 1.1 mSv. While radiation dose exposure with conventional invasive coronary angiography depends on equipment and operator technique, a benchmark for comparison is approximately 4–8 mSv.

FDA Status. Contrast-enhanced cardiac CT angiography can be performed using either multidetector-row CT (MDCT) or electron beam CT. Multiple manufacturers have received U.S. Food and Drug Administration (FDA) 510(k) clearance to market MDCT machines equipped with at least 16 detector rows and at least two models of EBCT machines have been cleared through FDA 510(k) clearance. Intravenous iodinated contrast agents used for cardiac CTA have also received FDA approval.

Methods

Search Methods

MEDLINE® was searched (via PubMed) through June 2006 to identify all articles pertaining to use of contrast-enhanced cardiac CT angiography. The key terms “X-ray computed tomography (MH) AND heart diseases (MH)” were used. The following search limits were applied: English-language reports, human subjects, and publication type (randomized, controlled trials; controlled trials; review, meta-analysis, editorial). Textword searches were also conducted. Additionally, the Cochrane Library was searched in a similar fashion.

Study Selection

For the clinical indication of CTA as an alternative to invasive angiography in diagnosing coronary stenosis, studies were required to meet all the following criteria in order to be included in the review of evidence. Single case reports were excluded.

- Used contrast-enhanced EBCT with slice thickness no greater than 1.5 mm or contrast-enhanced MDCT with at least 32 rows
- Applied the reference standard of invasive angiography to all patients

- Reported sensitivity and/or specificity of CTA or sufficient data to generate a 2×2 contingency table
- Included only human subjects
- Published in English as a full-length, peer-reviewed journal article

The selection of studies evaluating 32-slice or greater CTA represents different selection criteria than for the prior TEC Assessment of May 2005. At that time, there were no publications of CTA with machines greater than 16-row capability. Studies of 64-row CTA represent the best results available, and very shortly will be the standard technology. This TEC Assessment will include a brief summary of the prior TEC Assessment's review of 16-row CTA. However, subsequent to the MAP meeting in June 2006, 2 studies were published using 16-row CTA that were notably different from prior studies. They will be briefly summarized, but they do not change the results of the Assessment.

For the clinical indication of CTA as an adjunct to management of patients with chest pain in the ER setting, prospective studies were selected in which patients meeting specific chest pain and clinical criteria for evaluation with CTA were chosen to have the test. This broad selection criterion was used because at this point in time there are very few studies evaluating CTA for this indication.

Medical Advisory Panel Review

Current Assessment. This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on June 22, 2006. 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 that met the criteria for detailed review, the results of these studies were included in the table(s) and text where appropriate. There were no studies that would change the conclusions of this Assessment.

Previous Assessments. A previous Assessment on CTA was reviewed by the MAP on February 8, 2005. At that time, it was judged that the available evidence was insufficient to judge whether CTA improved the net health outcome or whether it was as beneficial as any established alternatives. At that time, published studies were only available regarding the performance of 16-row CTA.

Study Quality

For the studies in which CTA was evaluated in comparison to invasive angiography, the studies included in the evidence tables were classified according to a limited set of study quality characteristics. The studies were all structured in a similar fashion, in that patients who had been previously referred for invasive angiography were recruited to have CTA. Thus, all studies were prospective and were not subject to verification bias. Spectrum bias may be an issue, because CTA has been proposed as a test for low-risk patients who, nonetheless, have indications for angiography. Thus, the only characteristics that could vary among the different studies were:

- Whether the study population was clearly described was rated as "Y" for yes; "N" for no; or "?" when there was insufficient information to determine.
- Interpretation of CTA studies blinded to the results of other tests or the reference standard was rated.

Studies were coded with a question mark when insufficient information was provided to make a yes ("Y") or no ("N") determination. The study quality characteristics used here are among those described in a review of systems for rating the quality of studies of diagnostic tests (West et al. 2002) published by the Agency for Healthcare Research and Quality (AHRQ).

The few studies evaluating the use of CTA for chest pain in the ER did not have the formal structure of a diagnostic test assessment and were not subject to a formal evaluation of quality. Although sensitivity and specificity estimates were generated from these studies, results of CTA were used to determine the subsequent workup of patients, and the reference standard for disease was a mixed standard.

Formulation of the Assessment

Patient Indications

1. In patients in whom angiography is indicated for diagnosis of coronary artery stenosis, but do not have indications for emergent angiography.
2. In patients with acute chest pain of uncertain etiology, in whom a cardiac cause of pain is under consideration.

Technologies to be Compared

1. In the first indication, CTA is a noninvasive alternative to invasive coronary angiography, particularly in patients with a low probability of significant coronary artery stenosis. CTA in this indication is likely to be followed by confirmatory angiography in those who have positive tests (See Appendix: “Potential Management Decision Tree,” Figure A). The alternative strategy is to go straight to angiography. Patients have had sufficient prior workup such that angiography is the next logical step in the workup.
2. In patients being evaluated for chest pain in the ER, CTA is used instead of or in addition to other noninvasive cardiac tests and observation. The alternative technology is some combination of noninvasive tests and observation.

Health Outcomes

A diagnostic test affects health outcomes due to any morbidity caused by the test itself and due to the treatment decisions subsequent to the test. Unlike other diagnostic tests that simply give a binary “yes-no” result, CTA gives a picture of the coronary anatomy in which the extent and presence of coronary atherosclerosis may be evaluated. Depending on the clinical indications and particular patient, the test could be used in various ways to determine changes in patient management.

However, the current research studies of CTA simplify the evaluation of CTA to the question of whether CTA can identify stenoses greater than or equal to a certain amount, usually 50%, compared to a reference standard of angiography. This question can be answered by performing CTA and angiography on the same patients, and calculating sensitivity and specificity for a certain amount of coronary stenosis.

For the first indication in which CTA is used before coronary angiography, some health outcomes can be projected based on the diagnostic performance of CTA. Correct identification of patients without coronary stenoses with CTA obviates the need for coronary angiography, which is a benefit to patients. A false-negative CTA, however, results in missed coronary stenoses. The positive and negative health outcomes of the possible test results of CTA, when the test is used in such a binary fashion, are shown in Table 1. Note that there are no benefits associated with a positive CTA, either false positive or true positive, because these patients would have undergone angiography anyway under the alternative strategy.

For the second indication, evaluation of chest pain in the ER, evaluation of the health outcomes of using CTA is more complicated, because the diagnostic reference standard, angiography, is not the alternative strategy. The performance of CTA would need to be compared to an alternative strategy that does not use CTA. Each strategy produces a particular combination of test results, and the resulting harms and benefits need to be compared to each other.

The balance sheet of outcomes of using CTA or another strategy for patients with chest pain in the ER is shown in Table 2. If CTA is more accurate and more timely than a combination of other noninvasive tests and observation, this should result in better patient outcomes. Fewer patients might be inappropriately discharged, and more rapid determination of coronary artery disease or other conditions may improve treatment outcomes. Diagnostic test characteristics alone may not determine utility in the ER because many different types of information from the CTA might be used in the ER setting rather than just coronary stenosis.

Table 1. Balance Sheet of Outcomes when Using CTA as a Pretest for Those Patients Who Would Otherwise Go Directly to Angiography

Result of CTA	Harm	Benefit
True positive	radiation exposure of CTA	none
False positive	radiation exposure of CTA	none
True negative	radiation exposure of CTA	avoidance of negative angiography
False negative	missed diagnosis radiation exposure of CTA	none
Unsatisfactory test	radiation exposure of CTA	none

Specific Assessment Questions

1. What is the sensitivity and specificity of CTA compared to invasive angiography in patients referred for angiography?
2. Does use of CTA for the evaluation of chest pain in the emergency department improve outcomes compared to an alternative strategy of evaluation?

Review of Evidence

Summary of Prior TEC Assessment from May 2005

In the prior TEC Assessment of May 2005 (Vol. 20, No. 4), studies of 16-row CTA or greater than 1.5-mm slice thickness on EBCT were included. Twenty-two eligible studies (16 MDCT, 6 EBCT; total n=1,016) were included in the review of evidence. Fifteen of these studies (total n=809) addressed CTA for diagnosis of non-acute CAD. Invasive coronary angiography was used as the standard of reference in all but 1 study. Most of these studies were prospective and CTA was interpreted without knowledge of invasive angiography results.

The main weakness of this literature is that most studies used individual coronary vessels or vessel segments as the unit of analysis while only 4 studies reported the more clinically relevant analysis of diagnostic performance measures using the patient as the unit of analysis. Most studies gave overoptimistic estimates of sensitivity and specificity by excluding unevaluable arterial segments or patients with unevaluable scans.

Only the results of the 4 studies with complete patient-based analysis from the prior report will be shown. Studies by Mollet et al. (2005a and 2004), Hoffmann et al. (2005), and Ropers et al. (2003) reported complete diagnostic performance characteristics using the patient as the unit of analysis and not limited only to evaluable segments (Table 3). The range of reported sensitivity was 85–100% and 75–86% for specificity. The prevalence of significant CAD in these studies was 53 to 83%, the positive predictive value range was 81–97%, and the negative predictive value range was 82–100%. The high prevalence of CAD in these studies is notable, showing that very high risk patient populations were enrolled in the

Table 2. Balance Sheet of Outcomes for Test Strategies Evaluating Chest Pain in the ER

Result of CTA or Other Noninvasive Alternative	Harm (Other than Morbidity of Test*)	Benefit
True positive		Correct diagnosis of chest pain, prompt treatment
False positive	Morbidity of further workup for CAD, possibly angiography	none
True negative		Correct ruling out of coronary artery disease, discharge from ER
False negative	Missed diagnosis	none
Unsatisfactory test		none

*radiation exposure in the case of CTA, vs. any other morbidities of alternative test

Table 3. Results of Per-Patient Analysis of 16-Row CTA, Adapted from Prior TEC Assessment (2005; Vol. 20 No. 4)

Study	n (patients)	Prevalence of Stenosis (%)	Sensitivity (%)	Specificity (%)
Ropers 2003	77	53	85	78
Hoffmann 2005	33	67	90	75
Mollet 2004	128	83	100	86
Mollet 2005a	51	61	100	85

studies. However, it must be noted that the 2 studies with the higher reported sensitivity (Mollet et al. 2004, 2005a), restricted analysis of CTA results to segments ≥ 2 mm in diameter; whereas Ropers et al. (2003) included segments ≥ 1.5 mm and Hoffmann et al. (2005) included all segments.

Analyses using the vessel segment as the unit of analysis reported 63–95% sensitivity and 86–98% specificity, but only after excluding unevaluable vessels from the analysis. The proportion of evaluable segments in studies ranged from 79% to 93%. Thus in every study, CTA was unable to produce evaluable images for all arterial segments.

The prior TEC Assessment had no studies in which CTA was used in the evaluation of patients in the ER. In sum, the prior Assessment showed a relatively small body of evidence (4 studies with patient-based analysis) showing a range of diagnostic performance that made it uncertain as to whether CTA can substitute for angiography. Studies enrolled convenience samples of patients already being referred for angiography rather than patients who might specifically be selected for CTA.

Summaries of Notable Recent Studies. As this Assessment went to press, Garcia et al. (2006) published one of the few multicenter studies using 16-row CTA. Most noteworthy in the study was the high proportion of nonevaluable arterial segments. Of 1,629 segments in 197 patients, 71% were evaluable. If nonevaluable segments were considered positive, sensitivity on a per-patient basis was quite high at 98%, but specificity was only 54%. Considering nonevaluable segments as negative would have reduced sensitivity from 98% to 75%.

Nikolaou et al. (2006) published the only study on a predefined set of low-probability patients, again using 16-row CTA. Four patients were excluded because of poor-quality CTA images. For the remaining 60 patients, per-patient sensitivity was 80%, and specificity was 94.5%. Because the prevalence of significant stenosis was low in this study, only 8.3%, the negative predictive value of CTA was quite high at 98.1%, but the sensitivity was not optimal. The estimate of sensitivity is not very precise because it is based on detection of only 4 of 5 stenoses.

Although these studies were notable additions to the literature on 16-row CTA, one by being a multicenter study and the other by studying a specific low-risk population that is considered the target population for CTA, the results are not particularly favorable for CTA.

Current Assessment of 40- and 64-row CTA in Comparison to Angiography

Seven studies met selection criteria. Sample sizes ranged from 30 to 84 patients. Descriptive characteristics of the patients are shown in Table 4. The patients generally consist of patients who had already been selected to have angiography, and the CTA was simply added on to their evaluation. Since all patients had angiography, there is no verification bias, and the subjects had sufficient prior workup such that the prior probability of coronary disease was such that angiography was indicated. CTA has sometimes been proposed as a substitute for angiography in “low-risk” patients who nonetheless have sufficient risk that angiography is indicated. CTA would be largely redundant in patients at high risk, most who would go on to angiography anyway. None of the studies specifically studied such a “low-risk” subgroup, and thus all are potentially flawed by spectrum bias, if the intended use of CTA is for lower risk patients. With the exception of the study by Lim et al. (2006), all studies reported that the interpretation of both CTA and the reference standard of angiography was blinded.

Six studies reported a per-patient analysis. This type of analysis is the most relevant if CTA is to be used as a substitute test for invasive angiography with all positive tests confirmed by angiography. Three of the studies excluded patients with indeterminate test results. However, if these patients all go on to angiography, then they are treated as though the CTA were “positive,” and there is no loss of sensitivity due to these excluded patients. If these patients with indeterminate tests do not have coronary stenosis, then they should be considered “false positives” and the specificity estimates presented here are biased upward. None of the studies reported the results of these indeterminate tests, and thus the unbiased specificity estimates cannot be calculated.

With the exception of the study by Leber et al. (2005), the sensitivity of CTA in identifying patients with stenoses of at least 50% was

Table 4. Studies of Diagnostic Accuracy of CTA, Study Description, and Quality Evaluation

Author	Study Population	Definition of Stenosis	Population Clearly Described	Blinded Interpretation of CTA
Lim 2006	30 consecutive patients with 2 or more risk factors, symptomatic angina, suspected CAD	≥50% stenosis stented and occluded segments excluded	Y	?
Leber 2005	59 patients with stable angina, 10 with prior angioplasty	>75%, >50%	Y	Y
Pugliese 2005	35 patients with stable angina	≥50%	Y	Y
Leschka 2005	73 patients referred for angiography or bypass surgery, 24 with unstable angina, 43 for bypass	>50% in vessels >1.5 mm diameter	Y	Y
Mollet 2005b	52 patients referred for angiography with atypical chest pain, stable or unstable angina, or non-ST-segment MI	≥50%	Y	Y
Raff 2005	70 patients referred for elective angiography	>50%	Y	Y
Ropers 2006	84 patients referred for elective angiography	≥50% in vessels >1.5 mm diameter	Y	Y

95–100%, with 3 of the studies reporting 100% sensitivity (Table 5). With the exception of the study by Leber et al. (2005), specificities were all greater than 90%. Of note is the high prevalence of stenosis in the patient populations. With the exception of the study by Ropers et al. (2006), the prevalence is greater than 50% in all studies. This is to be expected, because the studies enrolled patients who were being referred for angiography, and did not specifically enroll “low risk” patients. Thus, with the possible exception of the study by Ropers et al. (2006), none of the studies examined specifically the performance of CTA in low-risk patients, who would benefit most from avoiding invasive angiography.

All studies also calculated per-segment diagnostic test characteristics using the arterial segment as the unit of analysis. These analyses are less relevant for clinical decisionmaking, and do not account for intercorrelations within patients. An important issue in understanding the per-segment analysis is how poorly visualized vessel segments are dealt with in the analysis. Several of the studies exclude either whole patients or certain segments from the analysis

because the images are unevaluable. In the study by Raff et al. (2005), the manuscript is unclear why 130 segments were excluded. This proportion of excluded segments is clearly a high outlier compared to other studies. Other studies did not count as exclusions segments distal to occlusions (nonexistent segments), but only counted as exclusions segments that were poorly imaged.

Per-segment sensitivities ranged from 79–99%, and specificities ranged from 95–98% (Table 6). Because of exclusions of patients or segments, these performance numbers are biased upward. If indeterminate segments are assumed to be positive, then the sensitivity remains as high as reported, but the specificity estimates would be lower than shown here.

In sum, regarding this indication, the performance of CTA using a patient-based analysis shows high sensitivities and specificities compared to the reference standard of invasive angiography. However, there are some concerns regarding these data. When sensitivity is not perfect, and the patient has been worked up to be a candidate for angiography, CTA could

Table 5. Per-Patient Diagnostic Test Characteristics of 64-Slice CT Angiography to Detect a Patient with at Least One Stenosis $\geq 50\%$

Study	Excluded Patients	n (patients)	Prevalence of Stenosis (%)	Sensitivity (%)	Specificity (%)
Mollet 2005b	1	51	75	100	92
Leber 2005	4	45*	56	88	86**
Raff 2005	0	70	57	95	90
Ropers 2006	3	81	32	96	91
Pugliese 2006	0	35	71	100	90
Leschka 2005	0	67	70	100***	100***

* Per-patient results only reported on patients without stents

** Specificity calculated based on threshold of 75% stenosis, different than the 50% threshold for sensitivity

*** Numbers not cited in paper, but stated in words: "In all patients with CAD at least one significant lesion was correctly classified... all patients without CAD could be correctly identified"

Table 6. Per-Segment Diagnostic Test Characteristics of 64-Slice CT Angiography to Detect $\geq 50\%$ Stenosis

Study	Excluded Segment	n (segments)	Prevalence of Stenosis (%)	Sensitivity (%)	Specificity (%)
Mollet 2005b	0***	725	13	99	95
Leschka 2005	0	1,005	18	94	97
Leber 2005	0*	798	9	79	97
Raff 2005	130**	935	10	86	95
Ropers 2006	45	1,083	4	93	97
Pugliese 2006	0	494	14	99	96
Lim 2006	0	460	20	99	98

* Four patients with unsatisfactory CTA excluded, but all segments in remaining patients included

** Unclear reasons for exclusion, possibly not all indeterminate images

*** Not including 1 patient excluded for development of arrhythmia during exam

miss some clinically important stenosis. The consequences of missed diagnoses would need to be compared to the consequences of avoided negative angiography to determine overall health outcomes. Second, the patient populations in which these studies have been performed have a very high prevalence of stenosis, and thus, relatively few negative angiographies are avoided for the effort of performing CTA on everyone. It is uncertain that the same performance characteristics would apply to patient populations that have a lower prevalence of stenosis, but are candidates for angiography anyway.

CTA for Evaluation of Chest Pain in the ER

Two studies have been performed in which CTA was done during evaluation of patients with undiagnosed chest pain in the emergency department (Table 7). These studies do not really allow a formal comparison of CTA to an alternative strategy of making a diagnosis, because there was no alternative strategy that was specifically defined in the studies. The results of the CTA were used in the management of the patient, and thus the diagnostic alternatives to CTA were often not performed or were used as a reference standard. The best that can be calculated from these studies is an estimate of the sensitivity and specificity of CTA compared to a mixed reference standard consisting of clinical data or angiography or other tests.

Sato et al. (2005) performed 4- or 16-row CTA on 31 patients admitted to the ER with chest pain, non-diagnostic EKG changes, and normal cardiac enzymes. Subsequent to this test, patients were assigned to a diagnosis based on either elevation of cardiac enzymes, angiography, or a perfusion test. Compared to this mixed reference standard, CTA had 1 false-positive result and 1 false-negative result, resulting in a sensitivity of 95.5% and specificity of 88.9%. Because of the altered workup of the patients and the mixed reference standard,

it is impossible to compare these results to an alternative strategy that does not use CTA.

White et al. (2005) performed a similar study, in which patients with chest pain in whom angina was considered to be definite (Category 2) to unlikely (Category 4) received 16-row CTA that was altered in order to diagnose pulmonary embolus and other sources of chest pain in addition to coronary stenoses. Of 69 patients enrolled in the study, 24 would have received a CT for these other indications. The final diagnosis was based on a combination of clinical data, radionuclide testing, coronary angiography, and stress echocardiography. CTA had a sensitivity of 83% and a specificity of 96% in diagnosing a cardiac cause of chest pain. For diagnosing all sources of chest pain, CTA had a sensitivity of 87% and a specificity of 96%. Like the other study, because of the altered workup of the patients and the mixed reference standard, it is impossible to compare these results to an alternative strategy that does not use CTA.

In neither of these studies was the result of the CTA available immediately in the ER, so it was not actually used to make acute discharge decisions. This allowed further testing of the patients so that the false-negative results of CTA could be determined. However, because a specific alternative strategy was not consistently performed in parallel with the CTA, comparable sensitivity and specificity estimates for an alternative strategy cannot be calculated.

Thus, these data do not demonstrate that CTA is an effective test for diagnosis of chest pain in the ER. The imperfect sensitivity means that some cardiac diagnoses may be missed, and the imperfect specificity means that some patients might be subject to unnecessary further workup including angiography. Because the results of CTA were used to determine subsequent management of the patients resulting in omission of the comparators to CTA, comparisons to alternatives not using CTA are not possible.

Table 7. Performance of CTA in Chest Pain Patients in the ER

Study	Excluded Patients	n (patients)	Prevalence of Stenosis (%)	Sensitivity (%)	Specificity (%)
Sato 2005	3	31	71	96	89
White 2005	0	69	17	83	96

Discussion

The studies evaluating the use of CTA in comparison to angiography are relatively small studies from single centers. Their major failing is that they enrolled convenience samples of patients being referred for angiography. The results from these studies may not generalize to lower-risk subsets of angiography patients. However, analyzing the information from these studies solely from the perspective of sensitivity and specificity in identifying a specific amount of coronary stenosis may shortchange the utility of CTA. Visualizing the coronary anatomy may provide useful prognostic information for optimally managing patients. However, in order to demonstrate improved patient outcomes, valid prognostication tied to improved management and outcomes must be demonstrated. Clinical trials comparing patients undergoing CTA as part of their diagnostic workup compared to patients not undergoing CTA may be required to demonstrate improved patient outcomes. There is no evidence except in the ER regarding the use of CTA in the early workup of patients in whom CAD is being considered.

Current published studies of CTA in the management of acute chest pain in the ER are clearly inadequate to determine utility. No comparator strategy was specified, and there was no solid reference standard for diagnosis. Clinical trials may be necessary to demonstrate utility in this setting.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether CTA for screening or diagnostic evaluation of the coronary arteries meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

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

Multiple manufacturers have received U.S. Food and Drug Administration (FDA) 510(k) clearance to market MDCT machines equipped with at least 16 detector rows and at least two models of EBCT machines have been cleared through FDA 510(k) clearance. Intravenous iodinated contrast agents used for cardiac CTA have also received FDA approval.

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

Current studies are inadequate to determine the effect of CTA on health outcomes for the diagnosis of coronary artery stenosis in patients referred for angiography or for evaluation of acute chest pain in the ER.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

The available evidence is inadequate to determine whether CTA improves the net health outcome or is as beneficial as established alternatives for diagnosis of coronary artery stenosis or for evaluation of acute chest pain in the ER.

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

Whether use of CTA improves health outcomes has not been established in the investigational setting.

Based on the above, CTA as a substitute for coronary angiography in the diagnosis of coronary artery stenosis does not meet the TEC criteria. CTA in the evaluation of acute chest pain in the emergency room also does not meet the TEC criteria.

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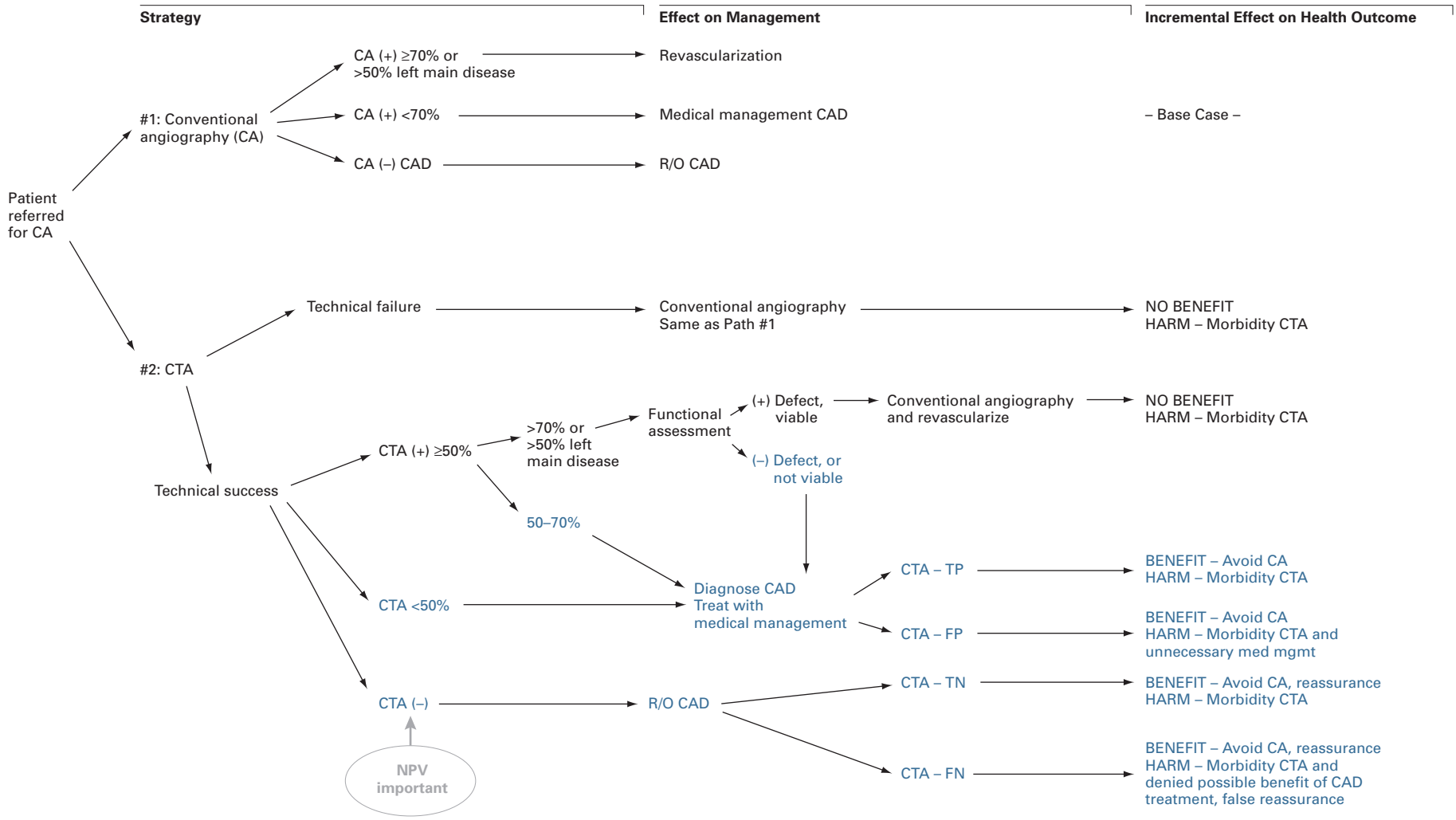
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Appendix

Figure A. Potential Management Decision Tree for Patients Being Referred for Conventional Angiography



CA: conventional angiography; CAD: coronary artery disease; CTA: computed tomographic angiography; FN: false negative; FP: false positive; NPV: negative predictive value; R/O: rule out; TN: true negative; TP: true positive



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