Health Technology Assessment

CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY FOR DETECTION OF CORONARY ARTERY DISEASE

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INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY FOR DETECTION OF CORONARY ARTERY DISEASE

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EXECUTIVE SUMMARY

Introduction

Coronary computed tomographic angiography (CCTA) is a minimally invasive radiological technique used to provide images of the heart and surrounding vessels. CCTA has been suggested as an alternative or useful complementary approach to other non-invasive methods of diagnosing coronary artery disease (CAD). In particular, because of its ability to visualize coronary anatomy, CCTA has been suggested as a strategy to rule out significant CAD among patients at low or intermediate risk of significant disease, thereby giving greater reassurance than other non-invasive methods and potentially reducing the number of patients ultimately sent for invasive coronary angiography (ICA). However, uncertainty remains regarding several important issues:

1) The diagnostic accuracy of CCTA relative to ICA and other possible comparator diagnostic tests
2) The impact on patient outcomes and health care utilization of alternative diagnostic algorithms that integrate CCTA in different ways into the diagnostic pathways for patients with suspected CAD, both in the general outpatient setting and in the Emergency Department
3) The most appropriate target populations for CCTA, based on level of risk and symptoms
4) The potential negative impact of increased radiation exposure of CCTA
5) The impact of incidental findings that trigger further evaluation
6) The potential impact of CCTA on the thresholds for clinician testing for coronary artery disease among the general population
7) The budget impact and cost-effectiveness of integrating CCTA into diagnostic pathways for patients with suspected coronary artery disease

Given the possible benefits of introducing a widely available non-invasive option for CAD detection, the potential clinical and financial impact that broad adoption of CCTA would have on systems of care, and the uncertainty over the evidence on the net health benefits and appropriate use of CCTA, all health care decision makers will benefit from a formal appraisal of the comparative clinical effectiveness and comparative value of CCTA as a modality for diagnosis of coronary artery disease.

Coronary Artery Disease Diagnosis Alternatives

For many years the most precise and definitive method for the evaluation and diagnosis of coronary artery disease has been invasive coronary angiography (ICA). ICA is typically an inpatient procedure. At the time of the procedure a catheter is inserted into an artery, usually the femoral blood vessel, and contrast dye is injected through the catheter. X-ray images are then captured and displayed on a video screen (a procedure known as fluoroscopy), and can be viewed either as images or in

motion picture form. While complications from ICA are relatively infrequent, they can be significant, and include myocardial infarction, cardiac arrhythmia, stroke, hemorrhage, infection, trauma to the artery from hematoma or from the catheter, sudden hypotension, and reaction to the contrast medium (Gandelman, 2006). The procedure also delivers a radiation dose lower than most CCTA protocols but similar to that of CCTA when it is performed using dose-saving protocols or dual-source scanners.

In part because of the invasive nature of ICA and its concordant risks, alternative non-invasive tests also are utilized for evaluation of chest pain symptoms considered suggestive of CAD. The first of these technologies to gain widespread use was the stress electrocardiogram (EKG); the major alternatives are stress echocardiography and single-photon emission computed tomography (SPECT), also known as nuclear stress testing or myocardial perfusion imaging.

Stress echocardiograms (ECHO) produce images of the heart through the use of sound waves. The test allows for the evaluation of blood flow in different areas of the heart to identify weak or damaged areas of the muscle. This is done through a comparison of images at rest and under cardiac stress induced by exercise or pharmacologic means. Clinically, the test is simple to perform, relatively inexpensive, and easily accessible. However, the image quality is lower in obese patients and those with chronic disease, which can account for almost 30% of candidates (Miller, 2006). It is recommended for use in intermediate-to-high risk patients (Anthony, 2005).

SPECT imaging involves the use of a tracer radiopharmaceutical to highlight areas of decreased blood flow in the myocardium. Images are captured via a gamma camera, and may be reconstructed to create two or three-dimensional films. The accuracy of SPECT imaging has improved to the point that it is often used for prognostic use in addition to diagnosis. However, it is not as effective in detecting perfusion defects in patients with milder stenosis (Jeetley, 2006). SPECT also involves the use of contrast media and delivers a radiation dose similar in magnitude to that of ICA and CCTA.

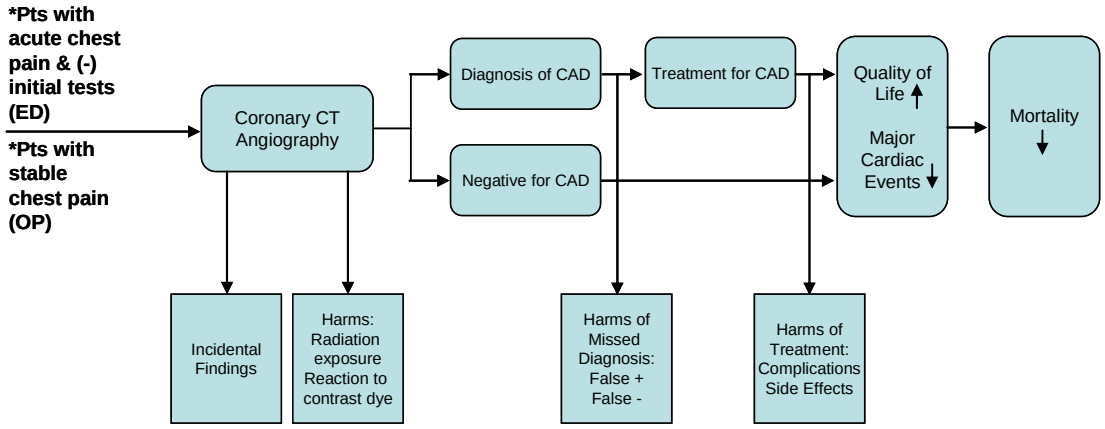
All of these alternative non-invasive diagnostic techniques measure in some way the functional impact on the heart of any underlying CAD. As noted above, none of the tests is perfect; each has the possibility of producing false positive and false negative results. Professional guidelines recognize all of these comparator techniques as appropriate initial investigations to evaluate possible CAD for most patients with stable symptoms (Gibbons, 2003).

Analytic Framework for Evaluation of CCTA

The analytic framework for this evaluation is shown in the Figure on the next page. As is the case for many diagnostic tests, there are no data directly demonstrating

CCTA's beneficial impact on long-term morbidity and mortality, so judgments about the effectiveness of the intervention must rest almost exclusively upon consideration of the strength of sequential conceptual links. For this evaluation, the primary conceptual links are those between detection of significant CAD, referral for appropriate treatment, major cardiovascular events, and mortality.

Analytic Framework: CCTA in ED and Outpatient Settings



CCTA Technical Evolution

CCTA is a technique in which a CT scanner is used to acquire multiple simultaneous tomographic sections ("slices") of the coronary arteries. At the time of this outpatient procedure, an IV is placed into a peripheral vein and a contrast dye is administered for the purposes of visually defining the arteries for the scan. Beta blockers may be given to the patient to slow the heart rate in order to prevent artifacts of heart motion that may affect image quality. The patient is positioned on the CT scanner and a large number of x-ray images are taken from multiple angles and reconstructed using computer software. Multi-detector row CT scanners contain rotating gantries that capture multiple images, or "slices". A 64-slice CCTA was introduced in 2004 and increased the number of captured images from the previous 16- and 32-slice technology. Improved spatial and temporal resolution from 64-slice machines has been found to shorten the time required to capture an image, decreasing motion artifact as well as reducing the time to conduct the entire scan to approximately 8 seconds (Mowatt, 2008).

The 64-slice scanner has rapidly replaced earlier versions and is currently considered to be the community standard for CCTA. In 2007, 256- and 320-slice CT scanners became available, but it is unclear whether the greater resolution of these versions will provide clinically relevant advances to 64-slice machines. Dual source 64-slice

scanners have also been introduced in which two scanners are mounted on the gantry at 90 degree angles (Matt, 2007). Dual source scanning is claimed by some to further decrease procedure time, reduce heart motion artifacts, and lower the effective radiation dose to the patient.

This review included studies of the performance of CCTA in diagnosing CAD using scanners with 64-slice or higher resolution (including dual-source scanners). Guidance from the ICER Evidence Review Group suggested that 64-slice scanners were now widely available in the community and had become viewed as the standard for CCTA, and that literature on earlier-generation scanners would not be viewed as relevant by the clinical and patient communities.

Target Population for Consideration of Triage and Diagnosis of CAD

The accumulation of atherosclerotic plaque that is characteristic of CAD typically gives rise to symptoms, such as chest pain and shortness of breath; in fact, the most important factors in determining CAD risk have been demonstrated to be age, gender, and the nature of chest pain (Diamond, 1979).

The relative effectiveness of any test used to detect CAD can be directly related to the perceived risk and/or underlying prevalence of significant disease. At the lowest levels of prevalence or risk, the benefits of accurate detection may be outweighed by the number of false positives generated by the test. Conversely, at the highest levels of prevalence or risk, patient populations are likely to benefit less from non-invasive diagnostic tests which will produce a relatively high rate of false negative results, and would instead benefit more from moving directly to definitive diagnostic testing and potential therapeutic intervention with ICA.

Following the guidance of the ICER Evidence Review Group (see section on Evidence Review Group starting on page 20) the target population for CCTA for this review was patients at *low-to-intermediate risk* of CAD, for the reasons given above. This review did not evaluate the performance of CCTA as a screening tool in very low-risk patients with non-specific chest pain or in asymptomatic patients. While the majority of diagnostic accuracy studies were conducted in relatively high-risk groups (i.e., patients already scheduled for ICA), we analyzed data separately by risk or pretest probability wherever feasible.

Evidence on Diagnostic Accuracy, Treatment Decisions, and Patient Outcomes

The available evidence on the impact of CCTA on clinician decision-making and patient outcomes is limited; nearly all available studies with these endpoints have been conducted in an ED setting; and, with the exception of one RCT, these studies have not prospectively compared the outcomes of "CCTA care" to the outcomes of standard care. The single published RCT compared a CCTA care strategy in the ED (n=99) to standard triage care alone (n=98) in an ED in Michigan (Goldstein, 2007);

findings suggested that 67 (68%) patients in the CCTA care arm were identified with no CAD and were able to be rapidly discharged from the ED with no adverse outcomes over a 6-month follow-up period. More patients were sent to ICA in the CCTA care arm of the study (11 vs. 5), but 9 of 11 catheterizations proved "positive" in the CCTA care arm. CCTA was found to be time- and cost-saving due to a greater number of patients discharged immediately following a normal CCTA, a result that was echoed in another ED case series (Savino, 2006). In a second study of CCTA care in the ED, physicians in Israel evaluated 58 consecutive ED patients with standard triage care and made initial recommendations for disposition (Rubinshtein, 2007). Physicians were then given the patients' CCTA results, and the impact on final disposition decisions and patient outcomes suggested that CCTA findings prevented unnecessary hospitalization or invasive treatment in 40-45% of patients.

There are two important considerations in these ED studies. First, they are small studies, and in both the overall risks of acute coronary syndrome and cardiac events were very low. As one of the authors notes, the lack of negative outcomes among CCTA-negative patients cannot be taken as conclusive evidence of the true incidence of false positive and false negative CCTA findings. These studies also highlight how critical the underlying prevalence and distribution of CAD is in understanding the relative effectiveness of CCTA as a diagnostic and triage modality.

In the outpatient setting, where the interest in the use of CCTA has been focused on the evaluation of patients with stable chest pain symptoms who are at low-to-intermediate risk of significant CAD, there are no published studies to date that have directly measured the impact of CCTA on clinical decision-making or on patient outcomes. The majority of available literature on 64-slice CCTA is limited to small, single-center studies of diagnostic accuracy compared to ICA, typically among consecutive patients at relatively high risk of CAD who are already scheduled to undergo ICA. This body of evidence has expanded rapidly from 2005-2008, and the findings are relatively consistent. Our pooled estimate (from meta-analysis of 34 studies) of the sensitivity of CCTA for significant CAD is high: 98%; 95% CI, 97%, 98%. This sensitivity compares favorably to estimates for alternative non-invasive techniques including stress ECHO (0.76-0.94) and SPECT (0.88-0.98) (Garber, 1999).

The specificity of CCTA can be calculated in two ways based on how scans with "non-diagnostic" segments are treated. When patients with non-diagnostic CCTA results were counted as false-positives, pooled specificity from the ICER meta-analysis was 82% (95% CI: 80%, 84%); when such patients were excluded from analyses (as they were in most of the studies we analyzed), specificity was calculated to be 87% (95% CI: 85%, 88%). This range for specificity is also comparable or superior to estimates for other non-invasive techniques: 0.88 for stress ECHO and 0.77 for SPECT (Garber, 1999).

Adopting the more conservative specificity estimate above, these diagnostic accuracy results can be extrapolated to a population perspective, as below:

- Using ICA as the reference standard, and assuming an "intermediate" level of 30% CAD prevalence of one or more coronary vessels with significant occlusion, for every 1,000 patients receiving CCTA there will be:
    - 574 patients who have a true negative test
    - 7 patients who have a false negative test
    - 293 patients who have a true positive CCTA (confirmed on ICA)
    - 126 patients who have an indeterminate or false positive CCTA (no significant CAD on ICA)

It is important to caution that this representation of CCTA diagnostic outcomes in 1,000 patients reflects a simplistic application of sensitivity and specificity estimates in a binary fashion to a hypothetical population. These figures do not suggest how CCTA results would affect clinical decision-making or patient outcomes. For one thing, CCTA results in practice are not interpreted in a binary fashion. Many patients will have "moderate" stenosis (20%-70%) in one or more arteries. One of the important unanswered questions about CCTA is the clinical significance and the impact on clinical decision-making of visual identification of moderate stenosis. Prior to CCTA these patients would have undergone either non-invasive tests, which would have evaluated *functional* signs of CAD, without any visual image, or these patients would have been sent directly for ICA. How CCTA would affect the diagnoses and pattern of care for patients with "moderate" stenosis is a controversial topic. Some authors have postulated that there may be an "oculostenotic reflex," through which cardiologists will feel compelled to aggressively treat any occlusion they see (Lin, 2007; Topol, 1995). Others have postulated that visualization of moderate stenosis, particularly at the lower end of the 20%-70% range, will prove reassuring to clinicians and patients, reducing repeat testing and inappropriately aggressive therapy. Unfortunately, there are no published data with which to evaluate the question of how clinical decision making for patients with moderate stenosis in the outpatient setting changes with the integration of CCTA into practice.

There are several other important issues to note regarding the evidence on diagnostic accuracy. The prevalence of underlying CAD is quite high (mean of 59%) in many of the accuracy studies, raising questions about the applicability of study results from these populations to those including a preponderance of "low-to-intermediate" risk. Although published data suggest that CCTA's accuracy is unaffected by the extent and distribution of CAD in the population, the absolute number of indeterminate and false positive results from CCTA would be higher in any population with a lower true prevalence of disease.

And finally, given the long-term progression inherent in CAD, and the uncertainties surrounding its natural history, the lack of published evidence makes it difficult to judge the magnitude of the benefits of reductions in false negative and false positive

diagnoses. There is no published evidence to judge the outcomes of patients with initially false negative stress ECHO, SPECT, or CCTA results. Some will suffer a preventable cardiac event; others will return in the near future for further evaluation, be correctly diagnosed, and will be treated appropriately with little negative impact on health outcomes. Similarly, the balance of net harms and benefits is unknown for patients receiving a false positive diagnosis of CAD with CCTA or any of the non-invasive testing strategies. These patients will receive the "harms" of unnecessary medical therapy in the short term but some will also accrue the "benefits" of this treatment given that some of these currently healthy patients would be expected to develop symptomatic CAD over time.

Harms

Review of the evidence confirmed clinical expert opinion that CCTA is a very safe procedure, with the only immediate complication being reactions to contrast media; the reported rates of serious contrast reactions or induced nephropathy has been very low for the technologies that require contrast, and the rate of reactions requiring serious intervention (e.g., dialysis, hospitalization) has been even lower.

To place the effective radiation dose received from CCTA in some context, the average reported range of radiation in our sampled studies is listed in the table below along with typical doses from other tests and exposures to x-rays. Note that the doses received from ICA and SPECT are similar to those delivered by CCTA:

Radiation exposure scenario	Approximate effective dose (mSv)
Chest x ray	0.02
Round-trip flight, New York-Seattle	0.06
Low-dose CT colonography	0.5-2.5
Head CT	2.0
Single-screening mammogram (breast dose)	3.0
Annual background dose caused by natural radiation	3.0/yr
CCTA (lower reported range)	**2.0-8.0**
Invasive coronary angiography	5.0-7.0
Adult abdominal CT scan	10.0
Single photon emission computed tomography (SPECT)	9.0-13.0
CCTA (higher reported range)	**12.0-14.0**
Typical dose to A-bomb survivor at 2.3 km distance from ground zero Hiroshima	13.0
Annual radiation worker annual exposure limit	20.0/yr
Annual exposure on international space station	170/yr

Sources: Brenner, 2005; FDA [www.fda.gov/cdrh/ct/risks.html]; ICER CCTA systematic review; Van Gelder 2004, Mettler 2008, Shuman 2008; Earls 2008; Husmann 2008

The potential for harm from radiation is more difficult to assess given the uncertainty around the relationship between low-level radiation exposure and cancer risk as well as whether an exposure threshold exists after which excess risk is realized. One published empirical attempt to quantify the lifetime attributable risk for cancer estimated that it is 0.22% and 0.08% in women and men aged 60 years respectively; prospective EKG gating would be expected to reduce this risk by about 35% (Einstein, 2007). Aggressive attempts are being made to reduce radiation dose to the patient during CCTA, with varying degrees of success; still, consideration of CCTA's radiation dose is important, particularly in light of the possible radiation exposure from other tests along the diagnostic pathway (e.g., SPECT, ICA).

Incidental Findings

The relative benefits and harms of incidental findings on CCTA are also difficult to judge empirically. Studies suggest that approximately 40-80% of patients will have an extra-coronary finding of some kind on CCTA, and 5-20% of patients would have a finding deemed clinically important enough for further evaluation. Were CCTA to be adopted broadly, this rate of extra-coronary findings would generate significant numbers of patients requiring further investigation. When investigated, some of these findings will be judged to have brought clinical benefit to the patient, most often by detection of a pulmonary malignancy or embolism, or possibly diagnosis of an abdominal or thoracic aortic aneurysm. However, findings from the few studies that have examined this question suggest that the proportion of patients receiving some clinical benefit is very low, while additional risks, anxieties, and costs are generated by follow-up investigations. The results of our analyses suggest that the additional costs of following patients for pulmonary nodules alone may be as high as $50 per patient undergoing CCTA. From both a clinical and a health systems' perspective, this is one of the most important uncertainties regarding CCTA. The determination of net health benefit for CCTA may hinge on decision-makers interpretation of the boundaries of risk, benefit, and cost of extra-coronary findings. As highlighted previously, this is but one of the key uncertainties around CCTA's diffusion in clinical practice; for example, if CCTA's use expands to low-risk populations in which the balance of true and false positives is less certain, the uncertainties around incidental findings take on added significance.

Clinical Effectiveness Results from ICER Decision Analytic Models

Because the clinical scenarios and patient populations related to CCTA use differ substantially between the ED and the outpatient settings, we decided to build two separate models that could help evaluate the likely impact of CCTA compared to alternative diagnostic strategies in these two settings. Due to lack of reliable data and no consensus among clinical and policy experts, neither model explicitly includes the potential benefits, harms, or costs of incidental findings or radiation exposure.

Triage of Patients in the ED

The model evaluating CCTA for patients with acute chest pain in the ED setting loosely follows the algorithm of the RCT by Goldstein (Goldstein, 2007). Standard of care includes admission to an ED observation unit to await final serum enzyme tests for myocardial damage, followed by stress ECHO. In the CCTA pathway all patients receive CCTA immediately, with subsequent triage determined by CCTA results. Details of the model are available in the body of the ICER review.

Table ES1 below depicts the results for a cohort of 1,000 55-year old men. The left hand column shows the result if all patients had undergone the standard of care (SOC) strategy and the right hand column depicts the results if the identical 1,000 patients had all undergone the CCTA strategy. Among the notable differences between CCTA and SOC are the number of patients sent immediately home without requirement for extended ED observation (456 vs. 0); the number of false negatives (5 vs. 51), the number of patients ultimately referred for ICA (380 vs. 464), and the number of patients sent for ICA who are found to have normal coronary arteries on ICA (116 vs. 246). Our model therefore is consistent with other published cost-effectiveness analyses in suggesting that when used as part of a triage strategy for low-to-intermediate risk chest pain patients in the ED, CCTA will allow the more rapid discharge of nearly half of all patients and decrease the number of false negative diagnoses while reducing the number of angiographies compared to the current standard of care.

Table ES1: Base case results of ED model

Outcomes (per 1,000)	SOC	CCTA
True positive	218	264
True negative	731	731
False negative	51	5
Referred for ICA	464	380
ICA negative results	246	116
ICA related deaths	0.05	0.04
Incidental findings	0	138

Notes: SOC: standard of care

Evaluation of Stable Chest Pain in the Outpatient Setting

The model evaluating CCTA as a tool for evaluating stable chest pain in the outpatient setting follows the CAD treatment recommendation derived from the recent COURAGE trial (Boden, 2007) and thus requires that the diagnostic tests not

only identify stenoses correctly but also differentiate between 3-vessel/left main artery disease and 1- or 2-vessel disease.

The base case population consisted of 55 year-old men with stable chest pain and with either low (10%) or intermediate (30%) risk of underlying significant CAD -- one or more vessels with occlusion >70% or left main occlusion at >50%. We considered 7 different strategies, alone and in combination, in order to capture a wide range of management approaches for evaluating patients with stable chest pain and a low-to-intermediate risk of CAD:

1. Coronary Computed Tomographic Angiography (CCTA)
2. Stress-Echocardiography (Stress-ECHO)
3. Stress- Single Photon Emission Computed Tomography (Stress-SPECT)
4. CCTA followed by Stress-ECHO
5. Stress-ECHO followed by CCTA
6. CCTA followed by Stress-SPECT
7. Stress-SPECT followed by CCTA

Table ES2 on the following page depicts the base case model results for 1,000 55-year old men with an underlying CAD prevalence of 30%. Each column represents the results if all patients had undergone the specific screening strategy.

The model results indicate that there are important trade-offs to consider when comparing these strategies. There is no single, simple axis of "effectiveness." For example, "*CCTA alone*" has the highest number of true positives at 288 and the lowest number of false negatives at 9 among all strategies, followed by "*SPECT alone*" which has 273 true positives and 24 false negatives. But CCTA strategies introduce the issue of incidental findings, estimated to require follow-up among 13.8% of all patients screened. CCTA (and SPECT) strategies also carry radiation exposure risks for all patients. By scanning and comparing the columns in the Table decision-makers can weigh the value they ascribe to these different aspects of the outcomes associated with various diagnostic strategies. A Table showing results for a lower-risk population with a 10% prevalence of CAD, shown in the review, also demonstrates how these various outcomes shift importantly with the underlying prevalence of disease in the population.

Table ES2: Diagnostic results in the Outpatient Setting (30% CAD prevalence)

Estimates	CCTA	SPECT	SECHO	CCTA -> SPECT	SPECT -> CCTA	CCTA -> SECHO	SECHO -> CCTA
True positive	288	273	251	266	268	245	246
False positive	87	145	71	24	29	12	22
True negative	616	558	632	679	675	691	682
False negative	9	24	46	31	29	52	51
Referred for ICA	108	166	200	106	91	120	87
ICA-negative results	22	65	95	9	6	13	5
ICA related deaths	0.11	0.17	0.20	0.11	0.09	0.12	0.09
Exposed to radiation	1,000	1,000	200	1,000	1,000	1,000	437
Incidental findings requiring f/u	138	0	0	138	57	138	48
Total costs/patient [excluding all FU costs, $]	764	1,221	849	1,004	1,205	891	702

Summary of Findings of Comparative Value

ED Setting

We performed cost-effectiveness analyses using the decision analytic models described above. According to the base case results of the ED model, CCTA is cost-saving, with about $296 in savings per patient in comparison to SOC. Taking into account the additional follow-up costs for the 14% of patients who undergo CCTA and have incidental findings, the cost-savings are reduced to $196, but remain in favor of CCTA. The following numbers represent the base case analysis and compare CCTA in addition to standard triage care to standard care alone:

- Cost of CCTA= $466
- CCTA cost savings relative to standard care (includes CCTA, ED triage, observation, cath lab) = $296

- CCTA cost savings w/incidental findings f/u costs = $196
- Threshold CCTA cost for cost savings in the ED = $762

Outpatient Evaluation: Diagnostic Phase

The Outpatient model was used to evaluate testing costs of the diagnostic phase, extending up through and including possible ICA but not beyond. Table ES2 above includes, in the final row, the average diagnostic costs per patient generated by the base case model at 30% CAD prevalence. The CCTA alone strategy was found to be less expensive ($764 per patient) than all other diagnostic strategies except for Stress ECHO followed by CCTA ($702 per patient).

Outpatient Evaluation: Lifetime Model

A formal cost-effectiveness analysis comparing all the outpatient evaluation strategies was performed considering a lifetime horizon for cardiac outcomes and costs. All strategies are dominated except for CCTA alone and Stress ECHO alone. Stress ECHO was the least expensive, and therefore an incremental cost-effectiveness ratio for CCTA alone was calculated:

- Cost per QALY* saved vs. Stress ECHO = $178,000

*QALY = Quality adjusted life year

We also performed threshold analyses within the base case assumptions on the reimbursed price of CCTA that would produce incremental cost per QALY vs. stress ECHO alone at boundaries familiar to policy-makers.

- **To achieve Cost/QALY Saved = $150,000**
  CCTA cost must = $439
- **To achieve Cost/QALY Saved = $100,000**
  CCTA cost must = $392
- **To achieve Cost/QALY Saved = $50,000**
  CCTA cost must = $345

At a cost of $300 or less, CCTA would be a dominant (i.e., cost-saving) strategy relative to stress ECHO.

Note that, when a 10% CAD prevalence is considered, the relative costs of strategies involving CCTA increase due to the greater number of false-positive results generated, and the absolute number of false-negatives is not markedly different between strategies. Because of this, strategies involving CCTA result in cost per QALY measures of between $500,000-$900,000.

DRAFT* ICER Integrated Evidence Rating™: CCTA vs. Standard ED Triage Care

***Integrated Evidence Ratings will not be formally assigned until after the ICER Evidence Review Group meeting on December 8, 2008**

The Comparative Clinical Effectiveness of CCTA for triage of patients with acute chest pain and at low to intermediate risk of acute coronary syndrome in an ED setting is rated as:

- **C --- Comparable**

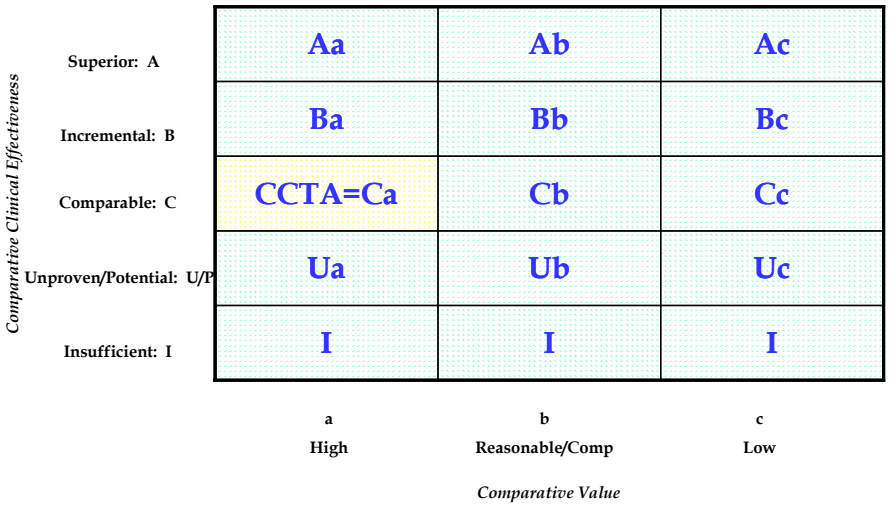
The Comparative Value of CCTA for triage of patients with acute chest pain in an ED setting is rated as:

- **a --- High***

The Integrated Evidence Rating = Ca*

*** Within assumptions of the economic analysis, including reimbursed price of CCTA assumed to = $466**

ICER Integrated Evidence Rating™: CCTA vs. Standard ED Triage Care



DRAFT* ICER Integrated Evidence Rating™: CCTA vs. Alternative Outpatient Strategies for Stable Chest Pain

***Integrated Evidence Ratings will not be formally assigned until after the ICER Evidence Review Group meeting on December 8, 2008**

The Comparative Clinical Effectiveness of CCTA for assessment of outpatients without signs or symptoms of unstable chest pain and at low to intermediate risk of significant coronary artery disease is rated as:

- **U/P – Unproven but with Evidence of Potential Net Benefit**

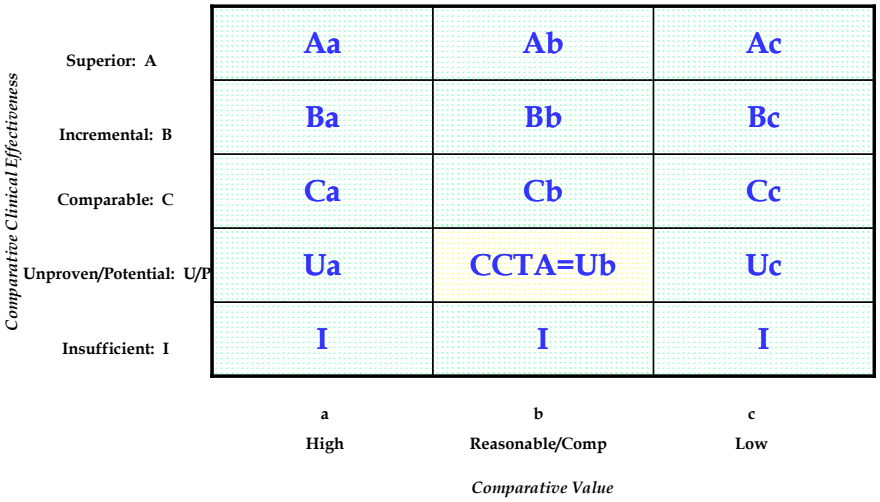
The Comparative Value of CCTA for assessment of outpatients presenting with stable chest pain is rated as:

- **b --- Reasonable/Comparable***

The Integrated Evidence Rating = Ub*

*** Within assumptions of the economic analysis, including reimbursed price of CCTA assumed to = $466**

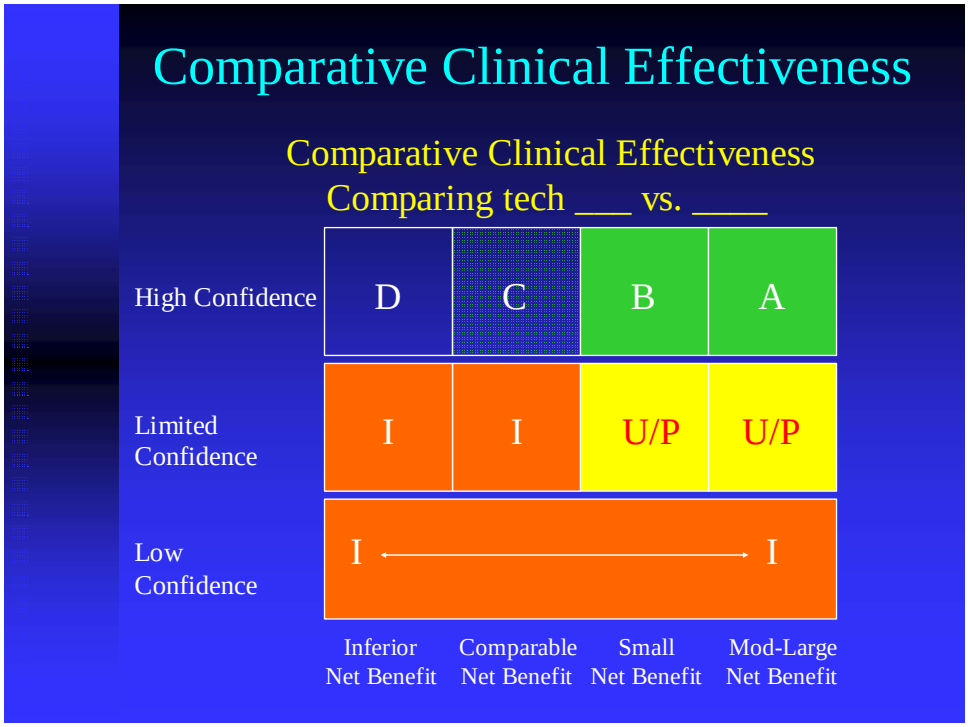
ICER Integrated Evidence Rating™: CCTA vs. Alternative Strategies for Stable Chest Pain



Methodology: ICER Integrated Evidence Rating™

Comparative Clinical Effectiveness

The ICER Integrated Evidence Rating™ combines a rating for comparative clinical effectiveness and a rating for comparative value. The clinical effectiveness rating arises from a joint judgment of the level of confidence provided by the body of evidence and the magnitude of the net health benefit -- the overall balance between benefits and harms. This method for rating the clinical effectiveness is modeled on the "Evidence- Based Medicine (EBM) matrix" developed by a multi-stakeholder group convened by America's Health Insurance Plans. This matrix is depicted below:



A = "Superior" [High confidence of a moderate-large net health benefit]
B = "Incremental" [High confidence of a small net health benefit]
C = "Comparable" [High confidence of a comparable net health benefit]
D = "Inferior" [High confidence of an inferior net health benefit]
U/P = "Unproven with Potential " [Limited confidence of a small or moderate-large net health benefit

This category is meant to reflect technologies whose evidence provides:

1) High confidence of *at least* comparable net health benefit
2) Limited confidence suggesting a small or moderate-large net health benefit

I = "Insufficient" The evidence does not provide high confidence that the net health benefit of the technology is at least comparable to that provided by the comparator(s).

Confidence

The vertical axis of the matrix is labeled as a degree of confidence with which the magnitude of a technology's comparative net health benefit can be determined. This operational definition of confidence thus is linked to but is not synonymous with the overall validity, consistency, and directness of the body of evidence available for the assessment. ICER establishes its rating of level of confidence after deliberation by the Evidence Review Group, and throughout ICER follows closely the considerations of evidentiary strength suggested by the Effective Health Care program of the Agency for Health Research and Quality (AHRQ) (www.effectivehealthcare.org) and the GRADE working group (www.gradeworkinggroup.org).

High Confidence:

An assessment of the evidence provides high confidence in the relative magnitude of the net health benefit of the technology compared to its comparator(s).

Limited Confidence:

There is limited confidence in the assessment the net health benefit of the technology. Limited confidence implies that the evidence is limited in one or more ways so that it is difficult to estimate the net health benefit with precision. ICER's approach considers two qualitatively different types of limited confidence. First, there may be limited confidence in the magnitude of any net health benefit, but there is high confidence that the technology is *at least* as effective as its comparator(s). The second kind of limited confidence applies to those technologies whose evidence may suggest comparable or inferior net health benefit and for which there is not nigh confidence that the technology is at least comparable. These two different situations related to "limited confidence" are reflected in the matrix by the different labels of "Unproven with Potential" and "Insufficient."

Limitations to evidence should be explicitly categorized and discussed. Often the quality and consistency varies between the evidence available on benefits and that on harms. Among the most important types of limitations to evidence we follow the GRADE and AHRQ approaches in highlighting:

1. Type of limitation(s) to confidence
    a. Internal validity
        i. Study design
        ii. Study quality
    b. Generalizability of patients (directness of patients)
    c. Generalizability of intervention (directness of intervention)
    d. Indirect comparisons across trials (directness of comparison)

e. Surrogate outcomes only (directness of outcomes)
f. Lack of longer-term outcomes (directness of outcomes)
g. Conflicting results within body of evidence (consistency)

Low Confidence:
There is low confidence in the assessment of net health benefit and the evidence is insufficient to determine whether the technology provides an inferior, comparable, or better net health benefit.

Net Health Benefit
The horizontal axis of the comparative clinical effectiveness matrix is "net health benefit." This term is defined as the balance between benefits and harms, and can either be judged on the basis of an empiric weighing of harms and benefits through a common metric (e.g. Quality Adjusted Life-Years, or "QALYs"), or through more qualitative, implicit weightings of harms and benefits identified in the ICER appraisal. Either approach should seek to make the weightings as explicit as possible in order to enhance the transparency of the ultimate judgment of the magnitude of net health benefit.

Whether judged quantitatively or qualitatively, there are two general situations that decision-making groups face in judging the balance of benefits and harms between two alternative interventions. The first situation arises when both interventions have the same types of benefits and harms. For example, two blood pressure medications may both act to control high blood pressure and may have the same profile of side effects such as dizziness, impotence, or edema. In such cases a comparison of benefits and harms is relatively straightforward. However, a second situation in comparative effectiveness is much more common: two interventions present a set of trade-offs between overlapping but different benefits and harms. An example of this second situation is the comparison of net health benefit between medical treatment and angioplasty for chronic stable angina. Possible benefits on which these interventions may vary include improved mortality, improved functional capacity, and less chest pain; in addition, both short and long-term potential harms differ between these interventions. It is possible that one intervention may be superior in certain benefits (e.g. survival) while also presenting greater risks for particular harms (e.g. drug side effects). Thus the judgment of "net" health benefit of one intervention vs. another often requires the qualitative or quantitative comparison of different types of health outcomes.

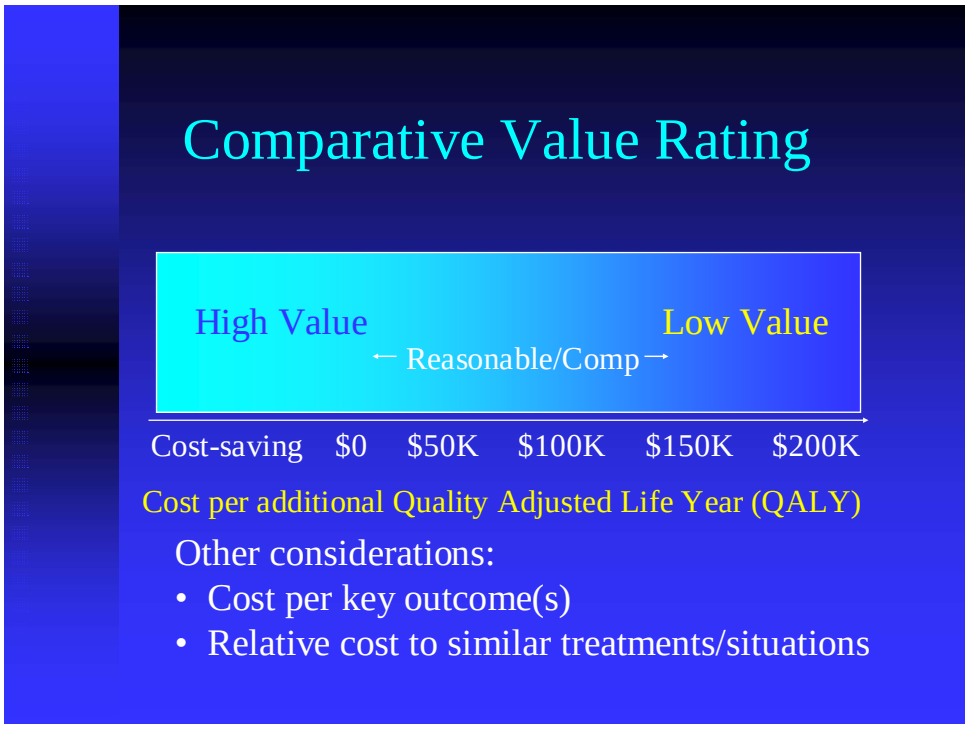
Since net health benefit may be sensitive to individual patient clinical characteristics or preferences there is a natural tension between the clinical decision-making for an individual and an assessment of the evidence for comparative clinical effectiveness at a population level. ICER approaches this problem by seeking, through the guidance of its scoping committee, to identify a priori key patient subpopulations who may have distinctly different net health benefits with alternative interventions. In addition, the ICER appraisal will also seek to use decision analytic modeling to

identify patient groups of particular clinical characteristics and/or utilities which would lead them to have a distinctly different rating of comparative clinical effectiveness.

The exact boundary between small and moderate-large net benefit is subjective and ICER does not have a quantitative threshold. The rating judgment between these two categories is guided by the deliberation of the Evidence Review Group.

Comparative Value

There are three categories of value: high, reasonable or comparable, and low. The ICER rating for comparative value arises from a judgment that is based on multiple considerations. Among the most important is the incremental cost-effectiveness of the technology being appraised The most commonly used metric for an assessment of cost-effectiveness is the quality adjusted life year, or QALY. This measure adjusts any improvement in survival provided by a technology by its corresponding impact on the quality of life as measured by the "utilities" of patients or the public for various health states. While ICER does not operate within formal thresholds for considering the level at which a cost per QALY should be considered "cost-effective," the assignment of a rating for comparative value does build upon general conceptions of ranges in which the incremental cost-effectiveness ratio can be generally assumed to indicate relatively high, reasonable, and low value compared to a wide range of health care services provided in the US healthcare system. These broad ranges and shown in the figure below. Details on the methodology underpinning the design and presentation of cost-effectiveness analyses within ICER appraisals is available on the ICER website at www.icer-review.org.



Although the cost per QALY is the most common way to judge the cost-effectiveness of alternative medical interventions, ICER also considers the sub-component parts of the QALY, including the cost per key clinical benefits. Additional data and perspectives are also considered whenever possible, including potential budget impact, impact on systems of care and health care personnel, and comparable costs/CEA for interventions for similar clinical conditions.

Integrated Ratings

The ICER Integrated Evidence Rating™ combines the individual ratings given for comparative clinical effectiveness and comparative value. The overall purpose of the integrated ratings is to highlight the separate considerations that go into each element but to combine them for the purposes of conveying that clinical benefits provided by technologies come at varying relative values based on their cost and their impact on the outcomes of care and the health care system.

Evidence Review Group Members

The Evidence Review Group (ERG) is an independent group brought together by ICER and composed of academic experts, patients, clinicians, epidemiologists, ethicists, and medical policy representatives of stakeholder groups including health plans and manufacturers.

The purpose of the ERG is to guide and help interpret the entire appraisal process. Members of the ERG are first convened to function as a "scoping committee" for the appraisal. During this phase the key questions for the appraisal are outlined, including elements such as the appropriate comparator technologies, patient outcomes of interest, patient subpopulations for which clinical and cost-effectiveness may vary systematically, time horizon for outcomes, and key aspects of the existing data that must be taken into account during the appraisal. The ERG may be divided into sub-committees that advise the ICER appraisal team at the mid-point of the appraisal on the early findings and challenges encountered.

At the final ERG meeting, members are asked to declare any interests in the technology or its comparator(s). The ERG meeting allows for in-depth deliberation on the findings of the ICER appraisal document and provides an opportunity for comment on the determination of the ICER integrated evidence rating. Although the ERG helps guide the final determination of the ICER Integrated Evidence Rating™, the final rating is ultimately a judgment made by ICER, and individual members of the ERG should not be viewed in any way as having endorsed this appraisal.

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INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

APPRAISAL OVERVIEW

CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY FOR DETECTION OF CORONARY ARTERY DISEASE

The overview is written by members of ICER's research team. The overview summarizes the evidence and views that have been considered by ICER and highlights key issues and uncertainties.

Final Scope

Rationale for the Appraisal
Coronary computed tomographic angiography (CCTA) is a minimally invasive radiological technique used to provide images of the heart and surrounding vessels. CCTA has been suggested as an alternative or useful complementary approach to other non-invasive methods of diagnosing coronary artery disease (CAD). In particular, because of its ability to visualize coronary anatomy, CCTA has been suggested as a strategy to rule out significant CAD among patients at low or intermediate risk of significant disease, thereby giving greater reassurance than other non-invasive methods and potentially reducing the number of patients ultimately sent for invasive coronary angiography (ICA). However, uncertainty remains regarding several important issues:

1) The diagnostic accuracy of CCTA relative to ICA and other possible comparator diagnostic tests
2) The impact on patient outcomes and health care utilization of alternative diagnostic algorithms that integrate CCTA in different ways into the diagnostic pathways for patients with suspected coronary artery disease, both in the general outpatient setting and in the Emergency Department
3) The most appropriate target populations for CCTA, based on level of risk and symptoms
4) The potential negative impact of increased radiation exposure of CCTA
5) The impact of incidental findings that trigger further evaluation
6) The potential impact of CCTA on the thresholds for clinician testing for coronary artery disease among the general population
7) The budget impact and cost-effectiveness of integrating CCTA into diagnostic pathways for patients with suspected coronary artery disease

Given the possible benefits of introducing a widely available non-invasive option for CAD detection, the potential clinical and financial impact that broad adoption of CCTA would have on systems of care, and the uncertainty over the evidence on the net health benefits and appropriate use of CCTA, all health care decision makers will benefit from a formal appraisal of the comparative clinical effectiveness and comparative value of CCTA as a modality for diagnosis of coronary artery disease.

Objective:
To appraise the comparative clinical effectiveness and comparative value of CCTA relative to the most relevant existing or emerging methods of CAD diagnosis and prognosis.

Key questions:

1. What are the sensitivity, specificity, and other test characteristics of CCTA in comparison to invasive coronary angiography as a reference standard but

also in context with other accepted non-invasive modalities for CAD detection?

2. What is the impact of CCTA on diagnostic and treatment decision-making among patients being evaluated for possible coronary artery disease?

3. What is known about the impact of CCTA on patient outcomes?

4. How do CCTA's test characteristics vary according to important patient subgroups, such as gender and perceived risk or pretest probability of CAD?

5. What evidence exists on the frequency and outcomes related to incidental findings with CCTA?

6. What is known about CCTA's possible harms, including radiation exposure and contrast reactions?

Key considerations highlighted by the Evidence Review Group:

1) Target Population: While there has been some talk of CCTA's use as a screening tool in an asymptomatic population, current clinical opinion favors the use of CCTA only within a target population of symptomatic patients with low-to-intermediate likelihood of CAD. Insurers and clinical experts believe that an assessment of CCTA use within this patient population would yield the most important results for decision-making.

2) Setting: The two most relevant scenarios for use of CCTA include its use in (a) an ED setting for evaluation of acute chest pain; and (b) outpatient presentation with stable chest pain symptoms. CT calcium scoring for risk evaluation should not be considered by ICER at this time, as the major question among clinicians and payers has been focused on the use of CCTA by itself to identify or exclude significant CAD.

3) Outcomes: While test performance is important to consider, emphasis should be given to consideration of evidence regarding CCTA's impact on diagnosis, therapeutic action, and patient outcomes. Within the literature on test performance, focus should be on "per-patient" findings rather than "per-vessel" or "per-segment", as clinical determination of CCTA interpretability in practice is made at the patient level.

4) Harms: Because other diagnostic tests used in combination with or instead of CCTA may also involve radiation, the total radiation dose of various diagnostic strategies should be considered. The fact that women often receive a higher dose of radiation should be noted. Also, new dose-reduction

protocols should be considered within the body of evidence on CCTA radiation dose.

5) Ethical considerations: There appear to be no distinctive ethical issues regarding the patient population or the interpretation of results from cost-effectiveness analyses.

1. Background

1.1 The Condition

Coronary artery disease (CAD) is the leading cause of death in the United States among both men and women, resulting in over 400,000 deaths annually (Centers for Disease Control and Prevention and American Heart Association, 2008). CAD also has a substantial impact on health care utilization. For example, approximately 6 million patients are seen each year at emergency departments for acute chest pain, the hallmark symptom of CAD (Gallagher, 2007). Greater than 60% of hospitalizations for chest pain, costing more than $8 billion annually, are ultimately deemed unnecessary (Hoffman, 2006).

CAD is caused by plaque accumulation and hardening in the coronary arteries, known as atherosclerosis. As buildup increases, the passage through the arteries narrows, decreasing blood flow and oxygen supply to the myocardium and causing angina and shortness of breath in many patients. Occlusion, or total blockage, of the arteries may result in myocardial infarction (Mayo Foundation for Medical Education and Research, 2008).

Due to its prevalence, and because several options (e.g., surgery, medication) exist to reduce CAD-related morbidity and mortality, accurate diagnosis of CAD is critical. Currently the definitive standard for diagnosis is invasive coronary angiography (ICA). There are risks associated with ICA, however, such as infection, artery trauma, and heart arrhythmias. For this reason non-invasive diagnostic methods have also been sought; the most common of these are the electrocardiogram (EKG), which measures cardiac activity via electrical signals, the echocardiogram (ECHO), which uses ultrasound to examine cardiac function, and single photon emission computed tomography (SPECT), which identifies abnormalities in cardiac perfusion using a radioactive tracer.

These tests differ in terms of their diagnostic accuracy, and their relative advantages and disadvantages. Because each test provides unique data, they are often used in combination when initial results are inconclusive. Given that none of the above-described tests provide a direct visual image of underlying coronary anatomy and degree of occlusion, interest has grown in using CT or MRI technology to evaluate patients with suspected CAD. Recently, the evolution of ultra-fast CT scanners has led to improved coronary imagery. Consequently, CCTA has received the endorsement of several clinical specialty organizations and is covered by many Medicare contractors and private insurers. Questions remain, however, regarding the relevant target populations for CCTA, its use alone or in combination with other tests, its prognostic ability, and its relative benefits and harms.

2. The Technology and its Comparators

2.1 Coronary CT Angiography

CCTA is a technique in which a CT scanner is used to acquire multiple simultaneous tomographic sections ("slices") of the coronary arteries. At the time of this outpatient procedure, an IV is placed into a peripheral vein and a contrast dye is administered for the purposes of visually defining the arteries for the scan. Beta blockers may be given to the patient to slow the heart rate in order to prevent artifacts of heart motion that may affect image quality. The patient is positioned on the CT scanner and a large number of x-ray images are taken from multiple angles and reconstructed using computer software. Multi-detector row CT scanners contain rotating gantries that capture multiple images, or "slices". A 64-slice CCTA was introduced in 2004 and increased the number of captured images from the previous 16- and 32-slice technology. Improved spatial and temporal resolution from 64-slice machines has been found to shorten the time required to capture an image, decreasing motion artifact as well as reducing the time to conduct the entire scan to approximately 8 seconds (Mowatt, 2008).

The 64-slice scanner has rapidly replaced earlier versions and is currently considered to be the community standard for CCTA. In 2007, 256- and 320-slice CT scanners became available, but it is unclear whether the greater resolution of these versions will provide clinically relevant advances to 64-slice machines. Dual source 64-slice scanners have also been introduced in which two scanners are mounted on the gantry at 90 degree angles (Matt, 2007). Dual source scanning is claimed by some to further decrease procedure time, reduce heart motion artifacts, and lower the effective radiation dose to the patient.

In the emergency department, CCTA can be used for the triage of patients experiencing acute chest pain to "rule out" CAD as the underlying cause. In comparison to standard triage care, which involves the use of serial cardiac enzyme testing as well as stress testing where warranted, some commentators have postulated that CCTA may rapidly identify patients without underlying CAD, thereby reducing the number of patients referred for ICA and the observation time required by many patients awaiting less precise evaluation.

In the outpatient setting, CCTA is most often used to evaluate patients with stable, non-emergent symptoms. For such patients CCTA can be used as an initial test or as a method for further evaluation following inconclusive results from another non-invasive functional test. As is the case among patients in the ED, CCTA's possible advantages in the outpatient setting include the ability to visualize and quantify underlying CAD, which may allow for greater precision in determining subsequent treatment (e.g., angioplasty, bypass surgery, or medical management).

Compared to other non-invasive diagnostic methods there are also potential disadvantages specific to CCTA, including a small risk of allergic reaction from the

use of contrast dye and the risk of renal damage from the dye among patients with pre-existing renal dysfunction. In addition, the increased precision from multi-detector row CT scanners is accompanied by a higher radiation dose to the patient. A number of protocols (e.g., prospective EKG gating, step-and-shoot methods) have been employed with varying degrees of success to reduce the radiation dose to the patient, but concern remains regarding the potential for increased risks of secondary malignancy.

Finally, the range of visualization of CCTA extends beyond the heart itself, creating the possibility of identification of "incidental findings" that may or may not be related to the patients' complaints of chest discomfort. The clinical impact of incidental findings is controversial and will be the subject of subsequent discussion within this report.

2.2 Coronary Artery Disease Diagnosis Alternatives

For many years the most precise and definitive method for the evaluation and diagnosis of coronary artery disease has been invasive coronary angiography (ICA). ICA is typically an inpatient procedure. At the time of the procedure a catheter is inserted into an artery, usually the femoral blood vessel, and contrast dye is injected through the catheter. X-ray images are then captured and displayed on a video screen (a procedure known as fluoroscopy), and can be viewed either as images or in motion picture form. While complications from ICA are relatively infrequent, they can be significant, and include myocardial infarction, cardiac arrhythmia, stroke, hemorrhage, infection, trauma to the artery from hematoma or from the catheter, sudden hypotension, and reaction to the contrast medium (Gandelman, 2006). The procedure also delivers a radiation dose lower than most CCTAs but similar to that of CCTA when it is performed using dose-saving protocols or dual-source scanners.

In part because of the invasive nature of ICA and its concordant risks, alternative non-invasive tests also are utilized for evaluation of chest pain symptoms considered suggestive of CAD. The first of these technologies to gain widespread use was the stress electrocardiogram (EKG); the major alternatives are stress echocardiography and single-photon emission computed tomography (SPECT), also known as nuclear stress testing or myocardial perfusion imaging.

Stress echocardiograms (ECHO) produce images of the heart through the use of sound waves. The test allows for the evaluation of blood flow in different areas of the heart to identify weak or damaged areas of the muscle. This is done through a comparison of images at rest and under cardiac stress induced by exercise or pharmacologic means. Clinically, the test is simple to perform, relatively inexpensive, and easily accessible. However, the image quality is lower in obese patients and those with chronic disease, which can account for almost 30% of candidates (Miller, 2006). It is recommended for use in intermediate-to-high risk patients (Anthony, 2005).

SPECT imaging involves the use of a tracer radiopharmaceutical to highlight areas of decreased blood flow in the myocardium. Images are captured via a gamma camera, and may be reconstructed to create two or three-dimensional films. The accuracy of SPECT imaging has improved to the point that it is often used for prognostic use in addition to diagnosis. However, it is not as effective in detecting perfusion defects in patient with milder stenosis (Jeetley, 2006). SPECT also involves the use of contrast media and delivers a radiation dose similar in magnitude to that of ICA and CCTA.

All of these alternative non-invasive diagnostic techniques measure in some way the functional impact on the heart of any underlying CAD. As noted above, none of the tests is perfect; each has the possibility of producing false positive and false negative results. Professional guidelines recognize all of these comparator techniques as appropriate initial investigations to evaluate possible CAD for most patients with stable symptoms (Gibbons, 2003).

3. Clinical Guidelines & Competency Standards

Published clinical guidelines on the use of CCTA are summarized here and presented in more detail in Appendix A.

- American Heart Association (2006)
  http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.178458

  CCTA has been shown to have a high negative predictive value, and therefore is useful in ruling out CAD. Evidence supports the use of CCTA for patients with low-to-intermediate probability of hemodynamically relevant stenosis and may obviate the need for ICA in these patients.

- Multi-Society Statement of Appropriateness Criteria for Cardiac Computed Tomography (2006) http://content.onlinejacc.org/cgi/content/full/48/7/1475

  Appropriateness reviews of CCTA and cardiac magnetic resonance imaging deemed the use of CCTA for detection of CAD to be appropriate for the following patient populations:
  - Presenting with chest pain syndrome with intermediate pre-test probability of CAD and uninterpretable EKG or inability to exercise
  - Presenting with chest pain and uninterpretable or equivocal stress test results
  - Presenting with acute chest pain with intermediate pre-test probability of CAD and no EKG changes and serial enzymes negative
  - Symptomatic patients requiring evaluation of suspected coronary anomalies

- American College of Radiology (2006)
  http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/pdf/ExpertPanelonCardiovascularImaging/ChronicChestPainSuspectedCardiacOriginUpdateinProgressDoc8.aspx

  An update to their 1995 recommendations determined that CCTA is appropriate for assessment of CAD, although its usefulness for patients with low pretest probability is unknown. On a scale of 9 to indicate appropriateness (with a score of 9 being most appropriate), CCTA was assigned a rating of 7 for the evaluation of chronic chest pain.

- SCCT/NASCI Consensus Update (2007)
  http://www.invasivecardiology.com/article/7959

  An update to their 2006 publication found CCTA to be appropriate in the following circumstances:

- To rule out significant coronary stenosis
- To evaluate patients with equivocal or discordant results on a stress perfusion or wall motion study
- To rule out stenosis in patients with a low pre-test likelihood of CAD
- To potentially replace diagnostic catheterization in patients undergoing non-coronary cardiac surgery

- ACCF/AHA Clinical Competence Statement (2005, updated 2007)
  http://www.scct.org/ct_mr_clinical_competence_statement_063005.pdf

  Guidelines for the assessment of clinical competence of physicians performing CCTA were established. The minimum training required to independently perform and interpret CCTA, both non-contrast and contrast, is as follows:
  - Board certification of eligibility and valid medical license
  - Eight weeks of specialized training in CCTA
  - 150 contrast CCTA examinations (at least 50 in-person)
  - Evaluation of 50 non-contrast studies
  - Completion of at least 20 hours of courses related to general CT or CCTA

- ACR Practice Guidelines (2006)
  http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/dx/cardio/ct_cardiac.aspx

  Physician competency in performing and interpreting CCTA is defined by the following qualifications:
  - For physicians with prior qualifications for interpretation of CT examinations, a minimum of 30 hours of training courses in cardiac anatomy, physiology, and pathology and at least 50 CCTA examinations supervised, interpreted, or reported in the last three years
  - For physicians with no prior qualification, a minimum of 200 hours of training on performance and interpretation of CT and supervision, interpretation, and reporting of at least 500 cases (at least 100 must be thoracic CT or CCTA), in addition to the training and interpretation requirements specified above
  - Understanding of administration, contraindications, and risks of pharmacologic agents used for CCTA
  - Continuous use of the technology, defined as a minimum of 75 cases per three years
  - Continuing medical education relevant to CCTA

NOTE: There is now a formal board certification process for cardiologists wishing to be certified in cardiac CT imaging that is being administered on behalf of multiple clinical societies (ACC, ASNC, SCAI, and SCCT). Candidates must meet minimum ACCF/AHA criteria, undertake a formal examination, and be re-certified every 10 years. (http://www.cbcct.org/index.cfm) A similar effort is being undertaken by the ACR on behalf of radiologists.

4. Medicare and Representative Private Insurer Coverage Policies

- In December 2007, citing CCTA as a promising but unproven technology, the Centers for Medicare and Medicaid Services (CMS) announced its intent to create a national coverage decision (NCD) allowing for "coverage with evidence development"—that is, coverage only for patients participating in clinical trials of the technology. After a period of public comment and discussion, CMS reversed its decision in March 2008, and stated that the local coverage determination (LCD) process would be left in place. Current LCDs allow for coverage of CCTA in symptomatic patients; below is an example from the coverage policy for the state of Washington:

    - "…CCTA can reliably rule out the presence of significant coronary artery disease (CAD) in patients with a low to intermediate probability of having CAD and can reliably achieve a high degree of diagnostic accuracy necessary to replace conventional angiography in selected situations.… CCTA may be used to guide further diagnostic evaluation and/or appropriate therapy … and this may over the long term influence the morbidity from CAD."

- Among private health plans with publicly available coverage policies for 64-slice CCTA, details of coverage differ. Representative examples of coverage policies include the following:

    - Aetna covers 64-slice CCTA for ruling out CAD in patients with low pre-test probability and equivocal or contraindicated stress testing, conducting pre-operative assessments for non-coronary cardiac surgery, detection of coronary anomalies, evaluating cardiac structures in patients with congenital heart disease, and calcium scoring.

    - CIGNA covers 64-slice CCTA for detection of CAD in symptomatic patients with intermediate pre-test probability and equivocal or contraindicated EKG, or with no EKG changes and negative enzymes.

    - United Healthcare considers 64-slice or better CCTA proven for evaluation of chest pain among patients with intermediate pre-test CAD probability and equivocal or contraindicated EKG, evaluation of chest pain among patients with prior uninterpretable or equivocal stress test results, assessment of acute chest pain in patients with an intermediate pre-test probability of CAD, no EKG changes, and negative enzymes.

    - The Regence Group and UniCare both consider CCTA to be investigational and will cover its use only if ICA was unsuccessful or equivocal for detection of CAD.

5. Previous Systematic Reviews/Tech Assessments

- U.K. National Health Service Research & Development Health Technology Assessment (2008)
  http://www.ncchta.org/execsumm/summ1217.shtml
  CCTA will most likely not replace ICA, but may be useful in ruling out significant CAD.

- BCBSA TEC (2006)
  http://www.bcbs.com/blueresources/tec/vols/21/21_05.html
  Evidence on CCTA for use in either diagnosis of coronary artery stenosis or evaluation of acute chest pain does not meet TEC criteria for widespread adoption and use. The only criterion that was met was the first, which states that "the technology must have final approval from appropriate government regulatory bodies". The following criteria were not met:
  - The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.
  - The technology must improve net health outcomes.
  - The technology must be as beneficial as any of the established alternatives.
  - The improvement must be attainable outside the investigational settings.

- Medical Services Advisory Committee (MSAC) (2007)
  http://www.msac.gov.au/internet/msac/publishing.nsf/Content/app1105-1
  In symptomatic patients, CCTA is as effective as ICA in ruling out significant CAD.

- California Technology Assessment Forum (CTAF) (2007)
  http://www.ctaf.org/content/general/detail/768
  CCTA for diagnosis of coronary artery stenosis and evaluation of acute chest pain failed to meet CTAF criteria for widespread adoption and use. Criteria utilized by CTAF were the same as those of BCBSA TEC; the only criterion that was met was Criterion 1, which states that "the technology must have final approval from appropriate government regulatory bodies".

- Medicare Coverage Advisory Committee (MedCAC) (2006)
  http://www.cms.hhs.gov/mcd/viewmcac.asp?where=index&mid=34
  While individual responses varied, the committee's response was "unsure" when questioned as to whether 64-slice CCTA would provide a net health benefit when (a) used as a non-invasive diagnostic test before ICA; or (b) used as a replacement for ICA.

- Ontario Health Technology Advisory Committee (2005)
  http://www.health.gov.on.ca/english/providers/program/ohtac/tech/reviews/sum_mdct_20070926.html
  There is insufficient evidence to suggest that 16- or 64-slice CCTA is equal to or better than coronary angiography to diagnose CAD in those with symptoms or to monitor progression in persons with prior cardiac interventions.

- National Institute for Health and Clinical Excellence (NICE)
  http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11953
  NICE has not reviewed this topic.

6. Ongoing Clinical Studies

Thirty clinical studies are currently recruiting patients for evaluation of CCTA as a diagnostic tool for CAD; four are randomized studies and two are employing within-subject designs to compare CCTA with ICA or SPECT. Several large cohort studies are documenting CCTA in clinical practice. Major studies are summarized below (details at http://clinicaltrials.gov).

Table 1. Summary of ongoing clinical studies

Trial Sponsor	Design	Primary Outcomes	Populations	Variables	Comments
Beaumont Hospitals (NCT00541203)	RCT	▪ Diagnostic/prognostic performance ▪ Prediction of major cardiovascular events	N=200 with inconclusive or indeterminate stress test results	CCTA vs. ICA	Outpatient setting; Estimated study completion date January 2012
Seoul National University (NCT00431977)	RCT	▪ Myocardial infarction ▪ Late revascularization ▪ Cardiac death	N=1,000 diabetics without coronary symptoms	CCTA+ standard care vs. standard care	Estimated study completion date December 2012
Intermountain Healthcare (NCT00488033)	RCT	▪ All-cause death ▪ Non-fatal MI ▪ Unstable angina	N=1,100 asymptomatic, high-risk diabetics	Screening with CCTA or calcium scoring vs. standard care	Estimated study completion date December 2011
Beaumont Hospitals (NCT00468325)	RCT	▪ Multiple efficacy, safety, and economic endpoints	N=750 ED patients with acute chest pain and low-to-intermediate CAD risk	CCTA vs. standard triage care	Emergency Department setting; Estimated study completion date December 2008
St. Joseph's Healthcare (NCT00371891)	Within-subject	▪ Sensitivity and specificity	N=900 scheduled for ICA	CCTA vs. ICA, single-blinded comparison	
GE Healthcare (NCT00486447)	Within-subject	▪ Sensitivity, specificity ▪ Negative predictive value ▪ Downstream cardiac testing ▪ Major cardiac events	N=300 with intermediate CAD risk and referred for myocardial perfusion scanning	CCTA vs. MPS, single-blinded comparison	Estimated study completion date August 2011

Table 1. Summary of ongoing clinical studies (cont'd)

Trial Sponsor	Design	Primary Outcomes	Populations	Variables	Comments
Brigham and Women's Hospital (NCT00321399)	Observational	▪ Referral to cardiac catheterization within 90 days of index test ▪ Predictive ability for cardiac death and non-fatal myocardial infarction ▪ Relative cost-effectiveness of each approach	N=4,000 referred for stress perfusion (SPECT, PET), CCTA, or combined perfusion-anatomy (PET/CT) studies with intermediate-to-high pretest probability of CAD	CCTA vs. PET, SPECT, and hybrid PET-CT	Estimated study completion date August 2009
William Beaumont Hospitals (NCT00640068)	Observational	▪ Patient characteristics ▪ Scanning acquisition techniques ▪ Quality of physician scan interpretation ▪ 90-day clinical outcomes	N=12,000 referred or self-referred for CCTA	CCTA	Study was a collaborative effort organized by Blue Cross/Blue Shield of Michigan; estimated study completion date October 2010

7. The Evidence

7.1 Systematic Literature Review

Objectives
The primary objective of the systematic review was to identify and summarize the published evidence on the test performance and impact on patient outcomes of CCTA in two key populations:

- Acute chest pain of unknown origin in an ED setting
- Stable chest pain symptoms among patients at low-to-intermediate CAD risk in an outpatient setting

We sought studies that examined the impact of CCTA, whether used alone or in combination with other diagnostic methods, on objective outcomes; these included treatment and testing decisions and major cardiovascular events. We also included studies that evaluated CCTA's diagnostic accuracy relative to a common reference standard (typically ICA). While we did not systematically search for evidence regarding test safety, incidental findings, and economic impact, we obtained such data within our selected clinical literature, supplemented with data from review articles and expert guidance.

Many candidate studies reported results on a "per-vessel" or "per-segment" basis, in addition to per-patient analyses. While these approaches are often useful for juxtaposing segment or vessel location against temporal and spatial resolution on CCTA, and provide a larger sample of observations in which to examine accuracy, they are not generalizable to clinical practice, in which decisions on patient management are made at the patient level. For example, a distal segment may be excluded from analyses of accuracy because of blurred imagery; in reality, any indeterminate finding on any segment can trigger further testing at the patient level. Because of our interest in examining the impact of CCTA on patient outcomes, and because per-vessel results alone can inflate test performance statistics, we included only those studies that reported results at the patient level or whose results could be used to construct per-patient analyses.

Methods
This review included studies of the performance of CCTA in diagnosing CAD using scanners with 64-slice or higher resolution (including dual-source scanners). Guidance from the ICER Evidence Review Group suggested that 64-slice scanners were now widely available in the community and had become viewed as the standard for CCTA, and that literature on earlier-generation scanners would not be viewed as relevant by the clinical and patient communities.

We also excluded studies that reported on the use of CCTA for applications other than CAD detection—for example, diagnosis of pulmonary emboli or detection of

congenital cardiac defects. We also excluded studies focused solely on the use of CT for so-called "calcium scoring", or measurement of coronary calcium as a marker for early-stage CAD, as the focus of our appraisal was on the diagnosis of obstructive disease among symptomatic patients.

Included studies were conducted in ED or outpatient settings (as described above) and had a study population of adults who underwent both CCTA and a clearly defined reference standard—either ICA alone, or ICA and/or a clearly defined algorithm that assigned a final diagnosis based on clinical outcomes. We searched for studies during the period January 2005 (the first year of published studies from 64-slice scanners) to the present. Other major eligibility criteria included:

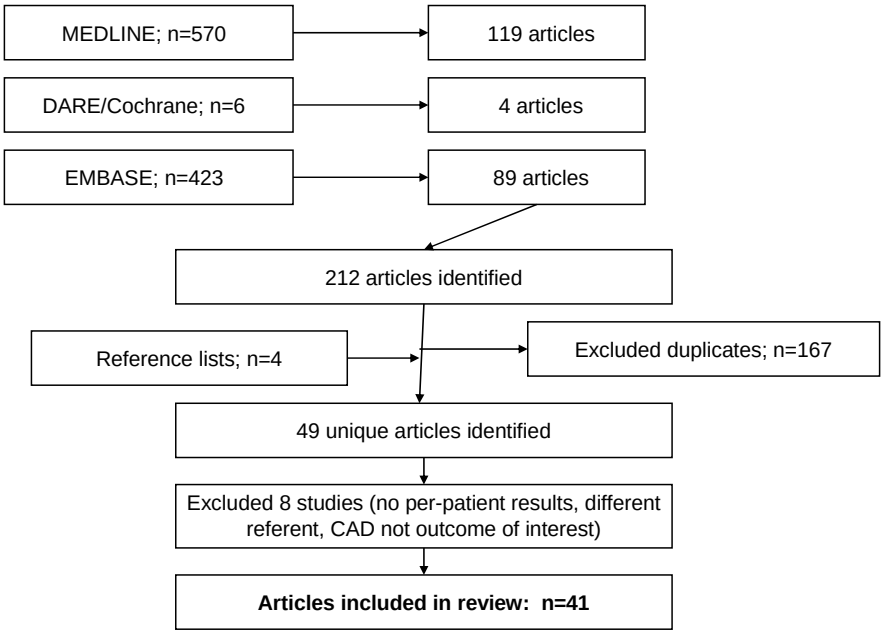
- Results reported on per-patient basis (or ability to construct per-patient findings)
- Receipt of reference standard by entire study population or random sample
- For diagnostic accuracy studies, time between CCTA and reference standard did not exceed 3 months
- Evaluation of native arteries only
- Blinded review of both CCTA and reference test

Studies were not restricted by CCTA instrumentation, imaging technology, method of heart rate control, or use and type of dose-sparing protocol.

Electronic databases searched included MEDLINE, EMBASE, and *The Cochrane Library* (including the Database of Abstracts of Reviews of Effects [DARE]) for eligible studies, including health technology assessments (HTAs), systematic reviews, and primary studies. Reference lists of all eligible studies were also searched. The search strategies used for MEDLINE, EMBASE, and *The Cochrane Library* are shown in Appendix B.

On the following page, Figure 1 shows a flow chart of the results of all searches for included primary studies. In addition to 41 primary studies, searches identified 2 systematic reviews and 2 HTAs.

Figure 1. QUORUM flow chart showing results of literature search
Data abstracted from each primary study included inclusion and exclusion criteria, patient demographics and risk status (if available), sample size, # of patients with known prior CAD, # of patients excluded for non-diagnostic CCTA results, stenosis threshold for CAD diagnosis, sensitivity, specificity, PPV, and NPV for significant CAD (by patient only), prevalence of CAD by number of diseased vessels (based on reference standard), complications, and effective radiation dose.



7.2 Data Analyses

Patient Outcomes Data

Because studies of the impact of CCTA on clinical outcomes varied in terms of their definitions of events, period of follow-up, and data collection methods, we made no attempt to formally meta-analyze these data. Study characteristics and major findings are presented in descriptive fashion only, and general trends and/or consistencies across the studies are discussed.

Diagnostic Accuracy Data

If sensitivity or specificity was not reported, we calculated these values. We calculated sensitivities whenever true positive and false negatives values were reported using the formula "true positive/ (true positive + false negative)"; negative predictive value (NPV) was calculated as "true negative/(true negative + false negative)". Specificity was calculated using the formula "true negative/(false positive + true negative)", and positive predictive value (PPV) as "true positive/(true positive + false positive)".

We present published data according to an "intent to diagnose" (ITD) paradigm; in this approach, patients with "non-diagnostic" or indeterminate CCTA tests are considered to have positive findings, as clinical expert guidance from the ICER Evidence Review Group suggested that clinicians commonly refer such cases to ICA

or further non-invasive testing. Our primary approach conservatively assumed that all such patients would be determined to be false positives on ICA, which materially affects only the calculations of specificity and PPV (i.e., as false positives are not included in calculations of sensitivity or NPV). This approach may under-represent the diagnostic accuracy of CCTA but avoids the equal or greater risk of overestimating accuracy when non-diagnostic CCTA results are excluded from consideration. This "conservative" approach has been employed by several investigators (Ropers, 2007, Shapiro, 2007) specifically to evaluate the impact of excluding non-diagnostic findings on test characteristics.

The quality of diagnostic accuracy studies is typically assessed using the QUADAS tool, a 14-item instrument evaluating internal validity developed by Whiting *et al* (2003). We modified the published tool by first eliminating 2 items that relate to sufficient description of the index test and reference standard to allow their replication, as it was felt that these items relate more to the quality of study reporting rather than any methodological deficiencies. We then added 4 items to the checklist, consistent with methods used in a recent HTA and systematic review of 64-slice CCTA (Mowatt, 2008):

- Use of an established threshold to define stenosis
- Presentation of data on inter-observer variation and results within acceptable ranges
- Data presented for appropriate patient subgroups
- Reporting of true disease prevalence on ICA (or ability to derive it)

The modified QUADAS tool is presented in Appendix C, along with the results of our study quality review.

Data Synthesis

Analyses of test characteristics were conducted by first using the reported or derived numbers of true positives, false positives, true negatives, and false negatives to calculate sensitivity, specificity, PPV, and NPV. These statistics were used in turn to generate the positive likelihood ratio (PLR, increase in odds of disease with positive test result) and negative likelihood ratio (NLR, decrease in odds of disease with negative test result).

We generated summary receiver operating characteristic (sROC) curves to assess whether any threshold effects appeared to be present, and correspondingly, whether symmetric or asymmetric distributions should be assumed. Pooled estimates of test accuracy were generated using the DerSimonian-Laird method for random-effects models (DerSimonian, 1986); 95% confidence intervals were also constructed.

In addition to primary analyses of data, alternative analyses were conducted to: (a) examine the influence of inclusion of patients with known CAD in the study sample by comparing pooled results between studies that did and did not include such

patients; and, (b) assess the effect of excluding patients with non-diagnostic results by comparing overall pooled results to findings recalculated using the ITD approach.

Meta-analyses were conducted using MetaDiSc software version 1.4 (Zamora, 2006).

7.3 Results

Selected Studies

A total of 49 studies were initially identified from the literature search; 8 of these studies were excluded because either no per-patient findings were available (n=4), the comparison performed was for an outcome other than detection of CAD (e.g., comparison to SPECT to assess myocardial perfusion, n=3), or identical findings were presented in another included study (n=1). Characteristics of excluded studies are presented in Table 2.

Of the remaining 41 studies, 34 were conducted in an outpatient setting, and 7 were conducted in an ED setting. Most studies were diagnostic accuracy studies using ICA alone as the reference standard (n=34; 1 ED, 33 outpatient), with most of these conducted in patients already scheduled for ICA. A total of 7 studies examined the impact of CCTA by evaluating subsequent clinical decisions and patient outcomes; while this approach was typically utilized in an ED setting (where definitive diagnosis by ICA is not universally feasible or warranted), one of the 7 studies identified was conducted among patients presenting on an outpatient basis with stable symptoms. Characteristics of included studies are presented in Table 3.

Because most of the included studies involved patients already scheduled for ICA, the prevalence of CAD in our sample was relatively high (mean [SD]: 59.0% [20.9%]; range: 18.2%-91.0%). Studies reporting results stratified by CAD risk or pretest likelihood are summarized below.

Major reasons for patient exclusion from these studies related primarily to ability to perform CCTA or obtain adequate image quality, and included known allergy to contrast media, impaired renal status, inability to follow breath-hold commands, obesity (typically, defined as BMI >40), and elevated heart rate after attempted pharmacologic control. Approximately two-thirds of studies also excluded patients with known prior CAD or revascularization. Finally, while not a criterion for *patient* exclusion, vessels smaller than 1.5 mm in diameter or those felt to be heavily calcified were often excluded from analysis, as CCTA image quality is often impaired in these vessel types (Schroeder, 2008).

All of the selected studies were conducted in single centers. Two randomized studies were identified; a randomized controlled trial of standard ED triage care to CCTA plus standard care (Goldstein 2007), and a randomized comparison of dual-source to single-source CCTA (Achenbach 2008). Characterization of selected studies according to a widely-accepted framework for assessing the level of evidence from diagnostic imaging studies (Fryback 1991) can be found below (from lowest to highest level of evidence presented):

1. Technical only: 0
2. Diagnostic accuracy: 34
3. Impact on diagnostic thinking: 2
4. Impact on therapeutic actions: 4
5. Impact on patient outcomes: 1
6. Impact on societal outcomes: 0

Importantly, while there were 7 studies in our sample that measured outcomes beyond test accuracy, only the Goldstein study evaluated the incremental effects of CCTA relative to a comparison group, and was therefore the only study identified as measuring the impact of CCTA on patient outcomes.

Description of Study Population

ED Studies

A total of 9 reports were initially identified that examined CCTA's impact on outcomes or diagnostic accuracy in the ED setting. Two of these were excluded from the final sample. One study used SPECT as a reference standard, focusing on CCTA's diagnostic ability for perfusion abnormalities, not for CAD detection (Gallagher 2007); the other (Rubinshtein 2007) was based on an identical sample reported in another publication that was included in our final sample.

The total sample size in the ED studies was 496 patients; sample size ranged from 33-104 by study. Mean age ranged from 46-58 years; approximately 60% of the overall sample was male. The presence of prior known CAD or ischemia was observed in about 7% of patients (n=34).

Outpatient Studies

A total of 40 reports were initially identified that examined CCTA diagnostic accuracy in the outpatient setting. Six of these studies were excluded, because results were not reported on a per-patient basis (n=4) or ICA was not part of the reference standard definition (n=2).

The total sample size in the remaining 34 studies was 3,349, and ranged between 30-279 patients per study. Mean age ranged between 46-69 years; 63% of the overall sample was male. The overall prevalence of prior known CAD was approximately 10%, and ranged between 2-40% in those studies including patients with known prior disease.

Studies of CCTA Impact on Clinical Decisions and Patient Outcomes
Details on the 7 studies that evaluated in some way the impact of CCTA on patient management and outcomes can be found in Table 4. The outcome measures employed, event definitions used, underlying CAD risk, and duration of follow-up varied significantly between studies. In addition, the lack of active or historical controls in all but one of these studies made CCTA's possible incremental benefits and health-system impacts difficult to ascertain. Brief descriptions and key findings of these studies are given below.

Goldstein (2007): This study was an RCT of CCTA plus standard triage care vs. standard care alone in 197 patients at very low risk of CAD. Following initial negative EKGs and serum enzymes for myocardial damage, patients in the CCTA arm were discharged home immediately if they had a normal study or only signs of insignificant CAD, referred for ICA if the CCTA indicated severe stenosis, or referred for standard triage care of 8 hours of observation and subsequent SPECT study if CCTA results indicated intermediate stenosis or were non-diagnostic. Seventy-five percent of patients in the CCTA arm were discharged home immediately, and none of these patients suffered major cardiac events over a 6-month follow-up period. A higher percentage of patients in the CCTA arm had ICA; 9 of the 11 catheterizations in the CCTA arm confirmed significant CAD. One of 9 patients (11%) with a positive CCTA was determined to be a false positive on ICA. Testing costs were higher in the CCTA arm, but due to shorter average ED stays total ED costs per patient were approximately $300 lower in these patients.

Rubinshtein (2007): This study evaluated CCTA's use in guiding triage among 58 patients with and without known prior CAD who presented to the ED with chest pain, intermediate CAD risk, negative initial enzymes, and no EKG changes. Patients received standard ED triage along with cardiology consultation, after which a presumptive diagnosis of acute coronary syndrome (ACS) was made where warranted along with recommendations for hospitalization and early invasive treatment. CCTA was then performed in all patients, and recommendations adjusted based on CCTA findings. Patients were followed for major adverse cardiovascular events (MACE) over a mean of 12 months of follow-up. CCTA results led to a revised ACS diagnosis in 18 of 41 patients, canceled hospitalizations in 21 of 47, and altered early invasive treatment in 25 of 58. One CCTA scan was deemed to be false positive; no MACE events were recorded in the 32 patients discharged from the ED.

Pundziute (2007): The prognostic significance of CCTA was evaluated in this study of 100 consecutive outpatients who were referred for further evaluation (stress EKG, SPECT, or ICA) based on suspicion of CAD. CCTA and calcium scoring were performed in addition to the standard workup. A total of 26 patients had at least one MACE event over a mean follow-up of 16 months. In Kaplan-Meier analyses of event rates at one year, a positive CCTA for any stenosis was associated with a significantly increased event risk (30% vs. 0%, p=.005); whether CAD was deemed to

be obstructive on CCTA, as well as location of obstructive disease, were significant and independent predictors of event likelihood.

Hollander (2007): A total of 54 patients presenting to the ED with chest pain who met criteria for low CAD risk and had negative initial enzymes were scheduled for EKG and CCTA in this study. The incidence of MACE events was recorded at 30 days post-ED visit. A total of 46 patients (85%) were immediately discharged from the ED after negative CCTA findings; no MACE events were recorded among these patients. Two of the remaining patients were hospitalized even though CCTA findings were negative (the ED physician did not yet have enough confidence in the technology); of the remaining 6 patients, 2 had high degrees of stenosis confirmed by ICA, and 4 were referred for subsequent non-invasive testing after moderate stenosis was observed on CCTA. No events were recorded in any of these patients at 30 days.

Johnson (2007): In this study, 55 patients with acute chest pain of unknown origin were referred from the ED for CCTA and followed for at least 5 months for the cause of chest pain (both CAD and non-CAD) as well as long-term outcomes. CCTA identified the cause of chest pain in 37 of 55 patients (67%); in 14 patients, neither CCTA nor clinical follow-up determined the cause of chest pain; and in 4 patients, a diagnosis was made from clinical follow-up only.

Savino (2006): Early experience with CCTA was documented in this study of 23 patients presenting to the ED with acute chest pain and no EKG or enzyme changes. Short-term outcomes, including length and costs of hospitalization, were measured for study patients in comparison to a demographically-similar control group undergoing conventional ED workup. Of the 23 patients, 8 were identified as having >50% stenosis in at least one artery, which was confirmed by ICA in all cases; 2 were identified as having mild stenosis, received medical therapy and were discharged; 2 were identified as having pulmonary embolism, and were treated and discharged; and 11 were CCTA-negative (9 of these were immediately discharged). Length of stay and costs were reduced by ~40% in the study group relative to controls.

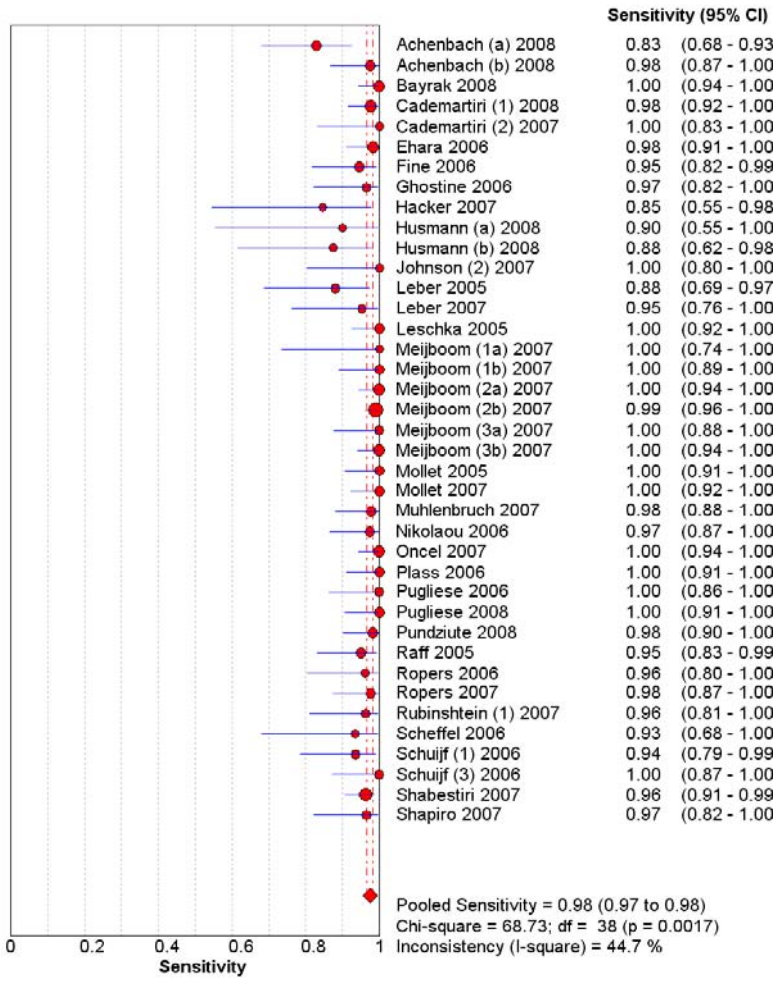
(Hoffmann, 2006). The potential effects of CCTA's identification of significant stenosis as well as calcified and non-calcified plaque were explored in this blinded prospective study of 103 patients presenting with acute chest pain, no EKG changes, and negative enzymes; all patients were hospitalized to rule out ACS. Patients were administered CCTA immediately prior to hospital admission. The presence of ACS was determined by and independent panel based on data collected during the index hospitalization and 5 months of follow-up. A total of 14 cases of ACS were identified; CCTA did not show evidence of significant stenosis in 73 patients (none of whom had ACS), detected significant stenosis in 13 patients (8 of whom had ACS), and could not rule out stenosis in 17 patients (6 with ACS). Quantification of plaque by CCTA was an independent and significant predictor of ACS on logistic

regression analyses that included traditional risk factors (e.g., age, gender, hypertension).

CCTA Diagnostic Accuracy vs. ICA

Figure 3 below presents the data on sensitivity of CCTA when compared directly to ICA, including the pooled results generated by quantitative meta-analysis. Where multiple subgroups (e.g., by CAD risk or gender) were reported, we considered these groups separately (yielding a total of 39 observations). The pooled sensitivity was 98% (95% CI, 97%, 98%); estimates were relatively homogenous across studies (see Figure 3 below). Summary ROC curves (Appendix D) showed no evidence of a threshold effect, which was likely due to a relatively standard cutoff for identifying stenosis (≥50% luminal narrowing). About 3% of patients had non-diagnostic CCTA results (range: 0-18%); as described above, we included these patients as false positives in primary calculations.

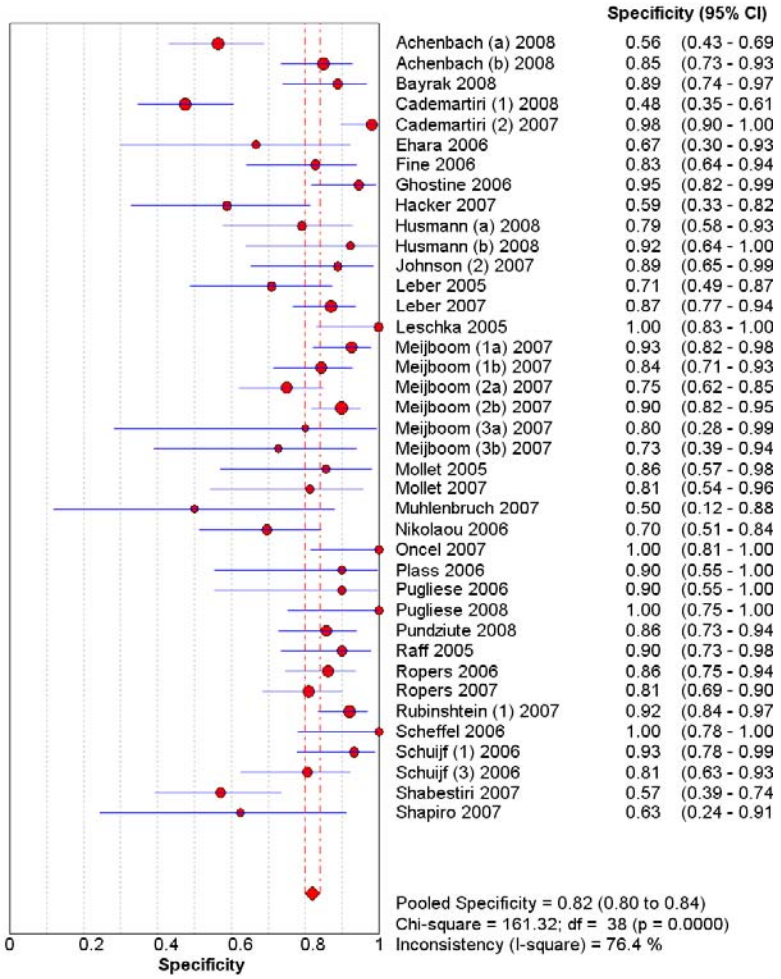
Figure 3. Pooled sensitivity of CCTA in diagnosing CAD (intent-to-diagnose analysis).



A greater degree of heterogeneity was observed in analyses of specificity; results by study ranged from 50-100%. No discernible pattern in study design or diagnosis

confirmation was observed among "outlier" studies. Consideration of patients with non-diagnostic findings as false positives resulted in a pooled specificity estimate of 82% (95% CI: 80%, 84%). Findings by study are displayed in Figure 4 below.

Figure 4. Pooled specificity of CCTA in diagnosing CAD (intent-to-diagnose analysis).



NLR and PLR findings echoed those of sensitivity and specificity (Appendix D). When results from the diagnostic accuracy studies were pooled but with non-diagnostic exams excluded from consideration, specificity rose from 82% to 87% (95% CI: 85%, 88%). Full results for this alternative approach are shown in Appendix E. As discussed earlier, whereas our primary approach to determining specificity may under-represent CCTA performance, it is not unreasonable given the likelihood that excluding non-diagnostic exams ignores the fact that many patients with such results will be felt to require further investigation, even though the true prevalence of significant disease among these patients is relatively low.

Given that CCTA has been a rapidly evolving technology, it is always possible that a pooling of evidence from studies published over several years will trail behind the most recent results. We examined this possibility but found that our estimates of

sensitivity and specificity from pooling of studies 2005-2008 are similar to those from the most recent reports of CCTA diagnostic accuracy (i.e., Budoff, 2008; Bayrak, 2008; Husmann, 2008; Pundziute, 2008).

Additional Recent Evidence

The results of the first multi-center evaluation of the diagnostic accuracy of CCTA, the Assessment by Coronary Computed Tomographic Angiography of Individuals UndeRgoing InvAsive Coronary AngiographY (ACCURACY) study, were very recently published and were not available in time to be incorporated into our meta-analysis (Budoff, 2008). In this study, data were obtained from 16 US sites, and included 230 patients who were referred for non-emergent ICA and also received CCTA. Certain exclusion criteria common to smaller validation studies (e.g., obesity, high calcium scores, vessel size) were not employed, as the study was designed to enroll a population similar to what might be expected in typical practice. The prevalence of CAD on ICA was 24.8%; mean (SD) age was 57 (10) years, and 59% of patients were male. Using a CAD threshold of ≥50% stenosis, patient-based sensitivity (95% [95% CI: 85%, 99%) and specificity (83% [76%, 88%] reported in this study were very similar to our pooled estimates. The study also employed an alternative definition of ≥70% stenosis; diagnostic accuracy was essentially identical to that observed in primary analyses.

Studies with Relevant Subgroup Data

Stratified by CAD Risk or Pretest Likelihood

One common criticism of the existing diagnostic accuracy studies of CCTA is that the populations examined tend to be at higher risk for underlying CAD than will be patients that are likely to receive the test in practice (Budoff, 2006). Two studies in our sample address this issue by stratifying the population according to risk or pretest likelihood of CAD:

- Husmann et al. (2008): A total of 88 consecutive patients with suspected CAD were scheduled for both CCTA and ICA; patients were stratified into low, intermediate, and high risk categories based on Framingham risk score. In this population, which had an overall CAD prevalence of 49%, findings suggested that CCTA performance at ruling out disease was similar across risk categories (sensitivity 90.0%, 87.5%, and 100.0% for low, intermediate, and high risk respectively, p=.33; NPV 95.0%, 85.7%, and 100.0%, p=.45); a trend toward higher positive predictive value was observed, however, with increased levels of risk (PPV 64.3%, 93.3%, and 89.5% for low, intermediate, and high risk respectively, p=.07).

- Meijboom et al. (2007): In one of the largest studies reported to date, a total of 254 patients referred for ICA in the Netherlands received CCTA within one week prior to or following CCTA. Pretest likelihood of CAD (i.e., low, intermediate, or high) was estimated for each patient using the Duke Clinical Score. Overall prevalence of CAD on ICA was 50%. Sensitivity and NPV were similar across

the three groups; consistent with findings from Husmann, there was a trend toward lower specificity (93%, 84%, and 74% for low, intermediate, and high) and higher PPV (75%, 80%, and 93%) as pretest likelihood increased.

Stratified by Gender

There has been considerable debate regarding the diagnostic performance of non-invasive CAD testing in men vs. women; some studies have suggested a greater challenge in women (Bairey Merz 2006), while others have found no differences (Gibbons 2002; Klocke 2003). Regardless, gender-based differences in anatomy, exercise tolerance, heart rate, level of coronary calcium, and other factors have led to continued interest in examining the influence of gender on diagnostic test results. Two studies have examined this issue with respect to CCTA:

- Pundziute et al. (2008): A total of 103 consecutive patients (51 male, 52 female) presenting with either known (34% of sample) or suspected CAD at Leiden University Medical Centre (Leiden, the Netherlands) were scheduled for ICA and received CCTA within a median of 4 weeks. Findings from this study suggested no material differences by gender in any measure of diagnostic accuracy.

- Meijboom (2007): In a larger sample from the same institution described above, a total of 402 patients (279 men, 123 women) scheduled for ICA (approximately 10% of whom had prior known CAD) received CCTA within one week. In this study, sensitivity and NPV were at or near 100% for both men and women; however, specificity (90% vs. 75%) and PPV (95% vs. 81%) were significantly greater in men.

Incidental Findings

A controversial feature of CCTA is its concurrent ability to detect abnormalities outside the heart; in particular, pulmonary nodules have been frequently reported as incidental findings of CCTA, likely due to both the adjacency of the pulmonary anatomy and the presence of standardized criteria for following "significant" nodules (MacMahon, 2005). Incidental lesions present a clinical and policy challenge because of the possible benefits of early detection of a small percentage of significant lesions relative to the costs and risks associated with further investigation of the majority of incidental findings whose identification and even treatment would be unlikely to provide a net health benefit to the patient.

We reviewed the current literature for studies that reported extra-coronary findings with multi-slice CCTA; because there are very few data from studies using 64-slice technology, we also reviewed studies based on earlier-generation multi-slice scanners. The results of our review are summarized in Table 6. Any summary of this literature is complicated by differing definitions of "clinically important" lesions, as these are typically based on the consensus of reviewing physicians. The reported rate of patients with *any* detected lesion ranged from 15% to 80%;

"clinically important" lesions presumed to require follow-up have been found in 5-20% of patients evaluated. An unusually high percentage of clinically important findings (56.2%) was reported in a recent series of 258 Israeli patients (Gil, 2007); these results were primarily manifested in pulmonary nodules, however, and this study featured both a lower cutoff for clinical significance of these nodules (>4 mm) and a higher percentage of current smokers than the other series analyzed. That said, current guidelines do suggest at least one further scan for even small nodules (MacMahon 2005). In addition to pulmonary nodules, the most common lesions deemed "clinically important" include thoracic or abdominal aortic aneurysms, pulmonary emboli, pleural effusion or infection, and hepatic or abdominal masses.

Despite the reported range and variability in defining clinical importance, it appears that relatively few lesions reveal significant pathology upon further investigation. In the largest series reported to date (Cademartiri, 2007), 81/670 (12.1%) patients had significant findings deemed to require follow-up or further investigation. Among these patients, 2 had newly-discovered pathologies (one pulmonary embolism and one bony metastasis from renal carcinoma). In another large series (Onuma 2006), 114/503 (22.7%) had clinically-significant findings; upon subsequent review of medical records, a total of 18 patients (3.6%) were found to have therapeutic consequences (i.e., further treatment was required) from these incidental findings, and 4 patients (0.8%) had newly-discovered malignancies.

None of the studies we reviewed attempted to estimate the costs of further investigation of incidental findings on CCTA. We discuss the potential short-term economic impact of incidental findings in the economic model component of this report (see Section 8).

Although incidental findings are not an issue for stress EKG or stress echocardiogram, a recent case series involving 582 consecutive patients undergoing myocardial SPECT imaging with a Tc-99m sestamibi tracer (Gedik, 2007) reported extra-cardiac findings in 7 patients (1.2%). These were noted via either increased or decreased extra-cardiac uptake of the tracer, and included cases of thymoma, goiter, and sarcoidosis.

Harms

Other than small percentages of patients who did not complete the CCTA exam because of refused consent or psychological reactions (e.g., claustrophobic reaction), no studies reported immediate adverse events directly due to CCTA. This is likely because the most common expected event (reaction to contrast media) was mitigated by excluding patients with known allergies or reactions to contrast media as well as those with compromised renal status. In general, the incidence of severe or permanent reaction to contrast media is low.

While a recent examination of the use of prophylactic measures to reduce contract-induced renal injury (Weisbord, 2008) indicated that the incidence of elevated serum

creatinine ranged from 0-11% after CT examination (depending on the threshold employed to indicate injury), this biochemical change was not independently or significantly associated with hospitalization or death. Findings from a meta-analysis of over 300,000 parenteral administrations of contrast media (Caro 1991) estimate the incidence of severe reactions or death at <0.01%. More recently, the renal effects of CCTA in 400 patients with chronic renal insufficiency was examined (El-Hajjar, 2008); the incidence of contrast-induced nephropathy was low (1.75%), and no patient required hemodialysis.

Radiation Exposure and Future Cancer Risk

Potential adverse health effects associated with radiation exposure is an important factor to consider in the evaluation of CCTA as a potential diagnostic tool in the ED and/or outpatient settings, particularly because patients may already be exposed to radiation at other points along the diagnostic pathway (e.g., ICA, SPECT). Radiation dose is a measure of ionizing energy absorbed per unit of mass, expressed as units of Gy (Gray) or mGy; it often is quoted as an equivalent "effective" dose, in units of Sv (Sievert) or mSv. For x-rays, which is the radiation produced by CT scanners, 1 mSv = 1 mGy. To place the effective radiation dose received from CCTA in some context, the average reported range of radiation in our sampled studies is listed in the table below along with typical doses from other tests and exposures to x-rays. Note that the doses received from ICA and SPECT are similar to those delivered by CCTA:

Radiation exposure scenario	Approximate effective dose (mSv)
Chest x ray	0.02
Round-trip flight, New York-Seattle	0.06
Low-dose CT colonography	0.5-2.5
Head CT	2.0
Single-screening mammogram (breast dose)	3.0
Annual background dose caused by natural radiation	3.0/yr
CCTA (lower reported range)	**2.0-8.0**
Invasive coronary angiography	5.0-7.0
Adult abdominal CT scan	10.0
Single photon emission computed tomography (SPECT)	9.0-13.0
CCTA (higher reported range)	**12.0-14.0**
Typical dose to A-bomb survivor at 2.3 km distance from ground zero Hiroshima	13.0
Annual radiation worker annual exposure limit	20.0/yr
Annual exposure on international space station	170/yr

Sources: Brenner, 2005; FDA [www.fda.gov/cdrh/ct/risks.html]; ICER CCTA systematic review; Van Gelder 2004, Mettler 2008, Shuman 2008; Earls 2008; Husmann 2008

The primary risk associated with exposure to ionizing radiation is cancer. According to the FDA, estimates based on the experience of A-bomb survivors suggests that a dose of 10 mSv may be associated with an increase in the possibility of fatal cancer of approximately 1 chance in 2000. This risk level is relatively small in comparison to the approximately 400 out of 2,000 individuals expected to develop cancer from all other causes combined.

There is considerable controversy on extrapolating cancer death risks from those experienced by adults with high radiation exposure at Hiroshima to the potential risks at much lower radiation doses. However, linear extrapolation has been the approach generally used, although the uncertainties inherent in this approach become progressively greater at lower doses. Also controversial is whether a natural threshold of radiation exposure exists before excess risk from specific exposures can be realized. The current guidance from a variety of regulatory authorities is that no threshold exists, but this has also been intensely debated.

Our evidence review found 17 articles in which the radiation dosage was estimated. Estimated radiation dosages for CCTA ranged widely, from 4.6 to 21.4 mSv. In general, the lowest rates in the reported range were from studies employing dose-sparing protocols such as tube current modulation (see discussion below) (Ropers, 2006, Nikolaou, 2006) as well as those using dual-source scanners (Johnson, 2007, Leber, 2007).

In general, calculated radiation doses were higher in women (range: 10.24-21.4 mSv vs. 7.45-15.2 mSv in men), due to the higher density of breast tissue in women. These estimates do not differ materially from those reported elsewhere in the literature for CCTA, which range from 5-32 mSv and average 16 mSv (Mettler, 2008).

Most of the studies we reviewed employed some form of dose-sparing protocol to attempt to reduce radiation exposure. The most common of these was prospective EKG gating, in which the heart is only scanned at certain times during the cardiac cycle, so the patient does not receive radiation during the entire examination (Healthcare Human Factors Group, 2006). In some settings, prospective EKG gating has been found to reduce average effective doses to 2-4 mSv (Shuman, 2008, Earls, 2008, Husmann, 2008); however, results from a recent presentation of data from a multicenter study suggest that effective doses still vary widely (reported range: 5-37 mSv) by institution, even with over 80% of centers employing prospective gating protocols (Hausleiter, 2008).

Other techniques to reduce radiation exposure from CCTA include automatic exposure control, in which the tube current is adjusted to the anatomy of the patient, and the so-called "step-and-shoot" strategy, in which images are acquired at predetermined stop points during the scanner's spiral revolution. In addition, it is thought that the introduction of 256- and 320-slice scanners may further reduce exam time; whether this leads to a net reduction in radiation dose is unclear, as the

higher precision of the newer machines may deliver increased radiation at the outset.

In an attempt to examine the attributable radiation-induced cancer risk from CCTA, a recent analysis used Monte Carlo simulation methods applied to mathematical phantom data on organ doses to men and women during 64-slice CCTA (Einstein, 2007). Findings indicated that the lifetime attributable risk for cancer was low but non-negligible (0.22% and 0.08% in women and men aged 60 years respectively); prospective EKG gating would be expected to reduce this risk by about 35%.

Prior Published Studies on Economic Impact of 64-Slice CCTA

Limited data are available on the potential economic impact of CCTA in coronary artery disease; studies that have been published are based on decision-analytic models or retrospective database analyses. The studies vary widely in terms of their structure, strategies evaluated, and assumptions about test characteristics and costs. Accordingly, direct comparison of the findings is difficult.

ED Studies

The model that formed the general structural basis for our ED model (see Section 8) has been previously published (Ladapo, 2008); in this model, patients presenting with chest pain (underlying prevalence of cardiac chest pain=12%; prevalence of CAD=27%) were evaluated alternatively with CCTA in addition to standard ED triage care (i.e., serial enzymes, stress testing, observation) or standard care alone. Separate strategies for men and women were evaluated; costs were estimated on a lifetime basis, and utilities for long-term outcomes of appropriate and inappropriate diagnosis were incorporated. Findings suggest that CCTA would be cost-saving in women and would generate slightly increased costs in men. On a lifetime basis, CCTA would dominate standard care in women and have an incremental cost-effectiveness ratio (ICER) of $6,400 per QALY in men.

Another recently published study (Khare, 2008) also examined CCTA's cost-effectiveness on a lifetime basis, in a population with very low CAD prevalence (6%). The competing strategies in this analysis (CCTA or standard care) produce either positive, indeterminate, or negative results; no distinction is made between "significant" or "mild" stenosis on CCTA, and all positive results result in referral to ICA. Results indicated that CCTA was cost-saving relative to standard care, regardless of whether stress ECHO or stress EKG was the modality used for functional testing.

Finally, the results of a recent retrospective evaluation of patients triaged in the University of Pennsylvania Health System compared duration of stay, resource utilization, and costs in 643 patients receiving immediate CCTA, observation unit care plus biomarkers and CCTA, observation unit care plus biomarkers and stress testing, or hospital admission with biomarkers and hospitalist-directed care (Chang, 2008). Patients were frequency-matched on age, race, gender, TIMI score, and initial

EKG evaluation. Findings suggested that immediate CCTA was associated with the lowest cost, shorter time to discharge, and lower rates of readmission at 30 days.

Outpatient Studies
Two decision-analytic models have examined CCTA's cost-effectiveness in an outpatient setting (Mowatt, 2008, Dewey, 2007). Mowatt and colleagues used the structure of a previous model examining the cost-effectiveness of SPECT (Mowatt, 2004) to estimate the effects and costs of multiple single- and dual-test strategies during both the diagnostic phase and over a lifetime horizon. Other strategies involved stress EKG and stress SPECT; in addition, two strategies examined the impact of having CCTA be the final test in the diagnostic pathway (rather than ICA). All positive or indeterminate findings in these strategies result in a subsequent test or confirmation, and all negative results stop the testing flow. At a CAD prevalence level identical to our model (30%), the most effective strategies are CCTA-ICA and ICA alone, while the lowest-cost strategies are stress EKG-CCTA and CCTA alone. In lifetime modeling, comparison of the strategies involving CCTA indicated that a stress EKG-CCTA-ICA strategy is a cost-effective alternative relative to the stress EKG-ICA (£9,200 per QALY gained) and stress EKG-CCTA (£1,400 per QALY gained) strategies. In addition, all CCTA strategies were dominant in comparison to strategies involving SPECT.

In the other model (Dewey, 2007), a total of 6 strategies were evaluated for patients presenting with stable chest pain: CCTA, calcium scoring using electron-beam CT, dobutamine stress MRI, stress EKG, stress ECHO, or immediate ICA. Multiple hypothetical cohorts were evaluated according to different pretest likelihoods of disease. As with the Khare model described above, this analysis assumes that *all* positive findings on the initial test are referred for ICA. Cost-effectiveness was expressed in terms of cost per correctly identified CAD patient; this appears to have been generated as a "stand-alone" result for each strategy, however, and was not evaluated incrementally among the strategies. CCTA generated the lowest cost per correctly identified patient at pretest likelihoods of 10-50%; ICA (which was assumed to be 100% accurate) performed best at pretest likelihoods of 70% or higher.

Several retrospective analyses of healthcare claims database have also been performed to evaluate CCTA's economic impact. These studies, all of which were conducted by the same group (Min et al., 2008), and involved matched comparisons of CCTA and SPECT, indicated lower cardiovascular-related and overall costs for CCTA and similar or lower rates of revascularization and hospital visits.

7.4 Summary

The body of published evidence on the impact on patient outcomes of CCTA as part of a diagnostic strategy compared to usual care is limited to six outpatient case series and a single RCT, all but one of which were evaluated in the ED setting. While the results of one study (Rubinshtein, 2007) suggest that use of CCTA in the ED may

prevent unnecessary hospitalization and additional procedures in many patients, these findings have not been confirmed by other studies or explicit comparisons to other diagnostic strategies. On the other hand, the literature on the diagnostic accuracy of CCTA vs. ICA has expanded rapidly over the last three years, and with notable consistency the evidence suggests that CCTA has a very high sensitivity (~98%) for significant occlusion and a moderately high specificity (~82% if non-evaluable scans are considered false positives, ~87% if such scans are excluded from consideration). These data have been generated in patient populations around the globe, often among patients with relatively high underlying prevalence of CAD, raising questions about the applicability of findings to patient populations at low-to-intermediate (10-30%) risk of CAD. Studies of diagnostic test accuracy can suffice if clinicians already have evidence from randomized trials showing that treatment of the cases detected by the diagnostic test improved patient outcomes, but the body of evidence on CCTA does not yet include studies to address this question.

There are a number of other questions that the current evidence does not address. For one, the lack of data on long-term outcomes with CCTA makes it difficult to ascribe value to its ability to reduce the rate of false-positive and false-negative findings relative to other strategies. Without these data, we do not know whether and when false negatives will re-present with symptoms and be diagnosed correctly, and whether they will suffer any health consequences in the intervening period. It is also impossible to know whether medical treatment of false positives would provide a net health benefit given that CAD will develop over time in many healthy individuals.

What is also unknown is whether the widespread adoption of CCTA will result in a shift in the distribution of candidates for such a strategy – for example, use of the test in very low risk individuals may shift the balance of true vs. false positives, thereby raising uncertainty as to its benefits on a population-wide basis; this uncertainty is particularly heightened in light of the unanswered questions around risks associated with CCTA's radiation dose as well as the health-system impacts of extra-coronary findings.

Also, because of CCTA's visual precision, "mild" levels of stenosis (i.e., 20-70%) can be detected; the benefits of aggressive management of this level of CAD are unknown, however, as such levels of stenosis cannot be directly linked to coronary insufficiency. While not a focus of our systematic review, several studies have attempted to examine CCTA's ability to diagnose functional cardiac deficits, using SPECT or another functional test as a reference (Gaemperli, 2007, Gallagher, 2007, Schuijf, 2006). While negative predictive value for these abnormalities was similar to that reported in the ICA-reference studies, positive predictive value ranged between 50-60%. Some have posited that, with increasingly precise technology, the ability to use CCTA to study blood flow and perfusion deficits will be heightened; evidence has not yet accumulated to support this, however.

Others argue that one of CCTA's utilities is in identifying so-called "vulnerable plaque"—i.e., coronary plaque that is at highest risk for rupture and formation of thrombi that cause acute cardiac events (Ambrose, 2008). Because CCTA's technology can be used to quantify the amount of calcified plaque (i.e., the "calcium score"), which has been cited as one of the risk factors in determining vulnerable plaque, some feel that detection of CAD in this earlier state would lead to more informed and efficient treatment decisions, reducing downstream risks and costs to the patient. The concept of vulnerable plaque is controversial in and of itself, however, as there are no current data on its natural history--the rate of plaque progression, the characteristics associated with rupture, and the association with the incidence and timing of cardiac events are therefore unknown (Lau, 2004). Until such data are made widely available, the utility of CCTA in preventing the progression of early CAD will be speculative.

CCTA is a very safe procedure; the immediate risks of the procedure itself are similar to those of other tests employing contrast media. The potential for harm from radiation, while modulated to some extent by the use of dose-sparing protocols, is still felt by some experts and commentators to be a significant concern , particularly if CCTA is being considered for use in combination with other radiation-based diagnostic tests (Einstein, 2007). However, there are many unanswered questions about the true risk function from test-induced radiation, and the role of radiation exposure in determining the net health benefits from CCTA will rely largely upon decision-maker values and judgment.

With CCTA the patient has the benefit of, but also potential harm from, extra-coronary findings. Clinically significant findings found during CCTA provide for early detection of a serious condition in some patients. Whether early detection leads to more effective treatment and improved outcomes cannot be determined from the available evidence. Similarly, there are no studies of the unnecessary expenses, inconvenience, and health risks attendant upon follow-up of less serious incidental findings.

Several large clinical studies are underway that may address concerns regarding CCTA's impact in clinical practice. Four RCTs are ongoing, all of which include major cardiovascular events as primary endpoints. In addition, a within-subject study sponsored by GE Healthcare is evaluating CCTA's diagnostic performance relative to SPECT as well as evaluating its impact on major cardiovascular events and the rate of downstream cardiac testing. Finally, a large observational study is underway at Brigham & Women's Hospital, Boston, following patients who are referred for stress perfusion with SPECT or PET, CCTA, or combined perfusion/anatomy studies; the primary endpoint of interest is referral for cardiac catheterization, as well as major cardiac events and the relative cost-effectiveness of each approach.

8. Decision Analytic/Economic Models

Objectives
The objectives of this decision analysis were to evaluate the clinical and cost-effectiveness of coronary computed tomographic angiography (CCTA) for the detection of coronary artery disease (CAD). Following the guidance of the ICER Evidence Review Group, the modeling was targeted to evaluate the use of CCTA for the following applications:

1. CCTA in the emergency department (ED) triage for patients with acute chest pain of unknown origin and a low-to-intermediate risk of acute myocardial infarction or unstable angina

2. CCTA as an outpatient screening tool for CAD in a low-to-intermediate risk population presenting with stable chest pain

Overview of Models
Because the clinical scenarios and patient populations related to CCTA use differ substantially between the ED and the outpatient settings, we decided to build two separate models that would most appropriately reflect the current standard of care and evaluate options for how CCTA could be introduced into these two settings.

The model evaluating CCTA for patients with acute chest pain in the ED setting loosely follows the algorithm of the RCT by Goldstein (Goldstein, 2007) such that in the CCTA branch, the detected luminal diameter of the stenosis determines further action for revascularization independently of the number of affected vessels (Ladapo, 2008).

The model evaluating CCTA as a tool for evaluating stable chest pain in the outpatient setting follows the CAD treatment recommendation derived from the recent COURAGE trial (Boden, 2007) and thus requires that the diagnostic tests not only identify stenoses correctly but also differentiate between 3-vessel/left main artery disease and 1- or 2-vessel disease. Both models will be described in more detail in the following sections.

In neither model are the potential benefits, harms, or costs of incidental findings included. This decision was made due to the lack of data describing the downstream balance of benefits and harms accrued through the identification and treatment of incidental findings. In addition, there is no consensus among clinical and policy experts on the likely balance of benefits and harms. Nonetheless, we did attempt to estimate the incidence of pulmonary nodules >4 mm in size, based on age- and gender-based data from the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) Lung Policy Model (http://www.cisnet.cancer.gov/profiles) and the follow-up recommendations of the

Fleischner Society (MacMahon, 2005). Briefly, the incidence of such nodules was estimated to be 19.8%, which we reduced by 30% (13.9%) due to the fact that CCTA visualizes approximately 70% of lung volume (Kirsch, 2007). We estimated follow-up costs based on Medicare reimbursements for the tests depicted in the guidelines, and arrived at a blended average rate of approximately $700 for follow-up of nodules 4-8 mm and >8 mm in size.

Our decision analytic models also do not explicitly attempt to model long-term consequences of radiation exposure. This decision was also determined by the lack of data with which to estimate the incidence and distribution of possible radiation-induced cancers attributable to CCTA. In the outpatient model we report the number of patients who would be exposed to *any* radiation during the diagnostic testing.

We adopted a payer perspective for costs and these estimates were largely based on CPT codes and national Medicare reimbursement as well as other studies. All costs were converted to 2008 US dollars using the medical care component of the Consumer Price Index. Following the current recommendation of the US Panel on Cost-Effectiveness in Health and Medicine, both costs and health outcomes were discounted at 3% annually (Gold, 1996).

8.1 ED Model

Overview

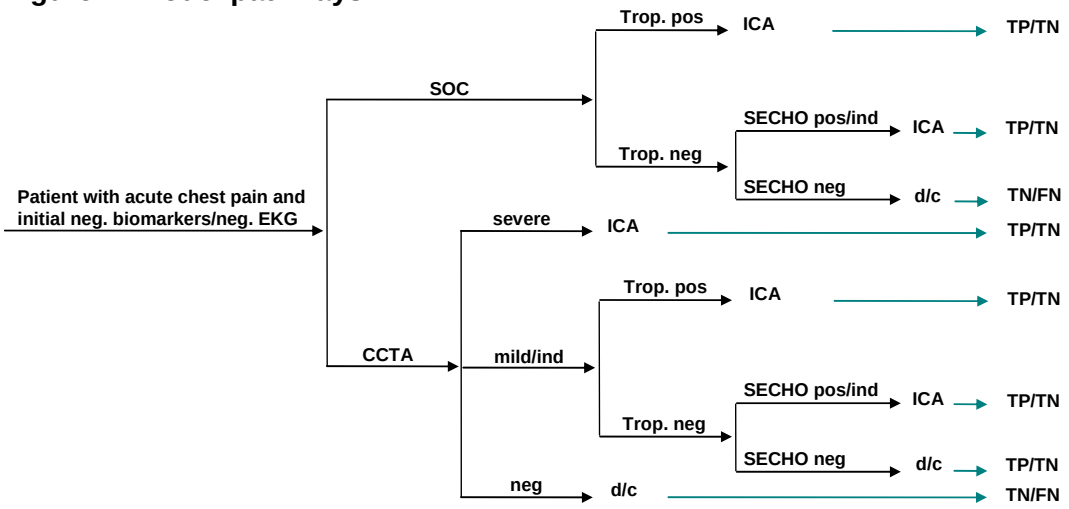
We modified a recently published microsimulation model, developed by Ladapo (Ladapo, 2008), to compare the diagnostic results of standard of care (SOC) to CCTA-based management in the triage of 55 year-old men with acute chest pain and at low-risk of an acute myocardial infarction or unstable angina. The model begins with a cohort of patients presenting to the ED with acute chest pain of unknown origin, initial negative biomarkers, and non-significant EKG changes.

Figure 1 depicts the possible pathways of the two strategies: In the SOC pathway, patients are re-evaluated with serial enzymes after 6-8 hours. Patients with elevated follow-up biomarkers are directly referred for invasive coronary angiography (ICA) and those with negative biomarkers receive a stress-echocardiography to further investigate the likelihood of a stenosis. Stress echocardiography was selected for the SOC pathway upon the guidance of clinical experts on the ICER Evidence Review Group. Patients who have a stress-echocardiography that suggests a severe stenosis (≥50% for left main or ≥70% for vessels) or those with indeterminate test results are referred for ICA; patients with negative stress-echocardiography are discharged without further testing or treatment.

In the CCTA pathway, CCTA is integrated into the standard of care triage: during the waiting period for the follow-up enzymes, patients are imaged and either

discharged, evaluated with a stress test, or sent directly to ICA depending on the severity of their atherosclerosis as suggested by CCTA. If CCTA reveals severe stenosis (≥50% for left main or ≥70% for any other vessel or vessels), the patient is immediately referred to ICA; if CCTA reveals no stenosis, the patient is immediately discharged. If CCTA reveals a mild stenosis (<50% for left main or <70% for any other vessel or vessels) or the result is indeterminate, the patient essentially follows the standard of care triage including serial enzymes and potential stress echocardiography.

Figure 1: model pathways



Notes: severe stenosis: 50% to 100% decrease in luminal diameter; mild stenosis: 1% to 49% decrease in luminal diameter; SOC: standard of care; CCTA: CCTA: coronary computed tomographic angiography; Trop.: troponin; ICA: invasive angiography; SECHO: stress echocardiogram

Because ICA is considered to be a gold-standard, it will reveal the patient's true disease status. As a result, patients who undergo ICA will always be correctly diagnosed as having a severe stenosis that requires invasive treatment (true positive) or not having a severe stenosis (true negative). Patients discharged without receiving ICA can either be correctly (true negative) or incorrectly (false negative) diagnosed as free of any severe stenosis.

Input Parameters

Clinical Parameters

To evaluate the effectiveness of CCTA as a diagnostic instrument for the work-up of acute chest pain patients, two distributions amongst this population are essential parameters: the distribution of acute coronary syndrome (ACS) and non-ACS diagnoses and the distribution of coronary atherosclerosis within these diagnostic

categories. All data were derived from the published literature and parameters were estimated as described by Ladapo (Ladapo, 2008) and explained further in the following paragraph. All parameters are provided in Table I.

The distribution of ACS and non-ACS diagnoses in the initial ED visit (Table I) was derived from several studies that totaled more than 1,000 acute chest pain patients who had no history of heart disease and were considered to be at low risk for ACS based on a clinical algorithm constructed by Goldman and colleagues (Goldman, 1988; Zalenski, 1997; Sallach, 2004). Patients were assumed not to suffer from life-threatening conditions other than ACS. Although such patients may be experiencing aortic dissections, pulmonary embolisms, and other serious conditions, our omission of these health events likely does not impact incremental cost-effectiveness, as they would be evaluated similarly under both strategies.

The distribution of coronary atherosclerosis within the ACS and non-ACS diagnoses were derived from a large cohort of patients with chest pain who underwent invasive angiography but were not diagnosed with ACS (Chaitman, 1981). This source was selected because it came from a very large national database (the CASS study) and provided data on the underlying distribution of atherosclerosis within diagnostic categories similar to those used to characterize chest pain in the ED. Patients were stratified by age, gender, and their type of chest pain complaints being "definite angina," "probable angina," or "non-specific chest pain".

Using the Chaitman prevalence data, patients in our model with ACS were assigned a distribution of vessel disease similar to the "definite angina" chest pain group; patients with stable angina were assigned a distribution of vessel disease that averaged results from the "definite angina" and "probable angina" groups, as we assumed these patients were healthier than patients with ACS; patients with non-cardiac chest pain were assigned a distribution of vessel disease similar to the "non-specific chest pain" group.

As shown in Table I, the majority (88%) of all acute chest pain patients in the ED experience non-cardiac related chest pain. However, the ICA data from Chaitman demonstrated that among 55-year-old men there is a total prevalence of severe stenoses of 27% and a prevalence of mild stenoses of an additional 28%. Thus our model assumes that some patients will present to the ED with non-specific chest pain due to other causes but who, if sent for stress echocardiography or CCTA, will ultimately be found to have at least one vessel with a stenosis >70%. This approach is the best way to create the parameters for a model that reflects the clinical reality that results of CCTA are not dichotomous but instead lead to multiple pathways of further evaluation/treatment.

Table I: Patient and diagnostic test characteristics

Variable	Base Case Estimate	Source(s)
Initial distribution of disease in ED		
Non-ST segment elevation MI	0.03	Ladapo, 2008; Sallach, 2004; Zalenski, 1997
Unstable angina	0.07	"
Stable angina	0.02	"
Non-cardiac chest pain	0.88	"
64-slice CCTA characteristics		
Probability of classifying severe coronary stenosis as		
Severe	0.92	Shabestari, 2007; Zalenski, 1997
Mild	0.07	"
Normal	0.01	"
Probability of classifying mild coronary stenosis as		
Severe	0.21	"
Mild	0.72	"
Normal	0.07	"
Probability of classifying normal coronary arteries as		
Severe	0	"
Mild	0.02	"
Normal	0.98	"
Indeterminacy rate	0.03	ICER Review
Stress-echocardiography		
Sensitivity for CAD	0.76	Garber, 1999
Specificity for non-CAD	0.88	"
Indeterminacy rate	0.13	Ward, 2007
Serial troponin measurement		
Sensitivity for NSTEMI	0.95	Lau, 2001
Specificity for patients not having NSTEMI	0.90	Lau, 2001
Mortality from ICA	0.001	Kuntz, 1999

Notes: CAD = coronary artery disease, ED = emergency department, MI = myocardial infarction. NESTEMI: non-segment elevation myocardial infarction

This approach creates a model which, in comparison to the clinical experience of many physicians, will result in a very high proportion of ED chest pain patients with

a positive troponin test or stress ECHO who will subsequently be sent for ICA. This feature arises because the cohort of 1,000 patients includes those 10% who have unstable angina or who will develop MI; they also include 880 patients who present with "non-cardiac chest pain," but who, given that the cohort represents 55-year old men, have an underlying 18% risk of significant CAD. In addition, our model sends patients with indeterminate stress ECHO or CCTA tests to further testing and/or ICA. When these features are combined it is not surprising to see relatively high total numbers of patients sent for ICA.

Test Accuracy

No published ED studies have reported all 64-slice CT coronary angiography test characteristics on a per-patient basis as required for the model, so Ladapo used data that applied to individual segments of the coronary arteries (see Table I). Note that this method of reporting will, on average, underestimate the diagnostic power of CCTA because many patients have multiple significant coronary lesions.

The diagnostic performance of other tests, including serial troponin measurements and stress echocardiogram (ECHO) for identifying coronary artery disease were derived from a published meta-analysis (Garber, 1999). Based on findings from ICER's systematic review, CCTA was assumed to provide non-diagnostic results at a rate of 3.2%, and patients with non-diagnostic exams were subsequently evaluated with a stress test (Goldstein, 2007).

Costs

ED costs were estimated using Medicare reimbursement data (Centers for Medicare & Medicaid Services, 2008). Table II depicts the detailed CPT codes associated with each cost item. To account for the costs of admission of patients to an ED observation unit when prolonged evaluation was required, we assumed that these "delay costs" would apply for all patients in the SOC strategy and for those in the CCTA strategy whose CCTA result indicates a "mild" stenosis and requires the patient to spend additional time undergoing further evaluation in the ED observation unit.

Table II: Cost Parameters

Procedure, CPT code (description)		Total costs ($)	Source
Delay	APC 0339	443	CMS, 2008
SECHO	93015 (cardiovascular stress test) 93350 (echo transthoracic)	300	"
CCTA	0145T (CT heart w/wo dye funct: $306) Physician fee ($159)	466	"
ICA	93508 (cath placement, angiography) 93510 (left heart catheterization) 93543 (injection for heart x-rays) 93545 (injection for coronary x-rays) 93555 (imaging, cardiac cath)	2,750	"
ED visit	Micro-costing study excluding costs for delay and diagnostic testing	890	Goldstein, 2007

Notes: Delay: delay cost attributed to those patients who are closely monitored for 6-8 hrs. as part of their diagnostic workup; SECHO: stress echocardiogram; CCTA: CCTA: coronary computed tomographic angiography; ICA: invasive coronary angiography;

Model Analyses

We ran a first-order Monte Carlo micro-simulation model and reported the average results for 1,000 patients. This model only considers the diagnostic results and reports the number of correctly diagnosed diseased patients with a severe stenosis requiring invasive intervention (true positives), correctly diagnosed patients without a severe stenosis (true negatives), and incorrectly diagnosed diseased patients (false negatives). Furthermore, the model reports the total number of ICAs performed the number of negative ICAs, and number of ICA-related deaths as well as the associated costs for both strategies. We also report the number of patients with incidental findings in the CCTA strategy who require diagnostic follow-up.

Results

Base Case Analysis

Table III depicts the results for a cohort of 1,000 55-year old men. The left hand column shows the result if all patients had undergone the SOC strategy and the right hand column depicts the results if the identical 1,000 patients had all undergone the CCTA strategy. Among the notable differences between SOC and CCTA + SOC are the numbers of false negatives (51 vs. 5), number referred for ICA (464 vs. 380), and

patients sent for ICA who return with normal coronary arteries (246 vs. 116). ED testing costs are higher for the CCTA + SOC pathway, but when the savings of fewer angiographies and lower delay costs are factored in, the base case produces an average savings of $296 per patient for the CCTA + SOC pathway. When the costs of following the 14% of patients in the CCTA + SOC with incidental findings were included, cost savings were reduced to $196, but remained in favor of CCTA.

Note that the number of patients referred to ICA is higher than many clinicians would expect based on their clinical experience; the reason for this is twofold: the rather high underlying CAD prevalence of 27% results in 218 necessary ICAs for SOC and 264 for CCTA + SOC. In addition, the model includes two different paths leading to unnecessary ICAs: (1) false-positive test results for severe stenosis (151 in SOC; 86 in CCTA) and (2) indeterminate test results (124 in SOC, 35 in CCTA + SOC), all of which are sent to ICA. If we assume that additional clinical expertise allows for re-evaluation of the patients with indeterminate tests and results in sending only those who indeed have a severe stenosis to ICA, the absolute number of ICAs would drop to 369 and 350 for SOC and CCTA + SOC, respectively, and reduce the cost-savings to $117. Finally, while not depicted below, the CCTA + SOC strategy will expose all patients to radiation, vs. 45% in the SOC strategy.

Table III: Base case results

Outcomes (per 1,000)	**SOC**	**CCTA + SOC**
True positive	218	264
True negative	731	731
False negative	51	5
Referred for ICA	464	380
ICA negative results	246	116
ICA related deaths	0.05	0.04
Incidental findings	0	138
Costs ($ per patient)		
ED/patient	1,152	1,421
Delay/patient	443	109
Cath lab/patient	1,276	1,045
Total/patient	**2,871**	**2,575**
Cost difference (CCTA vs. SOC)	**- $296**	

Notes: SOC: standard of care; CCTA: CCTA: coronary computed tomographic angiography

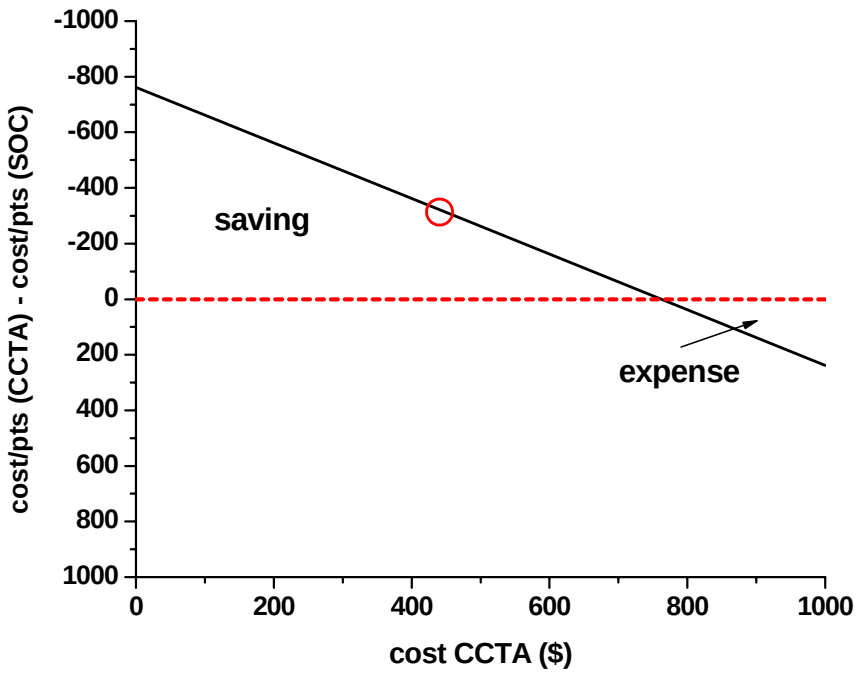
Sensitivity Analyses

Deterministic sensitivity analyses explore the effect that a change in one or more parameters over a plausible range of values will have on the results, in the case that all other parameters are held constant. This type of analysis is meant to answer 'what if' questions. We present the results of deterministic sensitivity analyses for the cost of CCTA and delay costs.

Sensitivity Analysis – Cost of CCTA

Costs of CCTA occur in the CCTA as one-time cost for all patients in this strategy and for no patients in the SOC strategy. For the base case, we assumed a cost of $466 resulting in an average cost-saving of $296 per patient. Figure 2 depicts the linear relationship between CCTA costs and the cost difference between the two strategies. For all CCTAs costing $762 or less, CCTA is cost-saving compared to SOC. For CCTA costs of more than $762, the higher effectiveness of CCTA compared to SOC with regard to more true positives and less true negatives comes with additional costs.

Figure 2: Sensitivity analysis on costs of CCTA



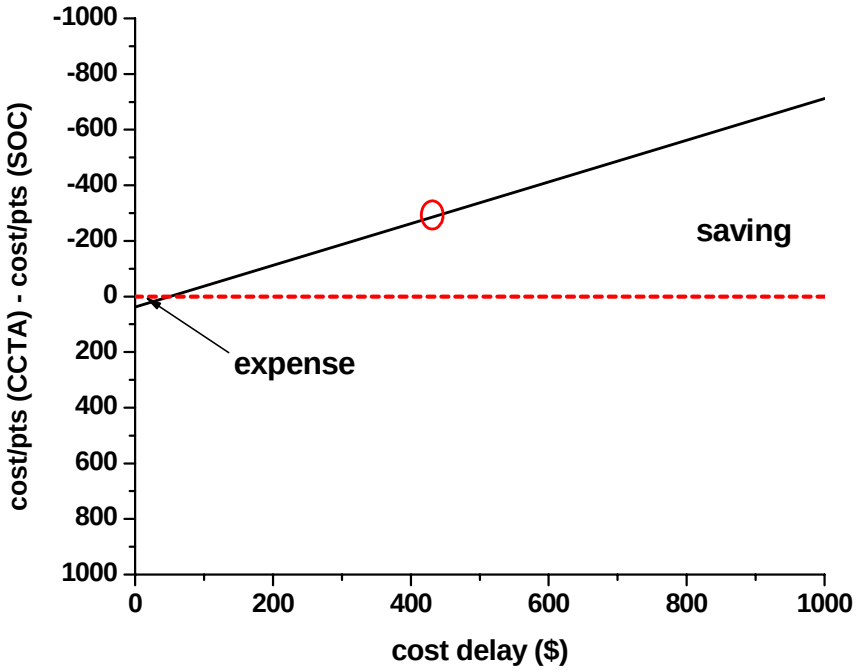
Note: circle: base case estimate for CCTA cost.

Sensitivity Analysis – Costs of ED Delay

Delay costs occur as a one-time cost in both strategies for all patients who have to be carefully observed until they have received their serial enzyme tests to rule in/out myocardial damage. These costs apply to all patients in the SOC strategy and to

those patients in the SOC strategy who have CCTA findings indicating a "mild stenosis" or indeterminate results. For the base case we assumed a cost of $443 resulting in an average cost savings of $296 per patient. Figure 3 depicts the linear relationship between delay costs and the cost differences between the two strategies. For delay costs of $47 or more, CCTA is cost-saving compared to SOC.

Figure 3: Sensitivity analysis on delay costs



Note: circle: base case estimate for delay cost.

Conclusions

Our model therefore is consistent with other published cost-effectiveness analyses in suggesting that when used as part of a triage strategy for low-to-intermediate risk chest pain patients in the ED, CCTA will allow the more rapid discharge of nearly half of all patients and decrease the number of false negative diagnoses while reducing the number of angiographies compared to the current standard of care. According to the model CCTA is also cost-saving, with about $296 in savings per patient in comparison to SOC. Taking into account the additional follow-up costs for the 14% of patients who undergo CCTA and have incidental findings, the cost-savings are reduced to $196, but remain in favor of CCTA. However, CCTA does expose every patient to radiation, whereas only about 45% of the patients in SOC are exposed via invasive angiography.

8.2 Outpatient Model

Overview
We modified an existing microsimulation model that was initially developed by Joseph Ladapo MD, PhD, as part of his doctoral dissertation at the Harvard School of Public Health to assess CCTA in the evaluation of patients with stable chest pain, using conventional diagnostic modalities as comparators.

The base case population consisted of 55 year-old men with stable chest pain and with either low (10%) or intermediate (30%) risk of underlying significant CAD -- one or more vessels with occlusion >70% or left main occlusion at >50%. The model reported multiple outcomes for each strategy: the intermediate diagnostic results, expressed as numbers of correctly and incorrectly indentified patients with CAD, the number of resulting invasive angiographies, the number of patients exposed to radiation, the cost for diagnostic work-up, and the long-term prediction of remaining quality-adjusted life years and lifetime medical costs.

Diagnostic Phase

Diagnostic Strategies
We considered 7 different strategies, alone and in combination, in order to capture a wide range of management approaches for evaluating patients with stable chest pain and a low-to-intermediate risk of CAD:

1. Coronary Computed Tomographic Angiography (CCTA)
2. Stress-Echocardiography (Stress-ECHO)
3. Stress- Single Photon Emission Computed Tomography (Stress-SPECT)
4. CCTA followed by Stress-ECHO
5. Stress-ECHO followed by CCTA
6. CCTA followed by Stress-SPECT
7. Stress-SPECT followed by CCTA

Diagnostic Pathways
The model begins in an outpatient setting with evaluation of patients with stable chest pain and it is designed to differentiate between the management of three different test results reflecting different levels of CAD severity:

1) Negative for CAD
2) Positive for CAD (if a functional test) or Positive for one- or two-vessel CAD (if CCTA); and
3) Markedly positive for CAD (if a functional test) or Positive for 3-vessel or left-main artery disease (if CCTA)

Generally, the alternative diagnostic pathways differ between 1-test and 2-test strategies. In the 1-test strategy (Figure 4a), a single test is performed and patients

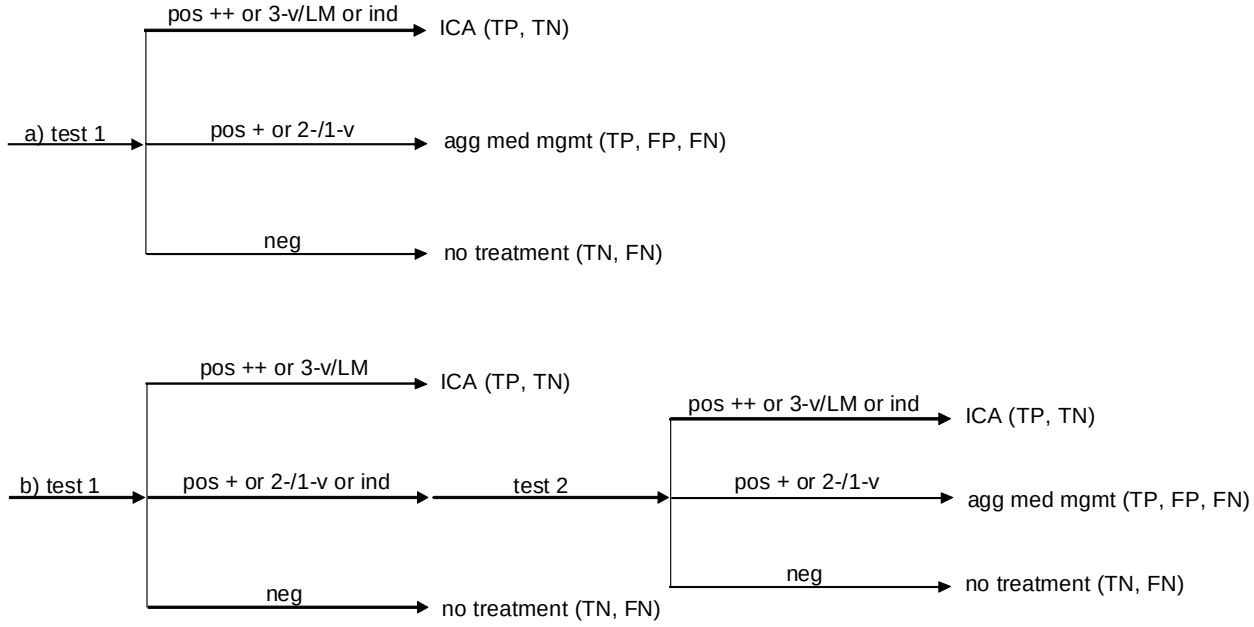
with markedly positive test results or whose test results are indeterminate are sent for ICA. Depending on the ICA findings, patients can either be true positive or true negative for three-vessel disease or left-main disease (3VD/LM). True positives are treated with aggressive medical therapy and revascularized with coronary artery bypass (CABG) surgery.

Patients whose diagnostic test is positive, but not markedly positive, for CAD are all started on aggressive medical treatment as per the treatment guidelines suggested by the COURAGE trial (Boden, 2007). As all non-invasive tests are not perfect and no ICA will be performed for mild stenosis to reveal the true underlying disease status, patients in this pathway can either be true positive, false negative (patients who actually suffer from 3VD/LM) or false positive (patients who actually don't suffer from CAD).

Patients whose diagnostic test indicates no evidence of significant CAD receive no additional therapies beyond baseline care. Depending on the true disease status, they can either be true negative or false negative.

The 2-test strategy (Figure 4b) differs from the 1-test strategy in a way such that patients whose initial test is indeterminate or positive, but not markedly positive, for CAD will not immediately start on aggressive medical treatment nor be sent for ICA, but will receive a second test. The second test will then have three possible outcomes and resulting consequences that are identical to the 1-test strategy. Patients whose first test is either markedly positive for CAD or indicates no evidence of CAD, will undergo no further testing and immediately receive the same management as outlined for the 1-test strategy.

Figure 4: Diagnostic pathways



Notes: pos ++: markedly abnormal test result, pos +: abnormal test result, ind: indeterminate results: TP: true-positive; TN: true-negative; FP: false-positive; FN: false-negative; ICA: invasive coronary angiography; agg med mgmt: aggressive medical management (according to AHA/ACC guidelines)

Input Parameters

Clinical Parameters

Our base case cohort is 55 year old men with a CAD prevalence of 30% (intermediate prevalence). The proportion of patients among the different CAD severity levels was derived by averaging the data for 55 year old men with "non-anginal chest pain" and "atypical chest pain" as observed by Diamond and Forrester: 22% for one- or two-vessel CAD, 5% for three-vessel, and 3% for left main artery CAD (Diamond, 1979). When the overall CAD prevalence was modified to 10%, the ratio between the severity levels remained constant.

Test Accuracy

Test characteristics for CCTA were derived from our systematic review on a per-patient basis, and we assumed equal accuracy for one- or two vessel CAD and three-vessel or left main CAD. Test characteristics for stress-echocardiography and stress-SPECT were derived from published meta-analyses (Garber, 1999). All tests were considered to be conditionally independent (Table IV).

Table IV: Patient and diagnostic test characteristics

Variable	Base Case Estimate	Source(s)
Diagnostic test characteristics		
64-slice CCTA		
Sensitivity for CAD (per patient)	0.98	ICER Review
Specificity for CAD (per patient)	0.87	"
Indeterminate results	0.03	"
Stress ECHO		
Sensitivity for one- or two-vessel CAD	0.76	Garber, 1999
Sensitivity for three-vessel or left main CAD	0.94	"
Specificity for CAD	0.88	"
Indeterminate results	0.13	Ward, 2007
Stress SPECT		
Sensitivity for one- or two-vessel CAD	0.88	Garber, 1999
Sensitivity for three-vessel or left main CAD	0.98	"
Specificity for CAD	0.77	"
Indeterminate results	0.09	Patterson, 1995
ICA-related mortality	0.001	Kuntz, 1999

Notes: CCTA=coronary computed tomographic angiography; CAD=coronary artery disease; ECHO=echocardiogram; SPECT=single-photon emission computed tomography; ICA=invasive coronary angiography

Costs

Cost were estimated using Medicare reimbursement data (Centers for Medicare & Medicaid Services, 2008). Table V depicts the detailed CPT codes associated with each cost item, including both the technical and the professional components for the reimbursement rate.

Table V: Cost estimates

Procedure, CPT code (description)		Total costs ($)	Source
SECHO	93015 (cardiovascular stress test) 93350 (echo transthoracic)	300	CMS, 2008
CCTA	0145T (CT heart w/wo dye funct: $306) Physician fee ($159)	466	"
SPECT	78465 (heart image (3d), multiple) 78478 (heart wall motion add-on) 78480 (heart function add-on) 93015 (cardiovascular stress test)	765	"
ICA	93508 (cath placement, angiography) 93510 (left heart catheterization) 93543 (injection for heart x-rays) 93545 (injection for coronary x-rays) 93555 (imaging, cardiac cath)	2,750	"

Notes: CCTA=coronary computed tomographic angiography; ECHO=echocardiogram; SPECT=single-photon emission computed tomography; ICA=invasive coronary angiography

Results

Base Case Analysis

Table VI depicts the results for 1,000 55-year old men with an underlying CAD prevalence of 30%. Each column represents the results if all patients had undergone the specific screening strategy.

From the data in Table VI it can be seen that there are important trade-offs to consider when comparing these strategies. For example, "*CCTA alone*" has the highest number of true positives at 288 and the lowest number of false negatives at 9 among all strategies, followed by "*SPECT alone*" which has 273 true positives and 24 false negatives. But CCTA strategies introduce the issue of incidental findings, estimated to require follow-up among 13.8% of all patients screened. CCTA (and SPECT) strategies also carry radiation exposure risks for all patients. The strategy "*stress-ECHO followed by CCTA*" has the lowest cost per patient of $702 followed by "*CCTA alone*" with a cost of $764/patient. "*Stress-ECHO alone*" has the lowest number of patients exposed to any radiation with 200 due to invasive angiographies.

Table VI: Diagnostic results (30 % CAD prevalence)

Estimates	CCTA	SPECT	SECHO	CCTA -> SPECT	SPECT -> CCTA	CCTA -> SECHO	SECHO -> CCTA
True positive	288	273	251	266	268	245	246
False positive	87	145	71	24	29	12	22
True negative	616	558	632	679	675	691	682
False negative	9	24	46	31	29	52	51
Referred for ICA	108	166	200	106	91	120	87
ICA-negative results	22	65	95	9	6	13	5
ICA related deaths	0.11	0.17	0.20	0.11	0.09	0.12	0.09
Exposed to radiation	1,000	1,000	200	1,000	1,000	1,000	437
Incidental findings requiring f/u	138	0	0	138	57	138	48
Total costs/patient [excluding all FU costs, $]	764	1,221	849	1,004	1,205	891	702

When considering the outcomes and costs for this diagnostic phase only, "*CCTA alone*" is cost-saving and has fewer false negatives than all other strategies except "*stress-ECHO followed by CCTA,*" This latter two-test strategy is less costly and exposes less than half as many patients to radiation but also has more false negatives.

Because the general perception of the true underlying CAD prevalence associated with a "low-to-intermediate risk" population varies, we present Table VII depicting the result of the identical strategies for a population with 10% CAD prevalence. Comparing these results to table VI shows the same ranking between the strategies with regard to accuracy, number of angiographies, number of incidental findings and radiation exposure. Regarding costs, "*stress-ECHO alone*" is now less expensive than "*CCTA alone*" whereas the order for the other strategies remained the same. However, when estimating the costs per false negative averted incrementally, "stress-ECHO alone" is weakly dominated and thus drops out. This results in a cost of about $5 per FN averted comparing "*CCTA alone*" to "*stress-ECHO followed by CCTA*".

Table VII : Diagnostic results (10% prevalence)

Estimates	CCTA	SPECT	SECHO	CCTA -> SPECT	SPECT -> CCTA	CCTA -> SECHO	SECHO -> CCTA
True positive	99	93	84	98	91	83	83
False positive	113	185	93	30	35	15	27
True negative	786	714	806	869	864	884	872
False negative	2	8	17	9	10	18	19
Referred for ICA	48	107	141	35	28	45	26
ICA-negative results	28	82	113	11	8	17	7
ICA related deaths	0.05	0.11	0.14	0.03	0.03	0.05	0.03
Exposed to radiation	1,000	1,000	141	1,000	1,000	1,000	300
Incidental findings requiring f/u	138	0	0	138	48	138	38
Total costs/patient [excluding all FU costs, $]	550	952	546	697	974	612	473

Lifetime Model

Survival

The basic approach taken to estimate the mortality risk ratios associated with one-, two-, three-vessel, and left main CAD was the development of a simulation model that predicted mortality in the COURAGE trial (Boden, 2007), generalizing the proportional relationship between risk ratios from a previous study (Kuntz, 1999). Specifically, survival was derived as a function of US life-tables stratified by age and gender and a factor accounting for the number of diseased vessels (1.4 for one- or two-vessel CAD, 2.2. for 3-vessel and 5.8 for left main artery disease). Lack of appropriate treatment (PCI or meds for one- or two-vessel CAD, PCI and meds for three-vessel CAD, PCI and CABG for left main CAD) increased mortality risk by 30% (LaRosa 1999). Note that CAD-negative patients could subsequently develop CAD and the disease could progress.

Utilities
Utilities were also derived from the COURAGE trial (Boden, 2007) and depended on whether the patient had no CAD (0.96), CAD without chest pain (0.88) or CAD with chest pain (0.78). Occluded arteries caused chest pain; appropriate treatment relieved chest pain, resulting in a pain-free fraction after one year of 74% for CABG (Hoffman, 2003), 66% for PCI (Boden, 2007), 58% for medical treatment (Boden, 2007), and in 13% for patients without treatment (Boden, 2007).

Costs
In addition to the one-time cost for the diagnostic work-up (Table IV), additional costs were accounted for as they occurred. PCI and CABG were assigned costs of $11,210 (Cohen, 2004) and $25,500, respectively (Reynolds, 2003). In addition, all patients received baseline prophylaxis consisting of Aspirin (81 mg QD) and simvastatin (20 mg QD) accounting for $310/year (Drugstore.com, 2007). Patients who suffered from chest pain also received symptomatic treatment for angina consisting of atenolol (50 mg QD) and isosorbide mononitrate (60 mg QD) assigned a cost of $170/year (Drugstore.com, 2007).

Effects of Diagnostic Accuracy
The effect of the different diagnostic strategies is modeled indirectly via the proportion of patients correctly and incorrectly classified with respect to CAD status and resulting treatment action. True positives are assumed to be treated accordingly, thus profiting from a survival and quality of life benefit while true negatives do not undergo an invasive angiography and thus do not experience the risk of intervention-related mortality and costs. False negatives do not profit from the treatment appropriate for their severity of disease and thus experience no benefit in survival and quality-of-life as compared to those who are treated appropriately. Lastly, a small portion of false positives will die from unnecessarily performed ICA and all false positives will generate costs due unnecessary treatment.

Results

Base Case Analysis: CAD Prevalence 30%
Table VIII depicts the remaining quality adjusted life years (QALY) and lifetime medical cost as predicted for the different strategies for 55 year old men with a CAD prevalence of 30%. Note that the QALY range between the most effective and least effective strategy is only 14 days. This small difference appears very reasonable as the diagnostic test is a one-time evaluation. The dynamic nature of the model is built to reflect clinical reality, allowing for initially healthy patients to develop disease over time and for CAD to progress, both situations that will require future treatment and revascularization.

Table VIII: Strategies ordered by increasing effectiveness (30% CAD prevalence)

Strategy	Effectiveness (QALY)	Costs ($)
CCTA-SECHO	15.146	16,751
SECHO-CCTA	15.151	14,851
CCTA-SPECT	15.154	19,514.
SPECT-CTA	15.157	23,662
SECHO	15.167	12,880
SPECT	15.172	21,506
CCTA	15.183	15,799

Notes: QALY: quality-adjusted life year

Incremental Cost-Effectiveness Analysis

Table IX presents the incremental cost-effectiveness ratios based on the results from table VIII. *"Stress-echo alone"* is the least expensive strategy but more effective than *"stress-echo followed by CCTA"* and thus *"stress-echo followed by CCTA"* is dominated (i.e., is more costly and less effective) by *"stress-echo alone"*. In other words, from a utilitarian point of view, *"Stress-echo followed by CCTA"* is inferior to *"Stress-echo alone"* as it provides fewer QALYs but generates higher costs and thus should not be recommended.

"CCTA alone" is more effective and less expensive than all other strategies except for *"Stress-echo alone"* and *"Stress-echo followed by CCTA"* and it thus dominates other strategies (rows 4-7) leaving only *"Stress-echo alone"* and *"CCTA alone"* as viable options to consider.

Table IX: Incremental cost-effectiveness analysis (30% CAD prevalence)

Strategy	Effect	Incr. Effect	Costs	Incr. Costs	Incr. C/E
SECHO	15.167		12,880		
SECHO-CCTA	15.151	-0.016	14,851	1,972	dominated by SECHO
CCTA	15.183	0.016	15,799	2,920	178,000
CCTA-ECHO	15.146	-0.038	16,751	952	dominated by CCTA
CCTA-SPECT	15.154	-0.029	19,514	3,714	dominated by CCTA
SPECT	15.172	-0.012	21,506	5,706	dominated by CCTA
SPECT-CCTA	15.157	-0.027	23,662	7,862	dominated by CCTA

Notes: CCTA: Computed Coronary Tomography Angiography, SECHO: Stress Echocardiogram, SPECT: Single Photon Emission Computed Tomography

Comparing these two options (Table X), "*CCTA alone*" gains an additional 0.016 QALYs and comes at an additional cost of $2,900, which can be converted into an incremental cost-effectiveness ratio of about $178,000/QALY.

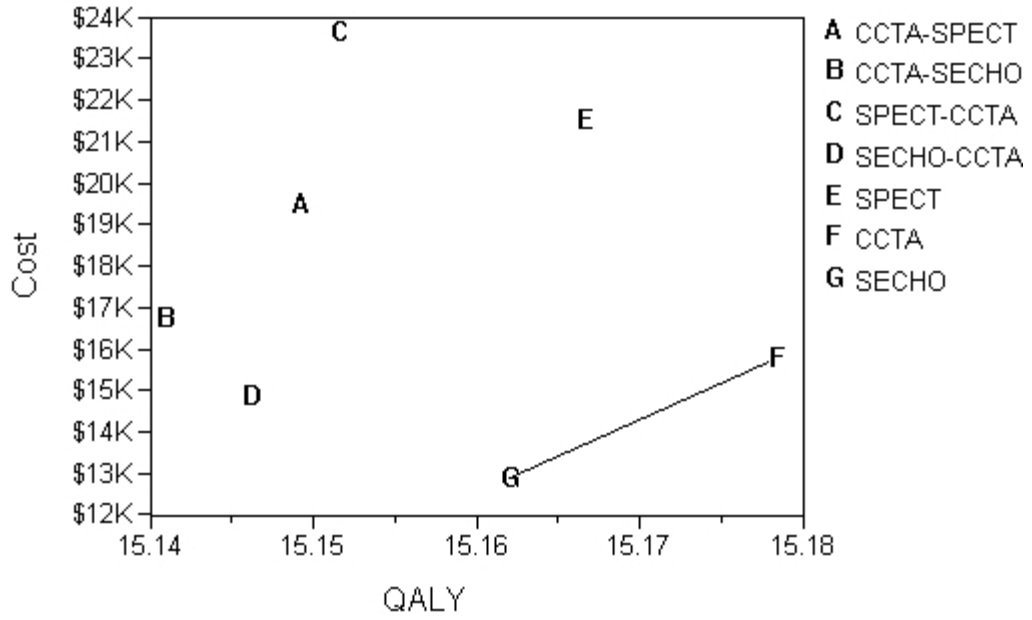
Table X: Incremental cost-effectiveness analysis (30% CAD prevalence)

Strategy	Effect	Incr. Effect	Costs	Incr. Costs	Incr. C/E
SECHO	15.167		12,880		
CCTA	15.183	0.016	15,799	2,920	178,000

Notes: CCTA: Computed Coronary Tomography Angiography, SECHO: Stress Echocardiogram, SPECT: Single Photon Emission Computed Tomography

Figure 5 depicts the results graphically. The y-axis shows the life-time medical costs and the x-axis the quality-adjusted life gained associated with each strategy. The line between "stress-echo alone" [G] and "CCTA alone" [F] shows the cost-effectiveness frontier; all strategies above this frontier are dominated.

Figure 5: Cost-effectiveness graph (30% CAD prevalence)



Notes: CCTA: Computed Coronary Tomography Angiography, SECHO: Stress Echocardiogram, SPECT: Single Photon Emission Computed Tomography

Base Case Analysis: CAD Prevalence 10%

Table XI on the following page depicts the remaining quality adjusted life years (QALY) and lifetime medical cost as predicted for the different strategies for 55 year old men with a CAD prevalence of 10%. Note that for a CAD prevalence of only 10%, the difference in QALYs between the most and the least effective strategy decreases to 6 days.

Table XI: Strategies ordered by increasing effectiveness (10% CAD prevalence)

Strategy	Effectiveness (QALY)	Costs ($)
SECHO	16.012	9,554
CCTA-SECHO	16.014	12,793
SECHO-CCTA	16.015	10,916
CCTA-SPECT	16.017	14,634
CCTA	16.018	12,433
SPECT-CCTA	16.024	19,850
SPECT	16.030	18,429

Notes: CCTA: Computed Coronary Tomography Angiography, SECHO: Stress Echocardiogram, SPECT: Single Photon Emission Computed Tomography

Incremental Cost-Effectiveness Analysis

Table XII on the following page presents the incremental cost-effectiveness ratios based on the results from table XI. "*Stress-echo alone*" is again the least expensive strategy Note that the situation of dominance between "*CCTA alone*" and "*SPECT alone*" changes between the analyses for 30% and 10% CAD prevalence resulting in "*CCTA alone*" being weakly dominated in the 10% prevalence population.

It is important to note the implications of the changes in cost-effectiveness results between the 30% and the 10% prevalence populations. As the prevalence of CAD in the tested population goes lower, the risk of false-negative results is diminished, whereas the risk of false-positive results is increased. This shift will tend to enhance the diagnostic utility of strategies with lower sensitivity and higher specificity relative to other strategies. Thus, in comparison to the results for the 30% prevalence population, the results for the 10% prevalence population are driven much more by the false-positive rate than by the false-negative rate. If the CAD prevalence in the tested population drops lower than 10%, the incremental cost-effectiveness ratios for CCTA and CCTA-based strategies will continue to rise in comparison to SECHO.

Table XII: Incremental cost-effectiveness analysis (10% CAD prevalence)

Strategy	Effect	Incr. Effect	Costs	Incr. Costs	Incr. C/E
SECHO	16.012		9,554		
SECHO-CCTA	16.015	0.003	10,916	1,361	weakly dominated by CCTA
CCTA	16.018	0.003	12,433	1,518	weakly dominated by SPECT
CCTA-ECHO	16.014	-0.004	12,793	360	dominated by CCTA
CCTA-SPECT	16.017	-0.001	14,634	2,201	dominated by CCTA
SPECT	16.030	0.012	18,429	5,996	511,749
SPECT-CCTA	16.024	-0.006	19,850	1,421	dominated by SPECT

Notes: CCTA: Computed Coronary Tomography Angiography, SECHO: Stress Echocardiogram, SPECT: Single Photon Emission Computed Tomography

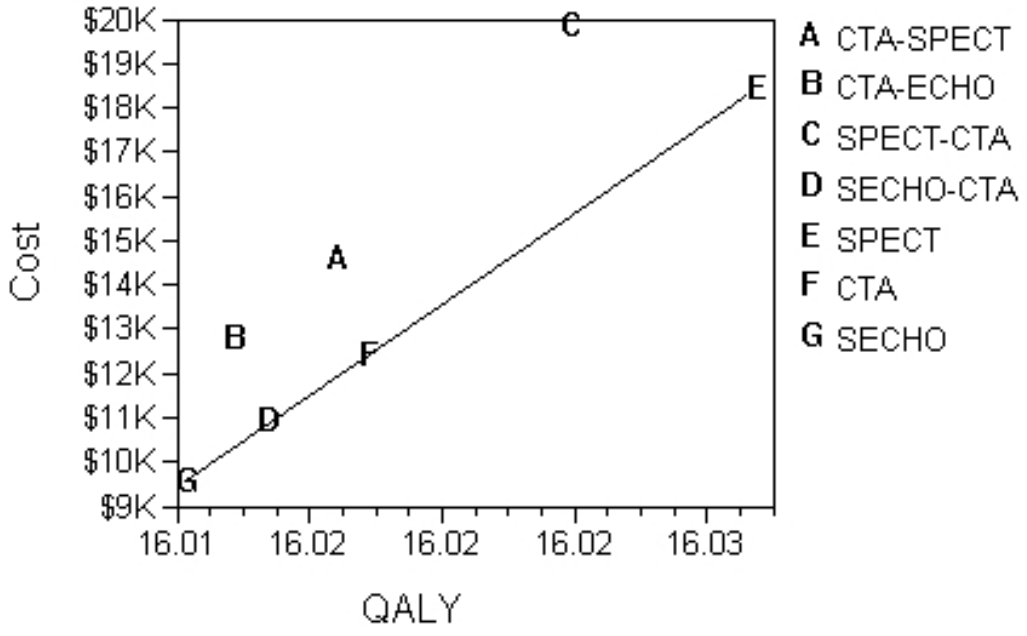
Comparing these two remaining options (Table XIII), *"SPECT alone"* gains an additional 0.018 QALY and comes at an additional cost of $8,900, which can be converted into an incremental cost-effectiveness ratio of about $493,000/QALY.

Table XIII: Incremental cost-effectiveness analysis (10% CAD prevalence)

Strategy	Effect	Incr. Effect	Costs	Incr. Costs	Incr. C/E
SECHO	16.012		9,554		
SPECT	16.030	0.018	18,429	8,875	493,000

Figure 6 depicts the results graphically. The y-axis shows the life-time medical costs and the x-axis the quality-adjusted life gained associated with each strategy. The line between "stress-echo alone" [G] and "SPECT alone" [E] shows the cost-effectiveness frontier; all strategies above this frontier are dominated.

Figure 6: Cost-effectiveness graph (10% CAD prevalence)



Because CCTA strategies were removed from the analyses above as less effective and more expensive than other competing strategies, we separately examined the cost-effectiveness of CCTA-based strategies relative to Stress-ECHO, the least expensive strategy. Specifically, we examined CCTA alone (Table XIV), SPECT-CCTA (the most effective strategy involving CCTA, Table XV), and SECHO-CCTA (the least expensive strategy involving CCTA, Table XVI). Incremental cost-effectiveness ranged from $513,000/QALY for CCTA alone to $883,000/QALY for SPECT-CCTA.

Table XIV: Incremental cost-effectiveness analysis (CCTA vs. SECHO)

Strategy	Effect	Incr. Effect	Costs	Incr. Costs	Incr. C/E
SECHO	16.012		9,554		
CCTA	16.018	0.006	12,433	2,879	513,000

Table XV: Incremental cost-effectiveness analysis (SPECT-CCTA vs. SECHO)

Strategy	Effect	Incr. Effect	Costs	Incr. Costs	Incr. C/E
SECHO	16.012		9,554		
SPECT-CCTA	16.024	0.012	19,850	10,296	883,000

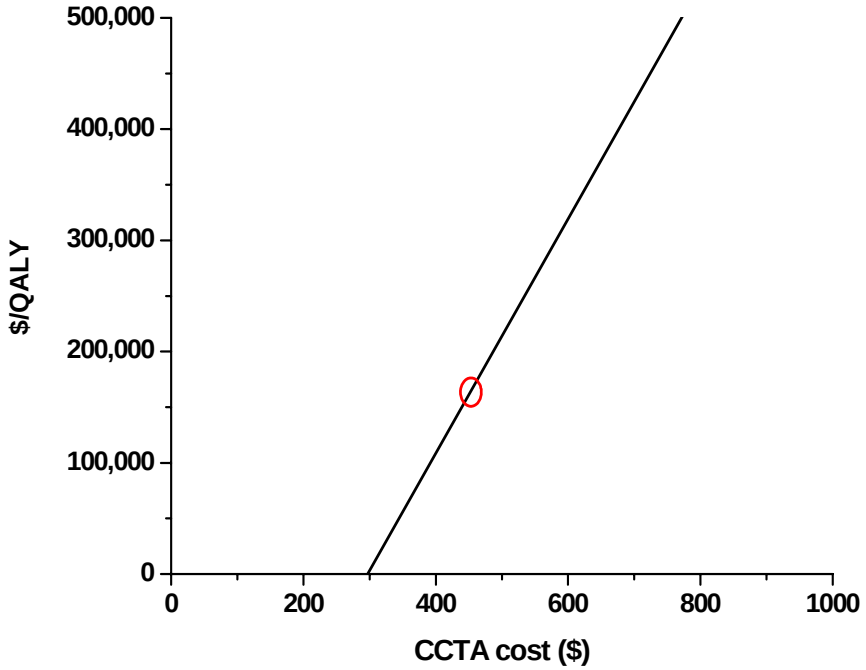
Table XVI: Incremental cost-effectiveness analysis (SECHO-CCTA vs. SECHO)

Strategy	Effect	Incr. Effect	Costs	Incr. Costs	Incr. C/E
SECHO	16.012		9,554		
SECHO-CCTA	16.015	0.003	10,916	1,361	534,000

Sensitivity Analyses (30% CAD Prevalence)

CCTA costs occur as a one-time cost for those patients who underwent CCTA as part of their diagnostic work-up. For the base case we assumed a cost of $466, resulting in an incremental cost-effectiveness ratio (ICER) of about $178,000/QALY. Figure 6 depicts the linear relationship between CCTA costs and the ICER comparing *"CCTA alone"* to *"stress-echo alone"*. For a CCTA cost of about $300 or less, CCTA is dominant.

Figure 6: Sensitivity analysis CCTA cost



Note: circle: base case estimate for CCTA cost.

Model Considerations
As with all decision analytic and cost-utility models, our models required many assumptions and judgments. Among these, it is important to note again that all analyses were performed without considering harm, benefit, or costs of radiation-exposure or incidental findings. "*CCTA alone*" resulted in about 14% incidental findings and thus required follow-up as compared to 0-5% in the other strategies. Strategies including either CCTA or SPECT as the first or only test exposed all patients to radiation, as opposed to 20-40% of patients exposed in strategies with stress-ECHO as the first or only test.

One aspect of the models that should also be noted is the way that the health impact of a "false positive" was modeled. While false negatives in the model experience a negative health outcome due to lack of appropriate treatment, there is no negative health impact of a false positive diagnosis; the model only accounts for the unnecessary health care costs for false-positives. Indeed, in the lifetime model some of the false positives develop CAD during the course of the simulation, in which case they would later profit from the initially unnecessary treatment.

Conclusions
Considering the short-term diagnostic results, "*CCTA alone*" has the highest number of true positives and lowest number of false negatives.

Considering a lifetime horizon, at a CAD prevalence of 30%, the effectiveness measured in quality-adjusted life years is very similar across all strategies, with a range of 14 quality-adjusted life years. All strategies except "*stress-echo alone*" and "*CCTA alone*" are dominated, resulting in an incremental cost-effectiveness ratio of about $178,000/QALY for "*CCTA alone*" compared to "*stress-echo alone*".

The incremental cost-effectiveness ratio (ICER) is extremely sensitive to the cost assumed for CCTA. For a cost of $300 or less, CCTA would be dominant while for CCTA costs of $345, $392, and $439, the ICERs would be $50,000/QALY, $100,000/QALY, and $150,000/QALY, respectively.

When a 10% CAD prevalence is considered, the importance of false-positives outweighs that of false-negatives; accordingly, the relative costs of CCTA increase without significant change in effectiveness, and cost-effectiveness ratios between $500,000-$900,000/QALY are generated.

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SYSTEMATIC REVIEW
TABLES

Table 2. Characteristics of excluded studies.

Author	Year	Sample Size	Referent Standard	Mean Age	% Male	Reason for Exclusion
Cademartiri	2008	170	ICA	58	73	No per-patient analysis
Gaemperli	2007	100	SPECT	61	70	For detection of functional abnormalities only
Gallagher	2007	85	SPECT	49	53	For detection of functional abnormalities only
Ong	2006	134	ICA	55	73	No per-patient analysis
Rubinshtein	2007	58	ICA/Other	56	64	Identical to Rubenshtein (3) study
Sato	2008	104	SPECT	67	73	No per patient analysis
Schlosser	2007	63	ICA	62	65	No per patient analysis
Schuijf	2006	140	SPECT	59	60	No per patient analysis

Table 3. Characteristics of included studies.

Author	Year	Sample Size	Referent Standard	Mean Age	% Male	% Known CAD	% Non-Evaluable	Comments
Achenbach (a)	2008	100	ICA	65	50%	0	18%	Single-source CT
Achenbach (b)	2008	100	ICA	61	64%	0	3%	Dual-source CT
Bayrak	2008	100	ICA	58	70%	16%	0	
Cademartiri	2008	145	ICA	63	63%	Unk	8%	
Cademartiri	2007	72	ICA	54	53%	Unk	0	
Ehara	2006	69	ICA	67	75%	57%	3%	
Fine	2006	66	ICA	62	48%	5%	6%	
Ghostine	2006	66	ICA	69	61%	0	0	
Goldstein (a)	2007	99	ICA/ Other	48	42%	0	0	CCTA arm
Goldstein (b)	2007	98	ICA/ Other	51	57%	0	0	SOC arm
Hacker	2007	38	SPECT/ ICA	62	74%	32%	0	Functionally relevant stenosis
Hoffmann	2006	103	Clin Dx	54	60%	10%	0	
Hollander	2007	54	Unk	47	46%	2%	0	
Husmann (a)	2008	34	ICA	63	29%	Unk	0	Low risk
Husmann (b)	2008	29	ICA	64	66%	Unk	0	Intermed risk
Johnson	2007	55	ICA/ Other	67	64%	Unk	2%	
Johnson	2007	35	ICA	60	69%	40%	0	
Leber	2007	90	ICA	58	63%	0	2%	
Leber	2005	59	ICA	64	--	17%	7%	
Leschka	2005	67	ICA	60	75%	Unk	0	
Meijboom (1a)	2007	66	ICA	50	41%	0	0	Low prob
Meijboom (1b)	2007	83	ICA	61	57%	0	0	Intermed prob
Meijboom (2a)	2007	123	ICA	62	0%	12%	0	Women
Meijboom (2b)	2007	279	ICA	58	100%	10%	0	Men
Meijboom (3a)	2007	33	ICA	58	70%	3%	0	low risk
Meijboom (3b)	2007	71	ICA	59	73%	24%	0	high risk
Mollet	2007	62	ICA	59	73%	Unk	5%	
Mollet	2005	52	ICA	60	65%	Unk	2%	
Muhlenbruch	2007	51	ICA	59	76%	Unk	0	
Nikolaou	2006	72	ICA	64	82%	40%	6%	
Oncel	2007	80	ICA	56	76%	0	0	
Plass	2006	50	ICA	66	78%	Unk	0	
Pugliese	2006	35	ICA	61	60%	9%	0	
Pugliese	2008	51	ICA	59	76%	Unk	0	
Pundziute	2008				--	--	--	
Pundziute	2008	103	ICA	60	49%	33%	3%	
Raff	2005	70	ICA	59	76%	Unk	0	

Table 3. Characteristics of included studies.

Author	Year	Sample Size	Referent Standard	Mean Age	% Male	% Known CAD	% Non-Evaluable	Comments
Ropers	2006	84	ICA	58	62%	Unk	4%	
Ropers	2007	100	ICA	61	63%	0	3%	
Rubinshtein (1)	2007	100	ICA	56	57%	0	3%	
Rubinshtein (3)	2007	58	ICA/ Other	56	64%	38%	0	Combination ICA/Dx protocol
Savino	2006	23	ICA	56	61%	0	0	
Scheffel	2006	30	ICA	63	80%	Unk	0	
Schuijf (1)	2006	60	ICA	60	77%	55%	2%	
Schuijf (3)	2006	58	ICA	63	66%	0	0	
Shabestiri	2007	143	ICA	63	72%	Unk	3%	
Shapiro	2007	37	ICA	63	78%	32%	14%	

Table 4. Studies examining prognostic ability of 64-slice or better CCTA based on clinical follow-up.

Author	Year	Study Type	Setting	Sample Size	Age (Mean, SD)	% Male	CAD Risk	Follow-Up	Diagnosis Method	Major Findings
Goldstein	2007	RCT	ED	99	48 (11)	43%	Very low	6 months	ICA, repeat testing (MACE)	CCTA correctly and definitively diagnosed 94 of 99 (95%)
Hoffmann	2006	Validation cohort	ED	103	54 (12)	60%	Low	Mean: 5.2 months	Record review (index visit only, ACS)	Sensitivity 100% for ACS, specificity 82%
Hollander	2007	Clinical practice algorithm	ED	54	46.5 (8.5)	46%	Low	30 days	Survey, record review (cardiac death/acute MI)	No events recorded; CAD confirmed in 4 of 6 CCTA-positive patients
Johnson	2007	Clinical practice algorithm	ED	55	67 (10)	64%	N/A	≥5 months	Record review, repeat enzymes (obstructive CAD)	CCTA correctly and definitively diagnosed 51 of 55 (93%)
Pundziute	2007	Clinical practice algorithm	OP	100	59 (12)	73%	Intermediate	Mean: 16 months	Record review, clinic visits, survey (MACE)	1-yr event rate 0% in CCTA (-) patients; 30% in CCTA (+)
Rubinshtein	2007	Clinical practice algorithm	ED	58	56 (10)	64%	Intermediate	12 months	Altered strategies, f/u survey	Revised ACS diagnosis, canceled hospitalization in ~45%; no events in CCTA (-) patients
Savino	2006	Validation cohort	ED	23	56 (13)	61%	N/A	ED visit only	Record review	All moderate/severe stenoses on CCTA confirmed by ICA

CAD: coronary artery disease; RCT: randomized controlled trial; MACE: major adverse cardiovascular event; CCTA: coronary computed tomographic angiography

Table 5. Sensitivity and specificity (intent-to-diagnose analysis).

Author	Year	TP	FP	TN	FN	Sensitivity	(95% CI)	Specificity	(95% CI)	PPV	NPV
Achenbach	2008	34	27	35	7	0.83		0.80		0.79	0.83
Achenbach	2008	39	9	51	1	0.98		0.89		0.87	0.98
Bayrak	2008	64	4	32	0	1.00	(.99-1.00)	0.89	(.80-.98)	0.94	1.00
Cademartiri	2008	82	32	29	2	0.98	(.91-.99)	0.58	(.43-.71)	0.80	0.94
Cademartiri	2007	20	1	51	0	1.00	(.83-1.00)	0.98	(.89-.99)	0.95	1.00
Ehara	2006	59	3	6	1	0.98		0.86		0.98	0.86
Fine	2006	35	5	24	2	0.95		0.96		0.97	0.92
Ghostine	2006	28	2	35	1	0.97	(.82-1.00)	0.95	(.82-.99)	0.93	0.97
Hacker	2007	11	7	10	2	0.85		0.59		0.61	0.83
Husmann	2008	9	5	19	1	0.90	(.56-.99)	0.79	(.58-.93)	0.64	0.95
Husmann	2008	14	1	12	2	0.88	(.62-.99)	0.92	(.64-1.00)	0.93	0.86
Johnson	2007	17	2	16	0	1.00	(.83-1.00)	0.89	(.65-.98)	0.89	1.00
Leber	2007	20	9	60	1	0.95	(.76-.99)	0.90	(.80-.95)	0.74	0.98
Leber	2005	22	7	17	3	0.88		0.85		0.88	0.85
Leschka	2005	47	0	20	0	1.00		1.00		1.00	1.00
Meijboom	2007	12	4	50	0	1.00	(.70-1.00)	0.93	(.81-.98)	0.75	1.00
Meijboom	2007	32	8	43	0	1.00	(.87-1.00)	0.84	(.71-.93)	0.80	1.00
Meijboom	2007	63	15	45	0	1.00	(.93-1.00)	0.75	(.62-.85)	0.81	1.00
Meijboom	2007	188	9	80	2	0.99	(.96-1.00)	0.90	(.81-.95)	0.95	0.98
Meijboom	2007	28	1	4	0	1.00	(.85-1.00)	0.80	(.30-.99)	0.93	1.00
Meijboom	2007	60	3	8	0	1.00	(.93-1.00)	0.73	(.39-.93)	0.95	1.00
Mollet	2007	46	3	13	0	1.00	(.92-1.00)	0.87	(.59-.98)	0.96	1.00
Mollet	2005	38	2	12	0	1.00	(.91-1.00)	0.92	(.67-.99)	0.97	1.00
Muhlenbruch	2007	44	3	3	1	0.98	(.88-.99)	0.50	(.11-.88)	0.94	0.75
Nikolaou	2006	38	10	23	1	0.97		0.79		0.86	0.96
Oncel	2007	62	0	18	0	1.00		1.00		1.00	1.00
Plass	2006	40	1	9	0	1.00		0.90		0.98	1.00
Pugliese	2006	25	1	9	0	1.00	(.87-1.00)	0.90	(.59-.98)	0.96	1.00
Pugliese	2008	38	0	13	0	1.00	(.88-1.00)	1.00	(.71-1.00)	1.00	1.00
Pundziute	2008	53	7	42	1	0.98	(.95-1.00)	0.91	(.83-.99)	0.93	0.98
Raff	2005	38	3	27	2	0.95		0.90		0.93	0.93
Ropers	2006	25	8	50	1	0.96	(.80-1.00)	0.91	(.80-.97)	0.83	0.98
Ropers	2007	41	11	47	1	0.98	(.88-1.00)	0.81	(.69-.89)	0.79	0.98
Rubinshtein	2007	26	6	70	1	0.96		0.96		0.90	0.99
Scheffel	2006	14	0	15	1	0.93	(.68-1.00)	1.00	(.78-1.00)	1.00	0.94
Schuijf	2006	29	2	28	2	0.94	(.86-1.00)	0.97	(.91-1.00)	0.97	0.93
Schuijf	2006	27	6	25	0	1.00		0.81		0.82	1.00
Shabestiri	2007	104	15	20	4	0.96	(.91-.99)	0.67	(.47-.83)	0.91	0.83
Shapiro	2007	28	3	5	1	0.97	(.80-1.00)	.63	(.20-.93)	.90	0.83

Table 6. Reports of incidental findings on multi-slice CCTA.

Author	Year	Sample Size	Mean Age	% Males	% with Incidental Findings	% with Significant Findings	% with Therapeutic Consequences
Cademartiri	2007	670	60	57	79	12	2
Dewey	2007	108	63	74	15	5	1
Gil	2007	258	54	78	--	56	--
Kirsch	2007	100	63	68	67	11	--
Onuma	2006	503	66	76	58	23	4

NOTE: "Therapeutic consequences" relate to findings that triggered treatment and/or resolution.

APPENDICES

APPENDIX A:

CLINICAL GUIDELINES

APPENDIX B:

LITERATURE SEARCH STRATEGY

The search strategy for MEDLINE was:

1. coronary artery disease [MeSH Terms]
2. coronary stenosis [MeSH Terms]
3. coronary disease [MeSH Terms]
4. 1 OR 2 OR 3
5. coronary angiography [MeSH Terms]
6. tomography, x-ray computed [MeSH Terms]
7. tomography, spiral computed [MeSH Terms]
8. 64-slice [keyword]
9. 5 OR 6 OR 7 OR 8
10. sensitivity and specificity[MeSH Terms]
11. predictive value of tests[MeSH Terms]
12. prospective studies[MeSH Terms]
13. 10 OR 11 OR 12
14. 4 AND 9 AND 13

The search strategy for EMBASE was:
1. coronary artery disease
2. coronary stenosis
3. 1 OR 2
4. angiography
5. computed tomography
6. 4 OR 5
7. sensitivity
8. predictive
9. 7 OR 8
10.[2005-2008]/py
11. 3 AND 6 AND 9 AND 10

The Cochrane Library was searched using the terms "angiography", "coronary angiography", or "computed tomography angiography"

APPENDIX C

MODIFIED QUADAS TOOL & ASSESSMENT OF STUDY QUALITY

Modified QUADAS* Quality Checklist
Studies of Diagnostic Accuracy (64-Slice or Higher)

Study ID: Paper # (if multiple):

Assessor Initials: Assessment Date:

Item	Yes	No	Unclear
Mandatory quality items			
1. Was the spectrum of patients representative of the patients who will receive the test in clinical practice?			
2. Were the selection criteria clearly described?			
3. Is the referent standard likely to correctly classify the target condition(s)?			
4. Is the time period between the referent standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?[a]			
5. Did the entire sample or random selection of the sample receive verification of diagnosis with the referent standard?			
6. Did patients receive the same referent standard regardless of the index test result?			
7. Was the referent standard independent of the index test?			
8. Were the index test results interpreted without knowledge of the results of the referent standard?			
9. Were the referent standard results interpreted without knowledge of the results of the index test?			
10. Were the same clinical data available when index test results were interpreted as would be available when the test is used in practice?			
11. Were uninterpretable/intermediate test results reported?			
12. Were withdrawals from the study explained?			
Additional items			
13. Was an established cut-off point used to define stenosis?[b]			
14. Were data on observer variation reported and within an acceptable range?			
15. Were data presented for appropriate groups of patients?[c]			
16. Was true disease prevalence reported or could it be calculated?[d]			

*Whiting P, et al. BMC Medical Research Methodology 2003;3(25):1-13.

NOTE: Original items 8 and 9 were removed from this modified list.

[a]Period of 3 months or less

[b]e.g., >50% stenosis

[c]i.e., suspected CAD, low-to-intermediate pretest CAD probability, acute chest pain of unknown origin

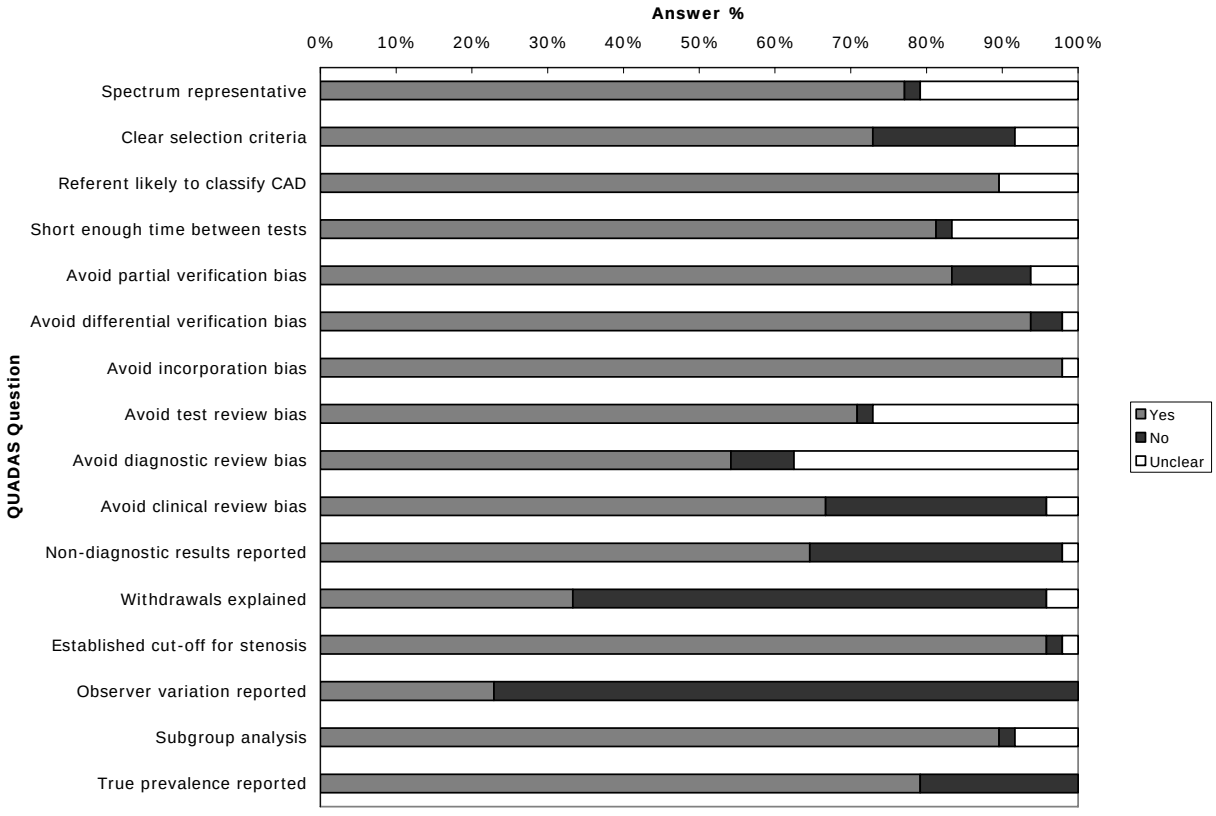
[d]Based on number of true-positives on referent standard divided by total sample

Study Quality

A total of 9 studies were rated as "good" quality by the QUADAS tool; in our modification, this represented an answer of "No" or "Unclear" on no more than 3 items. The remainder of studies were rated as "fair", meeting criteria on between 9 and 12 items. As can be seen in Figure 2 below, studies were most often deficient in explaining patient withdrawals and in reporting inter-observer variation; the latter was due in at least some cases to the use of only single blinded reviewers for the both the index and reference tests.

In certain studies, while blinded review of CCTA was clearly described, detail on the methods for review of the ICA results was insufficient or missing entirely. Thirty-five percent of studies did not report the number of patients with non-diagnostic findings. In approximately 30% of studies, the availability of other clinical data was different than in standard practice at the institution, or was unclear. Time between tests, blinding of index reviewers, and independence of the index and reference tests were generally consistently and accurately reported.

Figure 2. Study quality and internal validity, as assessed by modified QUADAS tool.

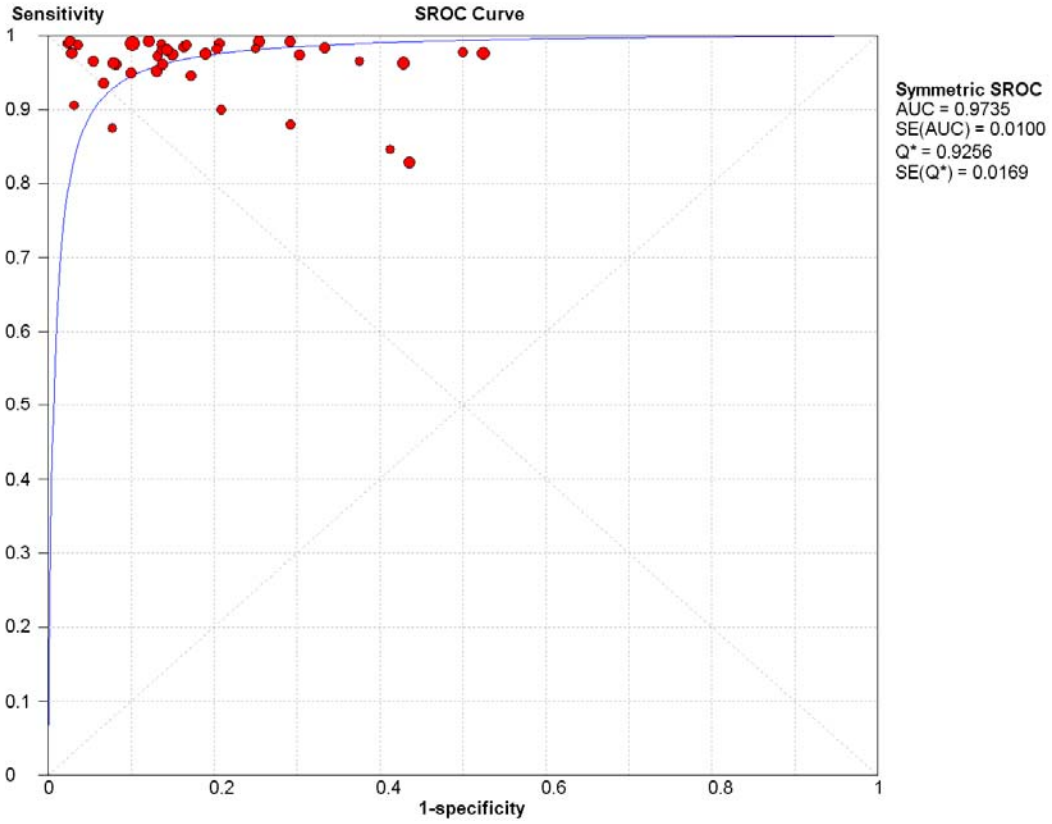


APPENDIX D

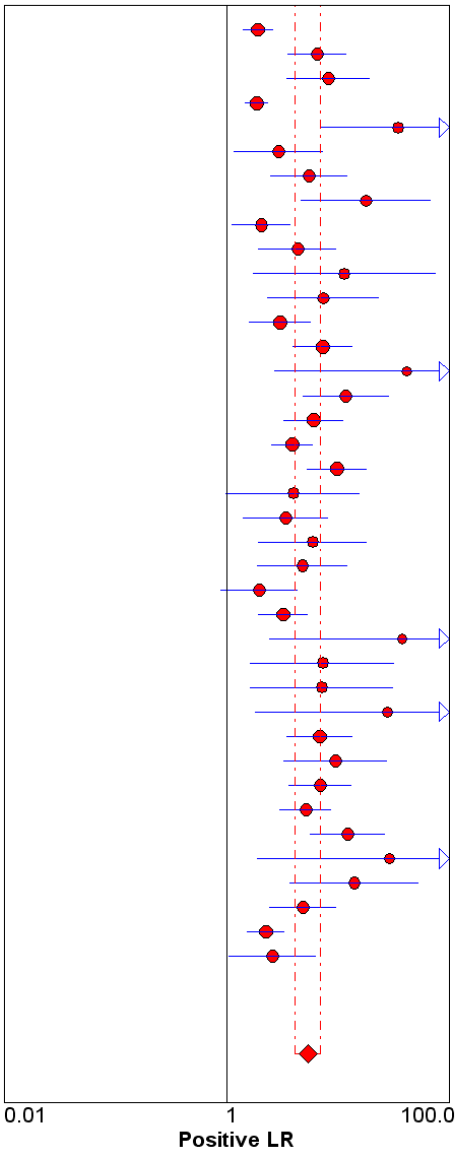
Summary Receiver Operating Characteristic (sROC) Curves & Pooled Likelihood Ratios:

Primary "Intent to Diagnose" Analysis

SROC Curve


Sensitivity
SROC Curve
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
1-specificity
Symmetric SROC
AUC = 0.9735
SE(AUC) = 0.0100
Q* = 0.9256
SE(Q*) = 0.0169

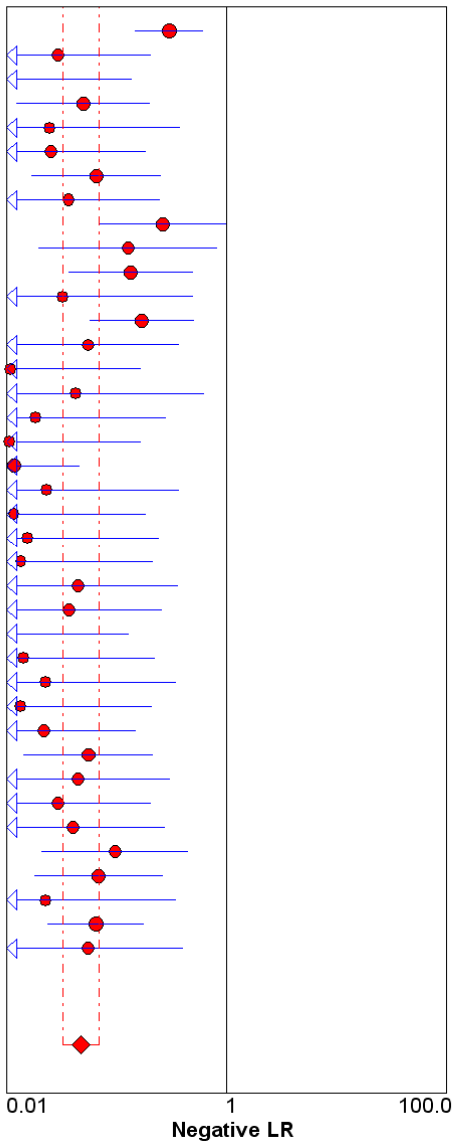
Positive Likelihood Ratio



	Positive LR (95% CI)
Achenbach (a) 2008	1.90 (1.39 - 2.61)
Achenbach (b) 2008	6.50 (3.55 - 11.90)
Bayrak 2008	8.16 (3.43 - 19.40)
Cademartiri (1) 2008	1.86 (1.46 - 2.37)
Cademartiri (2) 2007	34.49 (7.11 - 167.28
Ehara 2006	2.95 (1.17 - 7.44)
Fine 2006	5.49 (2.46 - 12.22)
Ghostine 2006	17.86 (4.63 - 68.88)
Hacker 2007	2.05 (1.11 - 3.80)
Husmann (a) 2008	4.32 (1.93 - 9.68)
Husmann (b) 2008	11.38 (1.71 - 75.46)
Johnson (2) 2007	7.39 (2.32 - 23.52)
Leber 2005	3.02 (1.59 - 5.72)
Leber 2007	7.30 (3.94 - 13.53)
Leschka 2005	41.56 (2.69 - 642.89
Meijboom (1a) 2007	11.75 (4.82 - 28.67)
Meijboom (1b) 2007	6.02 (3.25 - 11.16)
Meijboom (2a) 2007	3.90 (2.54 - 6.01)
Meijboom (2b) 2007	9.78 (5.27 - 18.18)
Meijboom (3a) 2007	3.93 (0.98 - 15.73)
Meijboom (3b) 2007	3.40 (1.41 - 8.21)
Mollet 2005	5.92 (1.91 - 18.38)
Mollet 2007	4.81 (1.89 - 12.23)
Muhlenbruch 2007	1.96 (0.88 - 4.36)
Nikolaou 2006	3.22 (1.91 - 5.41)
Oncel 2007	37.70 (2.45 - 581.03
Plass 2006	7.24 (1.64 - 32.06)
Pugliese 2006	7.19 (1.62 - 31.85)
Pugliese 2008	27.64 (1.82 - 420.48
Pundziute 2008	6.87 (3.46 - 13.65)
Raff 2005	9.50 (3.24 - 27.86)
Ropers 2006	6.97 (3.65 - 13.33)
Ropers 2007	5.15 (3.02 - 8.78)
Rubinshtein (1) 2007	12.20 (5.64 - 26.38)
Scheffel 2006	29.00 (1.89 - 445.86
Schuijf (1) 2006	14.03 (3.67 - 53.70)
Schuijf (3) 2006	4.84 (2.43 - 9.62)
Shabestiri 2007	2.25 (1.53 - 3.30)
Shapiro 2007	2.57 (1.05 - 6.32)

Random Effects Model
Pooled Positive LR = 5.34 (4.12 to 6.93)
Cochran-Q = 179.27; df = 38 (p = 0.0000)
Inconsistency (I-square) = 78.8 %
Tau-squared = 0.4467

Negative Likelihood Ratio



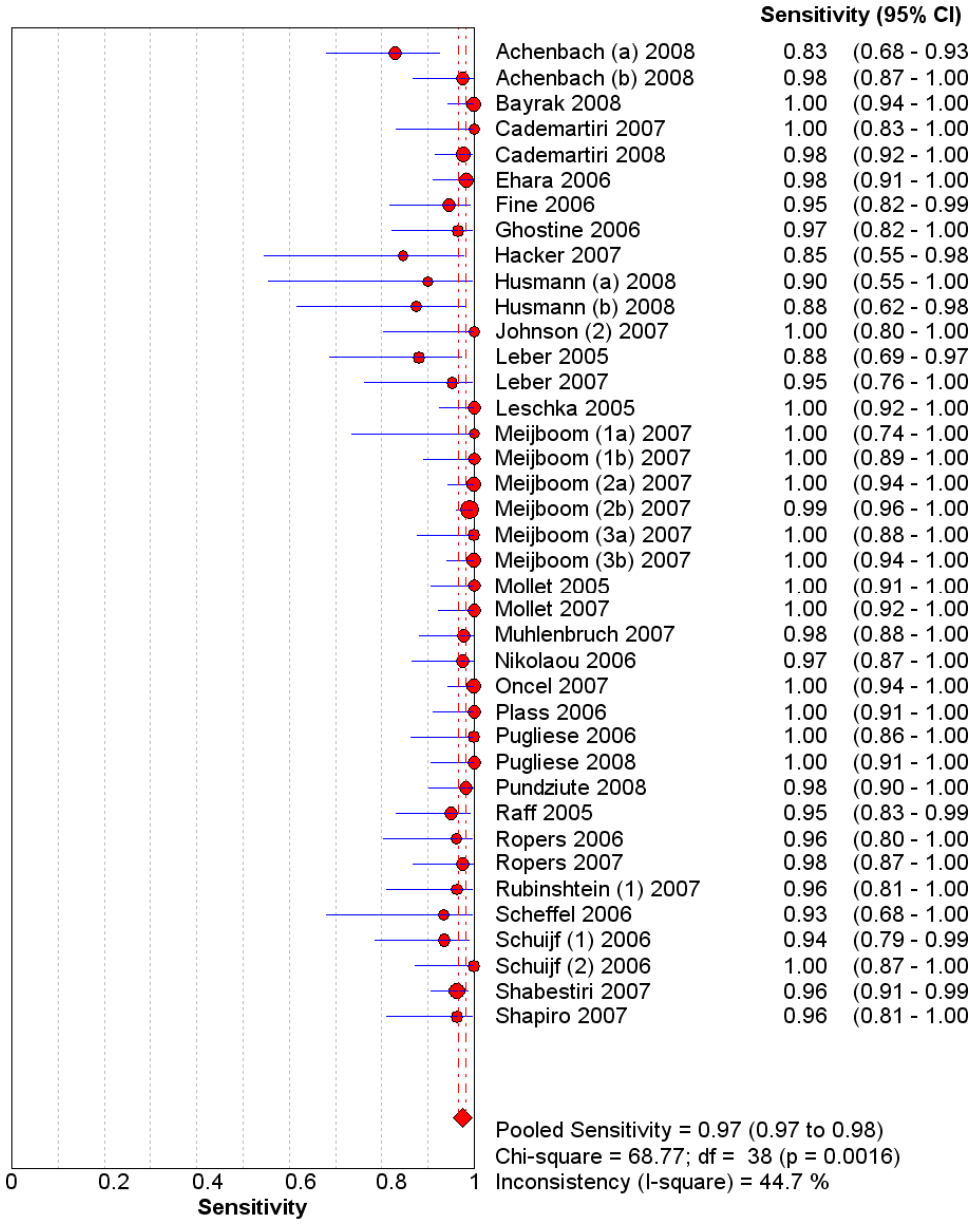
	Negative LR	(95% C
Achenbach (a) 2008	0.30	(0.15 - 0.61
Achenbach (b) 2008	0.03	(0.00 - 0.20
Bayrak 2008	0.01	(0.00 - 0.14
Cademartiri (1) 2008	0.05	(0.01 - 0.20
Cademartiri (2) 2007	0.02	(0.00 - 0.38
Ehara 2006	0.03	(0.00 - 0.18
Fine 2006	0.07	(0.02 - 0.25
Ghostine 2006	0.04	(0.01 - 0.25
Hacker 2007	0.26	(0.07 - 0.99
Husmann (a) 2008	0.13	(0.02 - 0.82
Husmann (b) 2008	0.14	(0.04 - 0.50
Johnson (2) 2007	0.03	(0.00 - 0.49
Leber 2005	0.17	(0.06 - 0.50
Leber 2007	0.05	(0.01 - 0.37
Leschka 2005	0.01	(0.00 - 0.17
Meijboom (1a) 2007	0.04	(0.00 - 0.64
Meijboom (1b) 2007	0.02	(0.00 - 0.28
Meijboom (2a) 2007	0.01	(0.00 - 0.17
Meijboom (2b) 2007	0.01	(0.00 - 0.05
Meijboom (3a) 2007	0.02	(0.00 - 0.37
Meijboom (3b) 2007	0.01	(0.00 - 0.19
Mollet 2005	0.02	(0.00 - 0.24
Mollet 2007	0.01	(0.00 - 0.21
Muhlenbruch 2007	0.04	(0.01 - 0.36
Nikolaou 2006	0.04	(0.01 - 0.26
Oncel 2007	0.01	(0.00 - 0.13
Plass 2006	0.01	(0.00 - 0.22
Pugliese 2006	0.02	(0.00 - 0.35
Pugliese 2008	0.01	(0.00 - 0.21
Pundziute 2008	0.02	(0.00 - 0.15
Raff 2005	0.06	(0.01 - 0.22
Ropers 2006	0.04	(0.01 - 0.31
Ropers 2007	0.03	(0.00 - 0.20
Rubinshtein (1) 2007	0.04	(0.01 - 0.28
Scheffel 2006	0.10	(0.02 - 0.45
Schuijf (1) 2006	0.07	(0.02 - 0.27
Schuijf (3) 2006	0.02	(0.00 - 0.35
Shabestiri 2007	0.06	(0.02 - 0.18
Shapiro 2007	0.06	(0.01 - 0.41

Random Effects Model
Pooled Negative LR = 0.05 (0.03 to 0.07)
Cochran-Q = 61.85; df = 38 (p = 0.0086)
Inconsistency (I-square) = 38.6 %
Tau-squared = 0.4905

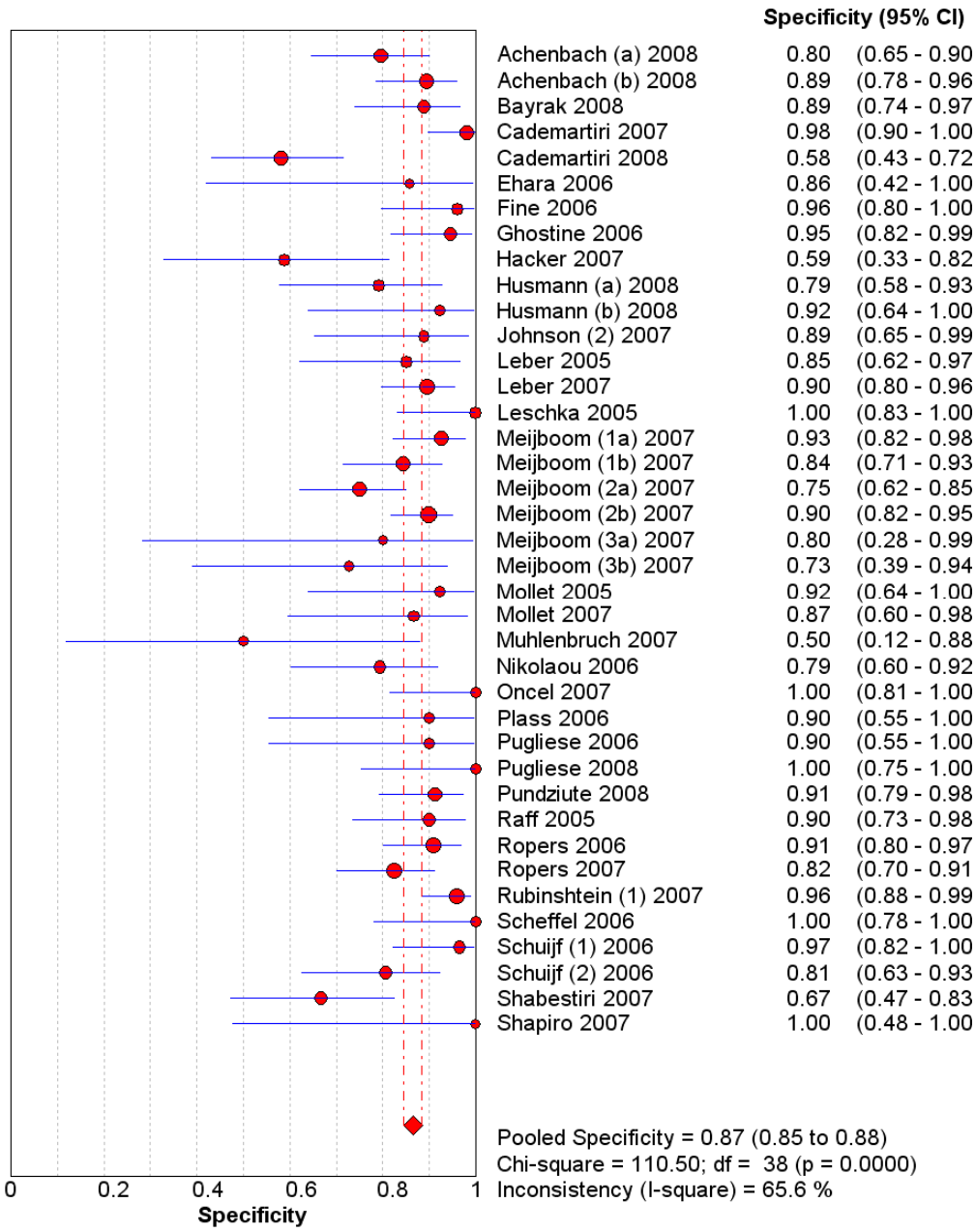
APPENDIX E:

META-ANALYSES OF "AS REPORTED" DATA

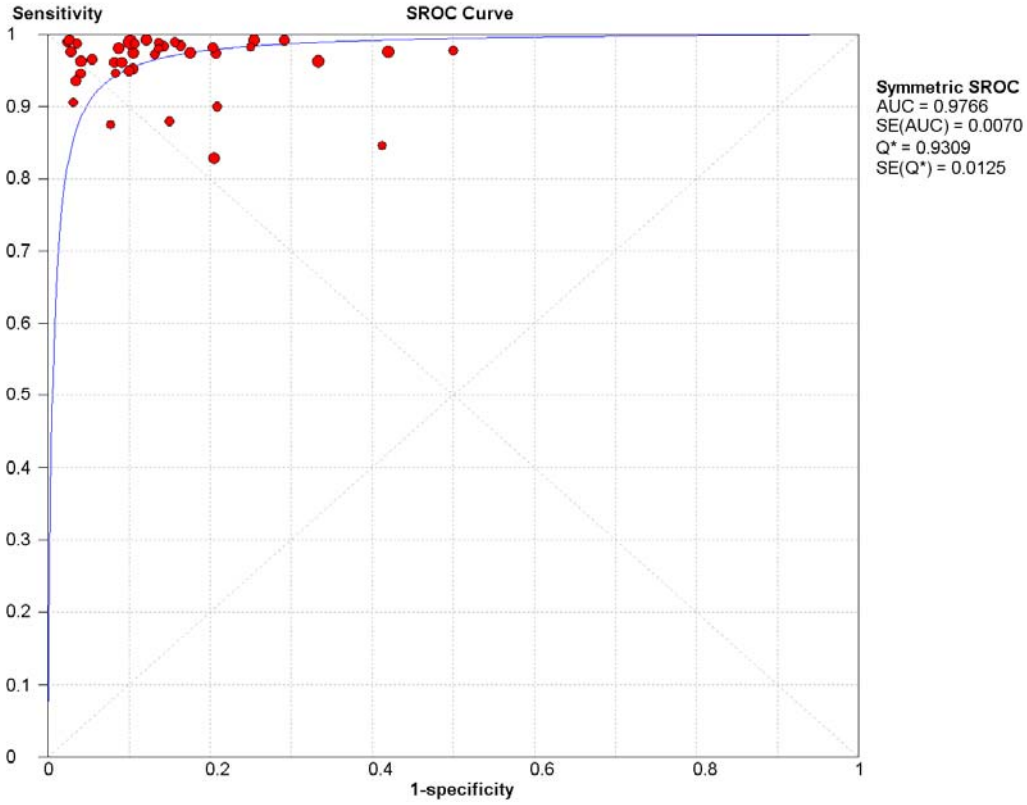
Sensitivity



Specificity



SROC Curve

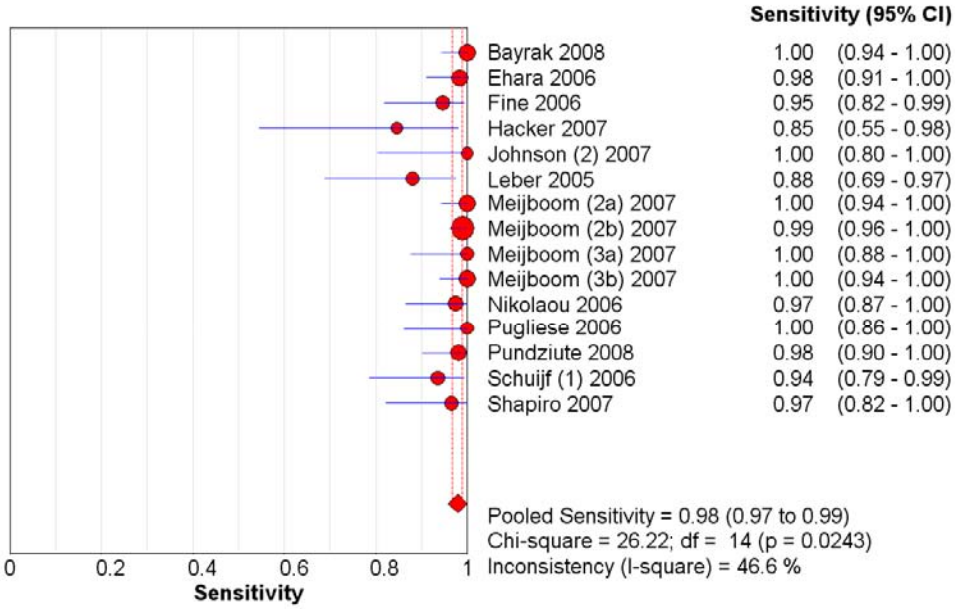

Sensitivity
SROC Curve
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
1-specificity
Symmetric SROC
AUC = 0.9766
SE(AUC) = 0.0070
Q* = 0.9309
SE(Q*) = 0.0125

APPENDIX F:

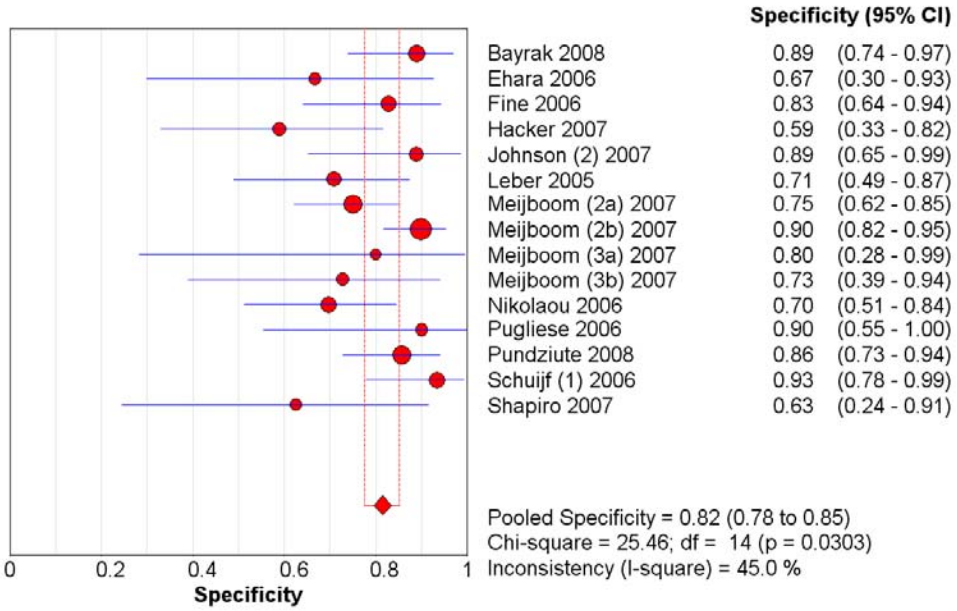
ADDITIONAL ANALYSES BASED ON POPULATIONS WITH AND WITHOUT KNOWN CAD

CAD Known

Sensitivity

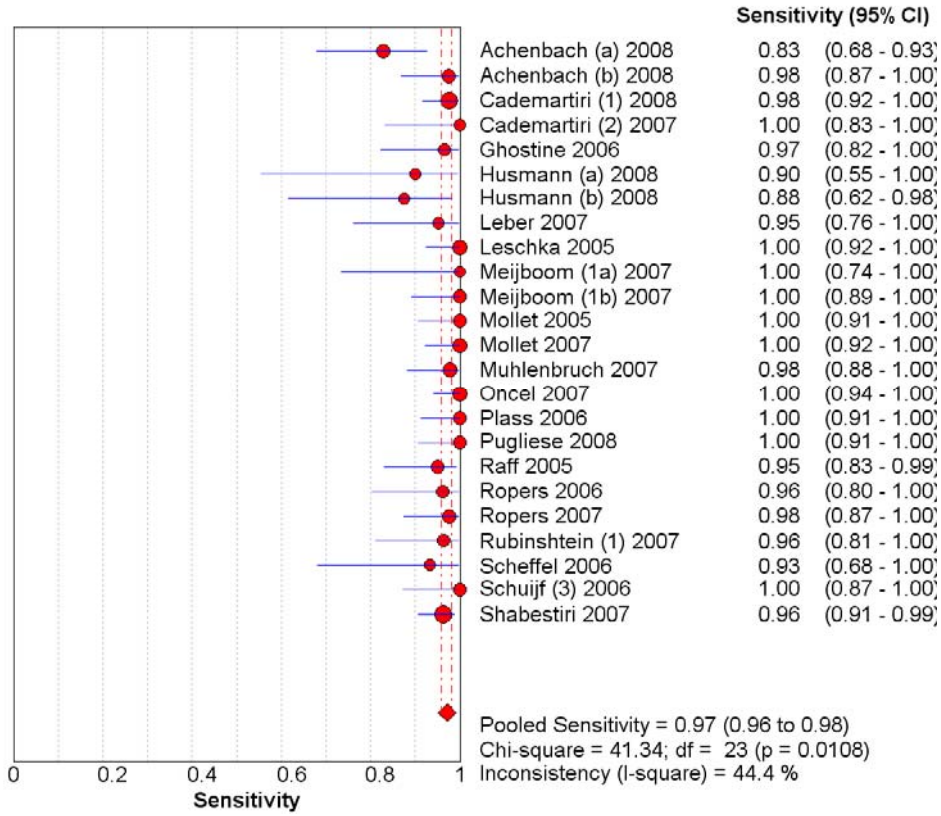


Specificity



CAD 0 or Unknown

Sensitivity



CAD Unknown

Specificity