Technology Assessment

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Non-Invasive Imaging for Coronary Artery Disease

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Duke Evidence-based Practice Center

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EXECUTIVE SUMMARY

This report describes an evaluation of the available scientific evidence on direct non-invasive imaging tests (NITs) for coronary artery disease. In particular, we focus on six key questions provided by the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Medicare and Medicaid Services (CMS). The objective of this report is to provide background information to the Medicare Coverage Advisory Committee (MCAC) in their review of these questions during their May 2006 meeting. The six key questions examine the degree to which current evidence supports confident judgments about the use of NITs in the assessment of coronary anatomy in clinical practice. The two NITs that are examined in detail in this report are computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) for evaluating native coronary arteries. In addition, we consider technologies on the horizon, as well as the general issue of establishing the value of NITs in specific clinical contexts in which coronary disease is being considered.

Methods

We performed a literature search of non-invasive coronary imaging tests using two strategies. First, we reviewed the search strategies used and the indexing terms of articles found in three recent systematic reviews of coronary CT and/or MRI.[1-3] We then devised an overall strategy to update those searches to the

present using the MeSH headings *Coronary Angiography* AND (*coronary disease* or *coronary stenosis*) AND (*tomography, x-ray computed* or *tomography, spiral computed* or *magnetic resonance imagin*g or *magnetic resonance angiography*) to search for articles published through the year 2005, limiting our search to articles published in English. Studies published prior to 2005 were identified from the three recent systematic reviews on this topic, which together included 92 studies, the vast majority of which were published before 2005. Our updated search resulted in 114 English language articles, 16 of which were previously identified in one or more of the recent reviews. Second, we searched for review articles published since the year 2002 up to and including through 2005 that included the following text words in title, abstract, or subject headings: *non-invasive, coronary, and imaging*. This resulted in 123 English language articles. Subsequently, we excluded all articles that did not address native coronary artery stenosis.

Articles were reviewed with regard to characteristics likely to influence the validity of the results and their applicability to individuals likely to be Medicare beneficiaries. For studies of clinical utility, we assessed whether the clinical context was clear and generalizable, and whether the outcomes assessed were clinically relevant.

Results

We identified 29 studies using 16-array or greater multi-detector computed tomography (MDCT) assessing coronary CTA for evaluation of native coronary arteries stenosis, and 13 MRA studies evaluating native coronary artery stenosis using more recent MRI imaging sequences. These studies were generally small, performed at single centers, and often did not include information that would serve to provide confident assessments of the key questions. In particular, we did not identify any studies evaluating the clinical impact of diagnostic strategies including NITs of coronary anatomy compared with strategies that did not include these techniques. The populations studied tended to be relatively young (<65 years of age), and limited results subgrouped by age were available. Future approaches to non-invasive imaging of the coronary arteries will consist of technical improvements to CTA and MRA, as well as combinations of these modalities with non-invasive studies of myocardial function at rest and during stress.

Conclusions

At present, there is limited evidence regarding test performance of NITs for identifying, quantifying, or otherwise characterizing coronary artery stenoses. The available evidence provides preliminary data on the ability of coronary MRA (1.5 T) and coronary CTA using at least 16-array MDCT technology to detect

obstructive coronary artery lesion in the proximal to mid coronary arteries. The evidence regarding detection of coronary lesions in branch vessels or distal coronary arteries remains unclear and may well improve as the technology improves. Studies conducted to date primarily fall into the “proof of concept” category with study patients having a high pre-test probability of CAD. Patients providing suboptimal images were often excluded from calculations of test accuracy. Future work will need to examine these tests in larger, less selected populations representing the clinical settings in which they are actually expected to be used.

CONTEXT OF THIS REPORT

The Centers for Medicare and Medicaid Services (CMS), through the Agency for Healthcare Research and Quality (AHRQ), have commissioned the Duke Center for Clinical Health Policy Research Evidence-based Practice Center (EPC) to perform an evaluation of the available scientific evidence on direct non-invasive imaging tests (NITs) for coronary artery disease relative to coronary angiography. Our report is focused around six key questions provided to us by AHRQ and CMS. The objective of this report is to provide background information to the Medicare Coverage Advisory Committee (MCAC) in their review of these six questions (see below) during their May 2006 meeting.

The six key questions examine the degree to which current evidence supports confident judgments about the use of NITs in the assessment of coronary anatomy in clinical practice. The specific focus of this report is computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) for evaluating native coronary arteries. In addition, the MCAC is interested in technologies on the horizon, as well as the general issue of establishing the value of NITs in specific clinical contexts in which coronary disease is being considered.

SIX KEY QUESTIONS

Based on an assembly of valid evidence:

1. How confident are you that there is sufficient valid evidence to determine if non-invasive technologies can detect obstructive coronary artery lesions?

    - Which non-invasive technologies have sufficient valid evidence to undertake such a determination?

2. How confident are you that there is sufficient valid evidence to determine if these non-invasive technologies can accurately assess the anatomic location of obstructive coronary artery lesions?

    - Which non-invasive technologies have sufficient valid evidence to undertake such a determination?

3. How confident are you that there is sufficient valid evidence to determine if these non-invasive technologies can accurately assess the relevant morphology (size, shape, ulceration, etc) of obstructive coronary artery lesions?

- Which non-invasive technologies have sufficient valid evidence to undertake such a determination?

4. How confident are you that non-invasive imaging can be used instead of coronary artery catheterization to determine treatment of coronary artery disease? If you are confident or very confident, in which populations should non-invasive imaging be used?

5. If non-invasive imaging were to be used in addition to coronary artery catheterization:

    - How confident are you that non-invasive imaging provides an incremental benefit or harm when used before coronary artery catheterization?
    - How confident are you that non-invasive imaging provides an incremental benefit or harm when used after coronary artery catheterization?

6. How confident are you that:
    a) The diagnostic test characteristics of the test are generalizable to the Medicare beneficiary population; and

b) Diagnostic and treatment strategies using non-invasive imaging of coronary artery disease provide a net health benefit to Medicare beneficiaries compared to strategies that use invasive imaging?

BACKGROUND

Introductory concepts and assessment of coronary artery anatomy

Atherosclerotic cardiovascular disease remains the primary cause of mortality and morbidity among adults in the United States. Coronary artery disease (CAD) refers to that portion of the spectrum of atherosclerotic disease in which significant amounts of atherosclerotic plaque builds up in the epicardial coronary arteries, reducing downstream blood flow to the heart muscle. CAD is a progressive process characterized by periods of apparent quiescence interspersed with active, sometimes life-threatening, manifestations of disease. The major clinical manifestations include angina pectoris, acute coronary syndromes (including both unstable angina and acute myocardial infarction), congestive heart failure, malignant ventricular arrhythmias, and sudden cardiac death. Unfortunately, the disease does not progress in a predictable fashion from less severe to more severe symptoms. Thus, the first evidence of coronary atherosclerosis may be a sudden cardiac death or a myocardial infarction causing permanent impairment of heart function.

For this reason, the appropriate diagnostic evaluation of patients who may have CAD is of considerable practical importance. Too little testing may fail to identify the disease at a stage when medical intervention can still save life or prevent

disability. Too much testing can lead to unnecessary therapies, to incidental findings that may induce additional testing with the attendant risks involved, to avoidable anxieties for the patient, and to wasteful use of scarce health care resources. Although a full discussion of this subject is considerably beyond the scope of this report, a few general concepts will be introduced as background to what follows.

A “diagnostic test” can be used to examine either diagnostic questions (e.g., does this patient have significant coronary artery disease?) or prognostic questions (e.g., what are the chances that this patient will die or have a heart attack in the next year?). Diagnostic questions are much more frequently represented in the medical literature because the studies are easier to perform. However, prognostic questions are ultimately more closely aligned with the concerns of the patient and the physician. The difficulty of performing prognostic studies lies in the large samples and extended periods (i.e., years) of follow-up required. All the studies reviewed in this report fall into the former category of studies addressing diagnostic questions.

The performance of diagnostic tests is typically judged against a reference standard (often termed the “gold standard”). In the case of the non-invasive tests considered in this report, that standard is invasive coronary angiography. Test performance is typically evaluated in terms of test “operating characteristics.” The operating characteristics measure how well the new non-invasive tests

correctly identify patients with disease (sensitivity or the proportion of patients with disease who have a “positive” non-invasive test) and patients without disease (specificity or the proportion of patients without disease who have a “negative” test). The ideal non-invasive test would have both a very high sensitivity and a very high specificity. In practice, however, there is typically a trade off between sensitivity and specificity such that only one can be maximized at a time.

The measurement of test operating characteristics is not a simple matter. Substantial biases can be introduced into the measurements by choice of the subjects to be studied. The ideal population is comprised of individuals for whom there is true diagnostic uncertainty and for whom the test in question would have the potential to influence management. However, most published studies of test operating characteristics select study subjects for convenience rather than relevance. Thus, inclusion of normal subjects without suspected CAD symptoms to define test specificity provides a biased assessment of specificity.[4] Similarly, inclusion of patients with known CAD (based, for example, on prior coronary angiography or prior myocardial infarction) will usually bias sensitivity upwards. These spectrum biases can result in substantially misleading estimates of test performance. Characteristically, overoptimistic measures of test performance appear early in the life cycle of a new test, only to be supplanted gradually over a period of years by more realistic performance statistics.[5, 6]

Diagnostic tests for CAD, whether addressing diagnostic or prognostic questions, do not by themselves alter outcome unless there is a complication during test performance. To have an impact on outcomes, test results must influence subsequent management for better, or perhaps, for worse. Thus, the test must be interpreted, placed into clinical context for each individual patient. In the case of CAD, the general treatment options are medical therapy and revascularization. Medical therapy is focused on two objectives: symptom relief and improvement of prognosis. For example, nitroglycerin can reduce the symptoms of angina, while aspirin does not affect symptoms but can reduce the chances that a CAD patient will die or have a heart attack. Some therapies, such as beta blockers can accomplish both objectives. Revascularization can be accomplished either with coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI). The latter includes both balloon angioplasty and coronary stenting. The decision about whether to initiate medical therapy for CAD and whether to add revascularization to medical therapy depends on the details of the clinical presentation including medical history, physical examination, and initial diagnostic tests. Once the physician has made an initial assessment, they may choose to start therapy, perform additional non-invasive tests, or refer for invasive angiography. The evaluation of what revascularization procedure a patient is eligible for is based heavily on a detailed assessment of the invasive coronary angiogram.

Since invasive angiography is not itself a therapy, it only provides benefit to the patient if it can lead to a change (improvement) in management. Depending on the population considered, a substantial segment of the more than one million diagnostic angiographies performed in the US each year do not lead to revascularization. The impetus behind the development of improved non-invasive diagnostic strategies for CAD is to allow confident identification of patients who do not need (or who are not candidates for) revascularization, thus sparing them an invasive procedure while still being able to identify that segment of the CAD population who will derive either prognostic or symptomatic benefit from revascularization.

The basic goal of the new direct non-invasive imaging studies for CAD is to be able to provide an anatomic evaluation of the epicardial coronary arteries without the risks of an invasive procedure. The technical challenges are considerable. The coronary arteries lie on the outer surface of the heart in a complex three-dimensional pattern that differs from one individual to the next. In addition, the coronary arteries are small, with internal dimensions from about 1 mm to over 4 mm, and the heart is in almost continual motion. Modern invasive coronary angiography has excellent spatial (approximately 0.2 mm) and temporal (50 milliseconds) resolution. The technical challenge in supplanting invasive angiography has been to develop new techniques that can approximate in quality what clinicians have been accustomed to using in making treatment decisions.

Much of the available literature on the new NITs addresses the question of whether non-invasive imaging has achieved this objective as a technical matter.

One of the main criticisms of treatment decision making based only on coronary angiography is that such an approach does not take account of the fact that a coronary lesion may appear “significantly” obstructive, but may not affect downstream myocardial performance and vice versa. To assess the “functional” importance of coronary disease, clinicians often use non-invasive tests such as exercise/stress echocardiography, exercise/stress single proton emission computed tomography (SPECT), myocardial perfusion imaging, and, more recently, stress magnetic resonance (MR) perfusion imaging. These tests evaluate the coronary circulation at rest and again during exercise or pharmacological stress either by looking at patterns of blood flow into the heart muscle (perfusion studies) or at the contraction patterns of the left ventricle. Comparison of the rest and exercise/stress images helps identify areas of reversible reduction in blood flow (i.e., ischemia) as well as areas of prior heart attack. A significant reduction in blood flow to a section of the heart muscle supplied by a narrowed coronary artery will show up during exercise or stress as an area of reduced uptake of perfusion imaging agent on SPECT imaging or as abnormal wall motion (contraction) on echocardiography. A heart attack causes irreversible damage to the heart muscle leading to an area of scarring, which does not have blood flow and does not contract.

Current practice involves many permutations in the use of tests to diagnose CAD. In the elective setting, patients may be referred initially for a stress test and only referred to invasive angiography if the stress test is sufficiently abnormal. In some cases, the clinician may start with a treadmill electrocardiogram (ECG) stress test. If the result is judged ambiguous (i.e., neither clearly positive nor clearly negative), the second test selected may be a stress imaging study, such as nuclear SPECT perfusion study or a stress echo, both of which have increased accuracy for diagnosis of CAD relative to stress ECG testing. In the acute setting, patients are often referred for early angiography as the initial risk stratification test although lower risk patients may be evaluated first with non-invasive testing. After cardiac catheterization, some patients may be referred for non-invasive stress testing to define the "functional significance" of a coronary stenosis that is borderline in severity, or is located in such a way as to increase the risk of treatment with percutaneous revascularization. Some cardiovascular experts advocate for a diagnostic strategy that includes both anatomy information (from direct coronary imaging) and functional information collected during exercise or pharmacological stress. There is no current gold standard test that achieves both of these objectives. The future evolution of non-invasive diagnostic strategies may seek not only to supplant some fraction of currently performed invasive angiographies, but also to provide a more comprehensive data base for clinical decision making that includes non-invasive data on both coronary anatomy and functional response of the coronary circulation to exercise/stress.

Technologies for imaging coronary artery anatomy

X-ray Angiography

Traditionally, coronary anatomy has been defined by x-ray angiography. This technique involves introducing a catheter into the femoral, brachial, or radial artery; passing that catheter up the aorta; and directly engaging the right and left coronary arteries and injecting an iodinated contrast agent into each while making digital x-ray images. Significant improvements in technique and equipment have been introduced over the past 20 years that have reduced the risks of the procedure to patients.[7, 8] These risks for diagnostic coronary angiography include arterial bleeding from the access site, embolization of atherosclerotic material causing stroke or heart attack due to catheter manipulation in the aorta and coronary arteries, anaphylaxis or renal injury from the contrast agent used to visualize the coronary arteries on x-ray images, and radiation exposure. The direct mortality risk from diagnostic cardiac catheterization is estimated to be 0.1%.[9] The limitations of invasive x-ray angiography as a gold standard for coronary artery disease including variability and the ability to only identify luminal obstruction are well known.[10, 11] However, x-ray angiography remains the routine standard for clinical care.

To avoid exposing patients to the risk of an unnecessary invasive angiography, diagnostic strategies have been developed using non-invasive myocardial

imaging techniques. These techniques, which include echocardiography and myocardial nuclear perfusion scanning, do not provide direct visualization of coronary artery anatomy. Rather, they evaluate myocardial wall motion or perfusion at rest and under stress and any abnormal findings are used to make inferences about the presence and severity of obstructive coronary artery disease and the resulting need for invasive coronary artery imaging. It is beyond the scope of the present review to more than note that these non-invasive cardiac tests have wide variability in reported sensitivities and specificities.[12] It is in this context that the NITs are being introduced.

CTA and MRA

Two non-invasive technologies to directly image coronary artery anatomy are available in the United States and are in active development: computed tomography angiography (CTA) and magnetic resonance angiography (MRA). For the purpose of this report it is particularly notable that neither of these imaging modalities has yet reached technological maturity. Ongoing research is particularly focused on the special challenges of coronary anatomy imaging: the need for excellent spatial resolution (to image very small vessels from 4 mm to <1.5mm in size) and superb temporal resolution (to image very quickly to reduce artifact from cardiac and respiratory motion).

Coronary artery CTA involves intravenous injection of an iodinated contrast agent followed by rapid imaging (over 10 to 15 seconds) of the heart with a multi-detector row computed tomography (MDCT) scanner. With increasing number of detectors (16, 40, 64) and faster tube rotation, MDCT scanners are now able to acquire images from the whole heart which result in fewer artifacts from both cardiac and respiratory motion. Risks involved in using this technique include radiation exposure (quantified at 3-4 times the radiation exposure for diagnostic invasive angiography)[13] and the use of iodinated contrast, which can be nephrotoxic for certain patients.

MRA of the coronaries can be performed with or without the administration of a gadolinium-based intravenous contrast agent during ECG gated magnetic resonance imaging of the heart. MRA techniques for coronary artery assessment have included both 2-dimensional and 3-dimensional image acquisition along the imaging plane of the coronary artery with different methods for motion artifact reduction (either breath hold or free breathing “navigator” sequences). Patients with severe claustrophobia or with certain metallic foreign bodies or implanted devices may not be suitable for this type of non-invasive imaging. This technique does not involve radiation exposure and the contrast agent, at the dose used for MRA, is not considered nephrotoxic. MRA sequences still require either breath hold of 16-30 seconds or free breathing with sequence calibration to respiratory motion. Respiratory motion artifact remains a significant concern for MRA imaging of the coronary arteries. Initial

investigations are now being conducted with the use of 3 Tesla MRI scanners (most MR scanners in current use are 1.5 Tesla) to image coronary arteries and the hope is that the superior signal to noise ratio of these new machines will allow improved imaging of the coronary circulation.

The potential for imaging artifacts and incorrect interpretation exists for both coronary CTA and MRA studies. Both modalities require image acquisition paired to cardiac motion so as to isolate imaging during a period of relatively limited cardiac motion (diastole) to decrease motion artifact, which is a blurring or ghosting of the image that can result in a poor-quality or unusable image. Reduction of motion artifact requires that image acquisition be timed to heart rhythm and rate, a process known as ECG-gating. Therefore, patients with either irregular heart rhythms, such as frequent premature atrial or ventricular contractions, or atrial fibrillation may have significant artifacts when tested with CTA or MRA. Pre-test administration of beta-blockers is routinely used to slow heart rates since faster heart rates decrease the time spent in diastole when the heart is (momentarily) at rest. Respiratory motion also presents imaging problems, some of which have been diminished by short (<20 second) imaging times with MDCT.

The presence of coronary calcium (a component of complex atherosclerotic plaques) also can present significant potential interpretation difficulty for CTA as coronary stenosis underlying coronary calcium may be obscured by x-ray beam

hardening artifacts depending on the degree of calcification of the vessel or degree of stenosis may be overestimated.[14] For coronary MRA, overcoming respiratory motion, results in long examination times. In contrast to coronary CTA, calcium results as an area of signal void and may result in overestimation of stenosis. These above artifacts are not routinely seen on traditional x-ray angiography due to its superior temporal and spatial resolution.

In addition to patient-related testing issues, the methodology and technology used in image reconstruction can also affect the accuracy of image interpretation and alter a test's clinical utility. Both CTA and MRA require complex post-processing reconstruction of images. At present, there is no agreed standard method for these computer-based reconstructions, which tend to be proprietary and vary by manufacturer.

Electron Beam Computed Tomography

Electron beam computed tomography (EBCT) technology is an imaging technology that uses electrocardiogram (ECG) gating and high-speed cine CT scanning to generate cross sectional images of the heart. EBCT has been used most successfully to quantitate calcium deposits in the coronary arteries. Coronary calcium has been correlated with overall atherosclerotic burden and with the risk of future myocardial infarction and death.[1-3] To date, this technology has not achieved the level of resolution required to image coronary artery

anatomy and stenosis well. Further, its role in clinical screening for CAD remains controversial.[15, 16] Consequently, it is not considered further in this report.

Combined Direct and Indirect NITs

While the focus of this report is on technologies for directly assessing coronary artery anatomy, work is ongoing to improve indirect tests of coronary artery disease, as well. These include research into contrast agents for perfusion echocardiography, radionuclide agents for both SPECT and PET imaging, and stress cardiovascular magnetic resonance evaluating both wall motion and myocardial perfusion. Because of the limitations of these technologies when used individually, there is particular interest in the potential for combining non-invasive myocardial imaging techniques with direct non-invasive coronary imaging. Examples of promising combinations include the use of PET with CTA or perfusion MRI with MRA angiography. These may provide a more complete evaluation of the epicardial coronary arteries and myocardial function and perfusion in a single setting.

METHODS

Overview

The six key questions which form the focus of this report examine the degree to which the available scientific evidence allows a confident assessment of specific clinically relevant questions. They fall into two general categories: test accuracy/performance (questions 1, 2, 3 and 6a) and clinical impact (questions 4, 5, and 6b).

Literature Review

Identification of the Literature

We performed a literature search of non-invasive coronary imaging tests using two strategies. First, we reviewed the search strategies used and the indexing terms of articles found in three recent systematic reviews of coronary CT and/or MRI.[1-3] We then devised an overall strategy to update those searches to the present using the MeSH headings *Coronary Angiography* AND (*coronary disease* or *coronary stenosis*) AND (*tomography, x-ray computed* or *tomography, spiral computed* or *magnetic resonance imagin*g or *magnetic resonance angiography*) to search for articles published through the year 2005, limiting our search to articles published in English. Studies published prior to 2005 were identified from

the three recent systematic reviews on this topic, which together included 92 studies, the vast majority of which were published before 2005. Our updated search resulted in 114 English language articles, 16 of which were previously identified in one or more of the recent reviews.

Second, we searched for review articles published since the year 2002 up to and including through 2005 that included the following text words in title, abstract, or subject headings: *non-invasive, coronary, and imaging*. This resulted in 123 English language articles. These reviews did not provide additional source articles related to the key questions, but served as a screen to identify possible technologies on the horizon.

The clinical inclusion criterion for articles was assessment of native coronary arteries. Subsequently, we excluded all articles that did not address native coronary artery stenosis.

Assessment of the literature

Articles were reviewed with regard to the following characteristics:

- Volume of patients evaluated
- Prospective assessment of consecutive patients
- Standardized image acquisition and reconstruction
- Blinded interpretation

- Information provided about images of coronary segments/arteries that were deemed low quality or were otherwise uninterpretable
- Comparison with a gold standard
- Ability to identify CAD on a patient level and on a segment/vessel level
- Inclusion of subjects representative of Medicare beneficiaries.

For studies of clinical utility, we assessed whether the clinical context was clear, generalizability, and whether the outcomes assessed were clinically relevant.

Because of the preliminary nature of the available data for non-invasive coronary imaging, a full critical appraisal, including an independent confirmation of the correctness of reported test parameters such as sensitivity and specificity, is not warranted at this time. In many studies, some tested patients had some or all of their results omitted from the reported operating characteristics due to technical or other problems. Such omissions bias the reported operating characteristics upward.

RESULTS

General observations

Based on our literature search, we identified 30 studies using 16-array or greater MDCT assessing coronary CTA for evaluation of native coronary artery stenosis and 13 MRA studies evaluating native coronary artery stenosis using more recent MRI imaging sequences. (Evidence Table, see Appendix)

The vast majority of CTA studies were performed on 16-MDCT scanners, with 6 studies using 64-MDCT scanners for CTA. To provide a clearer picture of the most recent and thus most relevant literature, Table 1 lists only the 64-array MDCT studies along with the 5 prospective 16-array MDCT studies that enrolled at least 100 patients. This table includes major characteristics reflecting study quality and relevance to the key questions. The 16-array MDCT studies demonstrate the general limitations of the CT technology in assessing coronary artery stenosis. Higher reported sensitivities and specificities resulted when patient enrollment was limited to individuals who were in sinus rhythm and able to breath hold for 20-25 seconds (this latter requirement was often tested prior to enrollment in the study).[17, 18] Additionally, coronary artery segments were excluded that were judged to be of poor image quality. In the largest consecutive prospective 16-array MDCT study with 149 patients in which all segments were analyzed, 23% of coronary segments were found to be poor quality.[19]

Additionally, 34% of the segments had notable coronary calcium and motion artifacts that limited evaluation in 24% of the patients. This study reported a sensitivity of 30% and a specificity of 91% when analyzed by coronary segments, and a sensitivity of 86% and a specificity of 49% when analyzed on a per patient basis.

Table 1 – Larger Prospective 16-array MDCT CTA and 64-array CTA

Article #	N=	Mean Age	Population Consecutive Y or N(no or not stated)	Prospective (Y) or Retrospective (R) or Not Stated (N)	Blinded read (Y) or N (no or not stated	Imaging Technology Scanner Type (CT16, CT64, MRA)	Image Reconstruction Vendor (V) and/or (S) Standardized or N (Not Stated)	% Images non-diagnostic or N (Not stated)	Gold Standard and % receiving X-Ray Angio (A)	Analysis method: Patient (P) Vessel (V) segment (S) or Both (B)	Reported Sensitivity	Reported Spec.	Reported Harm: Radiation (R), Nephrotoxicity (K), (O) Other or Not Stated (N)	Comment:
Burgstahler C 2005[20]	117	72 and 57	Y	R	Y	CT16 (Siemens)	N	6-B10% of segments not visualized, 11-18% stented or severe calcification, 17% only able to tell if presence or absence of vessel occlusion	A-100%	S	80-89% (eval seg)	96-98% (eval seg)	N	Two groups with mean age of 72 vs 57. Calcium score higher in older age cohort. Sensitivity decreased with age, but no sign difference in specificity. 3 patients overall excluded from lower age group due to technical problems with scan
Hoffmann MHK, 2005[17]	103	61.5	Y	Y	Y	CT-16 (Phillips)	S	6.4% segments 27% patients with only partial coronary tree coverage	A – 100%	B	95% (segs) 97% (pts)	98% (segs) 87% (all pts)	R – 8.3 mSv ave	Pts sinus rhythm able to breath hold 25 secs stent segs excluded
Mollet NR, 2004[18]	128	58.9	N	Y	Y	CT16 (Siemens)	S	1 pt excluded and stented segs excluded	A – 100%	B	92% (segs) 100% (pt)	95% (segs) 86% (pt)	N	Only vessels > 2 mm, sinus rhythm, pts can hold breath 20sec prior to enrollment, 60% beta-blocker, stented segs excluded
Kaiser C, 2005[19]	149	63.9	Y	Y	Y	CT16 (Siemens)	N	23% segments poor quality	A – 100%	S	30% (all segs) 86% (all pts)	91% (all segs) 49% (all pts)	N	Large study – analysis in all segs and pts, 34% segs with Calcium, motion artifacts 24% pts
Kuettner A, 2005[21]	124	64.1	Y	Y	Y	CT16 (Siemens)	S	4 patients excluded, 19% poor image quality	A – 100%	S	85% (per patient)	98% (per patient)	N	All segments, analysis only by patient, but for distal vessel segments did not perform well
Leschka S, 2005[22]	67	60.1	Y	N	Y	CT64 (Siemens)	S	No segs excluded	A – 100%	B	94% (all segs)	97% (all segs)	N	Sinus rhythm, > 1.5 mm vessels
Fine JJ, 2006[23]	66	62	Y	N	Y	CT64 (Siemens)	N	No exclusions, vessel only analysis	A – 100%	V	95% (by vessel)	96% (by vessel)	N	> 1.5 mm vessels,
Raff GL, 2005[24]	70	59	Y	Y	Y	CT64 (Siemens)	N	12% segs not evaluable	A – 100%	B	86% (eval segs) 95% (eval pts)	95% (eval segs) 90% (eval pts)	N	All segments including < 1.5 mm vessels, 26% with Ca+ agaston > 400, BMI>30 reduced accuracy
Leber AW, 2005[25]	59	64	Y	Y	Y	CT64 (Siemens)	V	4/59 (7%) patients non-evaluable images	A – 100%	B	73% (eval segs)	97% (eval segs)	N	Entire tree seen in 55 of 59 patients and used for analysis
Mollet NR, 2005[26]	51	59.6	Y	Y	Y	CT64 (Siemens)	S	I patient scan not evaluable	A – 100%	B	99% (eval segs) 100% (eval pt.	95% (eval segs) 92%(eval pts)	N	75% of patients with disease, multivessel in 45% patients, Ca+ agaston >400 in 18 pts

Table 1 – Larger Prospective 16-array MDCT CTA and 64-array CTA

Article #	N=	Mean Age	Population Consecutive Y or N(no or not stated)	Prospective (Y) or Retrospective (R) or Not Stated (N)	Blinded read (Y) or N (no or not stated	Imaging Technology Scanner Type (CT16, CT64, MRA)	Image Reconstruction Vendor (V) and/or (S) Standardized or N (Not Stated)	% Images non-diagnostic or N (Not stated)	Gold Standard and % receiving X-Ray Angio (A)	Analysis method: Patient (P) Vessel (V) segment (S) or Both (B)	Reported Sensitivity	Reported Spec.	Reported Harm: Radiation (R), Nephrotoxicity (K), (O) Other or Not Stated (N)	Comment:
Ropers D, 2006[27]	84	58	N	N	Y	CT64 (Siemens)	V	4% patients and segs non-eval.	A – 100%	B	93% (eval seg) 96% (eval pt)	97% (eval seg) 91% (eval pt)	R Ave. 7.45 mSv men and 10.24 mSv women	> 1.5 mm vessels only

The 64-array MDCT studies overall have more consistent diagnostic image quality with higher reported sensitivity and specificity in the detection of coronary artery stenosis. Compared to 16-MDCT technology, scan time is faster for the 64-MDCT scanners and while spatial resolution is unchanged, temporal resolution may be improved. The representative study by Raff et al.[24] was conducted with 70 patients with all vessels, including vessels <1.5 mm in diameter, analyzed. This study found 12% of segments were unevaluable. An Agatston calcium score >400 was observed in 26% of patients. In this subset, sensitivity appeared preserved (93% versus 94%) for patients with a calcium score <100, but specificity was reduced (67% versus 95%) for patients with calcium scores >100.

The majority of the coronary MRA studies were often unable to visualize the entire coronary tree or even the full extent of the major vessels. These studies often report the length of the major coronaries visualized, indicating incomplete coverage. In one prospective multi-center study of 109 patients evaluating MRA for coronary artery stenosis,[28] 16% of coronary segments were excluded due to poor image quality. Although the findings in evaluable segments were encouraging (sensitivity 100% and specificity of 85%), this study along with the other studies reviewed for this project demonstrate that there are still significant limitations of this technique in evaluating the entire coronary tree. By inference, these limitations constitute a barrier to the routine use of these tests in the clinical management of patients.

Question 1: How confident are you that there is sufficient valid evidence to determine if non-invasive technologies can detect obstructive coronary artery lesions?

The Evidence Table provides an appendix of studies that met the inclusion criteria, and Table 1 presents the studies highlighted for discussion. Only five studies of coronary CTA used 16-array MDCT and prospectively enrolled more than 100 patients (Table 1). Six additional studies have evaluated CTA with a 64-array MDCT. All of these were single center and examined fewer than 100 patients. Disease detection was defined as >50% stenosis. Analysis by coronary segment produced sensitivity estimates ranging from 30% to 99% and specificity estimates ranging from 91 to 98%. For patient level analysis, reported sensitivity ranged from 85% to 100% and specificity ranged from 49% to 98%. Limitations include exclusion of segments of the coronary arteries and some of the studies report only analysis of evaluable segments or patients, not both.

MRA evaluation of obstructive coronary artery lesions is limited to the proximal and mid coronaries at this time, with a significant number of coronary segments or patients excluded from the analysis. The meta-analysis of Schuijf and colleagues published earlier this year identified 28 studies with a total of 980 patients.[29] Operating characteristic estimates by coronary segment level analysis varied widely. Only four of the 28 studies included more than 50 subjects and only one enrolled consecutive subjects. We reviewed 12 studies with more recent technology (see Evidence Table).

The largest was a prospective multi-center study with 109 patients.[28] Analysis was only reported by segment, with 16% of segments excluded due to technical problems. Sensitivity for evaluable segments was 100% with specificity of 85%. In the Schuijf meta-analysis, sensitivity overall in the 28 studies was 72% but fell to 58% when non-evaluable segments were included. Specificity was 87% but fell to 70% when non-evaluable segments were included.

Question 2: How confident are you that there is sufficient valid evidence to determine if these non-invasive technologies can accurately assess the anatomic location of obstructive coronary artery lesions?

The anatomic location of coronary stenosis significantly affects the ability of NITs to detect and assess coronary stenosis and determine management plans. The available evidence suggests better performance with both CTA and MRA in assessment of more proximal portions of the coronary tree, particularly the left main coronary artery and the proximal segments of the left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA). As with question 1, the reported results in the studies we reviewed were biased by exclusion of coronary segments due to inadequate image quality.

Question 3: How confident are you that there is sufficient valid evidence to determine if these non-invasive technologies can accurately assess the relevant morphology (size, shape, ulceration, etc) of obstructive coronary artery lesions?

There are very limited data evaluating NIT's ability to assess coronary artery lesion morphology. We identified five studies[30-34] comparing NITs with intravascular ultrasound (IVUS) for coronary morphology. These studies included less than 50 patients and typically involved IVUS examinations of only one coronary artery. In these reports, NITs were able to identify some of the characteristics of plaque morphology such as calcification and plaque area.[33] However, comparisons were largely made in segments without significant obstructive lesions. In addition, no attempt was made to link the angiographic findings to clinical outcomes.

Question 4: How confident are you that non-invasive imaging can be used instead of coronary artery catheterization to determine treatment of coronary artery disease?

Question 5: If non-invasive imaging were to be used in addition to coronary artery catheterization, how confident are you that it provides incremental benefit or harm when used a) before catheterization, and b) after catheterization?

The responses to questions 4 and 5 are combined as in both cases there are no direct data to support the substitution of the newer non-invasive coronary imaging techniques for invasive catheterization in order to select treatment for patients with suspected or known CAD, or use of such tests as an adjunct to x-ray angiography. The answer to this question at present can only be inferred using the limited evidence available on questions 1-3 along with some assumptions based on past experience with older diagnostic technologies. However, such an inference is not straightforward, and cannot be made on the basis of general principles of test use. The optimal decision depends on the complex relationship between pre-test probability of disease, test operating characteristics, and expected benefits and harms of various plausible management options. For example, test sensitivity and specificity estimates derived from high pre-test probability patients cannot be applied to low pre-test probability patients without adequate validation. The reason for this lies in the different operating characteristics of tests when applied to different stages/severity levels of a disease (in this case, CAD). Low pre-test probability populations not only have fewer patients with clinically significant disease, but also the cases of disease in this population are typically less advanced than in a high pre-test probability population.[35]

In the absence of direct evidence, decision models can be used to provide preliminary insights into the potential harms and benefits of different imaging technologies and strategies. While we did not identify such a published study of NITs for coronary anatomy, the model developed by Garber et al.[36] provides some general insights about

the potential impact of NITs as an alternative to initial x-ray angiography. This work provides two observations relevant to the current report. First, there was a very narrow range of quality-adjusted life years (QALY) across all strategies. The difference between the strategy with the highest QALY (catheterization alone) and the lowest was only 0.025 QALY for men and 0.028 QALY for women. Second, cost effectiveness did not vary much by age (only ages 45, 55 and 65 years were examined) but was sensitive to the severity of CAD. Older patients, who have more CAD and more severe CAD in particular, had more favorable incremental cost effectiveness ratios than younger ones.

A more recent, but currently unpublished, model developed by Dr. Gillian Sanders and colleagues at the Duke Clinical Research Institute and Stanford includes CT angiography as a testing strategy.[37] This model, which was funded by Blue Cross Blue Shield (BCBS) Technology Evaluation Center, analyzes the effectiveness and cost effectiveness of non-invasive CTA compared with existing non-invasive tests (including exercise electrocardiography, single-photon emission tomography, and echocardiography) or immediate x-ray angiography. Analyses performed using this decision model demonstrate that, given a pre-test probability of 50% prevalence of coronary disease, in each age and gender group studied, proceeding directly to x-ray angiography produced the greatest quality-adjusted life expectancy while also being the most expensive testing strategy. Similarly, for all ages and genders, exercise electrocardiography was the least costly and least effective. The incremental quality-adjusted life expectancy benefit of angiography compared to exercise

electrocardiography ranged from a low of 6.4 days in 45-year old women, to 18.3 days in 65-year old men. CTA had the highest quality-adjusted life expectancy of the non-invasive tests studied and the analysis suggested potential value (in terms of incremental cost effectiveness) of CTA as an alternative to other non-invasive tests and immediate x-ray angiography in select groups of symptomatic patients. Immediate x-ray angiography, although more effective than CTA, only increased quality-adjusted life expectancy by a low of 0.22 days in 45-year old women, to a high of 2.63 days in 65-year old men with an incremental cost effectiveness compared with CTA ranging from $133,400/QALY to $2,202,200/QALY. Notably, for the context evaluated with the model – individuals with a 50% pre-test probability of CAD, and accepting a plausible range of test operating characteristics from the literature as accurate and appropriate – CTA was not projected to provide a better net health outcome (in terms of QALYs) than immediate x-ray angiography.

Question 6a: How confident are you that the diagnostic test characteristics of the test are generalizable to the Medicare beneficiary population.

Only two studies listed in Table 1 have a mean age of 65 or greater. Thus, the data on test performance in the Medicare aged population remains quite limited. Only one of the studies provided an explicit subgroup analysis by age.[20] As the presence of calcium is associated with aging, as expected that for patients over the age of 65, when coronary artery disease is more prevalent and coronary artery calcium is more prevalent

and severe, the operating characteristics of the test may change. Raff et al.[24] noted sensitivity and specificity of 77% and 98% for individual segments when no calcium was noted in the coronary arteries and 93% and 72%, respectively, when severe calcium was present. Mollet[26] also noted a drop in specificity with increasing coronary artery calcium. Burgstahler et al.[20] demonstrate that in an older aged patient cohort (mean age 72 years vs 57 years) the sensitivity for detecting coronary artery stenosis was reduced from 89 to 80% with minimal change in specificity (96% vs 98%). It should be noted that in this study the calcium Agaston scores were not significantly different among the two populations. Stratification of data related to age, clinical pre-test probability of disease, and coronary artery calcium in multicenter large cohort group studies would give added strength to improve confidence of generalization of this technique to the Medicare patient population.

Question 6b: How confident are you that diagnostic and treatment strategies using non-invasive imaging of coronary artery strategies provide a net health benefit to Medicare beneficiaries?

There are no empirical data that examine this question directly. Just as with our response to questions 4 and 5, the answer to this question at present can only be inferred using the limited evidence available on questions 1-3. Assessing the net benefit will require data on the relative risks and benefits of the NITs in a Medicare population. Unfortunately, there are no data on the beneficial effects of the NITs on

clinical decision making and subsequent clinical outcomes. Risks that should be considered in such studies should include direct risks at time of non-invasive coronary evaluation (including metallic risk, risk of contrast and radiation) and the downstream effects of poor test performance, such as unwarranted tests or missed diagnosis.

DISCUSSION

There is limited evidence regarding test performance of NITs for identifying, quantifying, or otherwise characterizing coronary artery stenoses (Key Questions 1, 2, 3, and 6a). Specifically, there is a paucity of prospective studies evaluating NITs in a blinded fashion against the gold standard, x-ray angiography. While there has been reported variability in the quality of the gold standard[10], it is nevertheless accepted in clinical practice as the imaging study to diagnose and manage coronary artery stenosis. The available evidence allows some preliminary judgments on the ability of coronary MRA (1.5 T) and coronary CTA using at least 16-array MDCT technology to detect obstructive coronary artery lesion in the proximal to mid coronary arteries. The evidence regarding detection of coronary lesions in branch vessels or distal coronary arteries remains unclear. There is no direct evidence regarding the clinical utility of NITs in terms of the incremental benefits or risks relative to alternative testing strategies (Key Questions 4, 5, and 6b). Indirect evidence based on modeling studies is also limited; existing analyses suggest that individuals with mid range pretest probability of CAD do not have a net benefit from CTA, but non-invasive testing can lead to more rational application of resources by influencing the use of further tests and treatments.

FUTURE RESEARCH

NIT imaging may be particularly attractive for individuals in whom invasive catheterization holds an exceptionally high risk for complications. This would include patients who have a higher risk of an embolic stroke due to extensive vascular disease in the aorta or endocarditis involving the aortic valve or those who are at high risk for development of a pseudoaneurysm at the site of catheter insertion due to underlying vascular disease. Additionally, potentially, any clinical indication for coronary angiography may be able to be evaluated with NIT, although data to evaluate individual clinical indications will be required.[38]

A variety of management strategies can be envisioned in which NIT imaging serves a gatekeeper role for the use of invasive catheterization. In this situation, invasive angiography will largely serve as a prelude to percutaneous revascularization. NIT imaging would generally not be used after invasive x-ray angiography since, at present, there is no evidence that the NIT provides incremental information.

In order to make a confident assessment of the clinical role of NITs in coronary artery disease, it will be crucial to assess test performance (sensitivity and specificity) with high quality studies in appropriate clinical contexts that extend beyond small, primarily single-center, proof-of-concept studies. In addition to establishing high test operating characteristics, it is essential to evaluate the utility of NITs in representative clinical

settings. While it may be reasonable to assume that good operating characteristics will translate into improved clinical outcomes, this is not necessarily the case. For NITs in coronary artery disease, use of an NIT may have unintended consequences; at the individual level these may result from false positives or negatives, and at the population level these may relate to undesirable changes in practice patterns such as relatively indiscriminate testing in low risk settings.

There are three primary types of evidence that could address the question of substitution of non-invasive for invasive imaging: a randomized trial, an observational study ("natural experiment"), or a decision model.

A randomized trial could take several forms and could use either surrogate or patient-related outcomes. For example, patients with suspected CAD could be randomized to a strategy of "usual diagnostic evaluation," including invasive angiography when indicated, or usual diagnostic evaluation plus option for non-invasive coronary imaging. Alternatively, the patients could be randomized between early invasive and early non-invasive coronary imaging. Outcomes could include hard events such as death or MI, as well as efficiency measures including resource consumption and costs.

A "natural experiment" observational study would examine apparently similar patients referred for alternative diagnostic strategies, including early invasive, early non-invasive coronary imaging, and stress imaging. The notion of a "natural experiment" assumes

that there is an element of randomness in clinical practice that can be exploited analytically. If the use of a technology in the practice community has matured to the point where there is significant confounding with patient characteristics, even advanced statistical adjustment techniques may not suffice to uncover unconfounded outcomes.

A decision model would examine the most likely diagnostic strategies of interest along with predicted health outcomes and resource use. Since there is a high level of dependency of test performance and treatment benefit and harm on clinical context, such considerations would likely require separate models. Further, sensitivity analyses to identify effects on decision thresholds are a central part of such an exercise.

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APPENDIX (Evidence Table)

Evidence Table

Article #	N=	Age mean	Population Consecutive Y or N(no or not stated)	Prospective (Y) or Retrospective (R) or Not Stated (N)	Blinded read (Y) or N (no or not stated	Imaging Technology Scanner Type (CT16, CT64, MRA)*	Image Reconstruction Vendor (V) and/or (S) Standardized or N (Not Stated)	% Images non-diagnostic or N (Not stated)	Gold Standard and % receiving X-Ray Angio (A)	Analysis method: Patient (P) Vessel (V) segment (S) or Both (B)	Reported Sensitivity	Reported Spec.	Reported Harm: Radiation (R), Nephrotoxicity (K), (O) Other or Not Stated (N)	Comment:
Achenbach S, 2005[39]	50	62	Y	Y	Y	CT16 (Siemens)	N	2 patients excluded 4% segs	A – 100%	B	94% (eval segs) 100% (eval pts)	96% (eval segs) 83% (eval pts)	N	> 1.5 mm vessel only, 128 distal segments excluded prior to analysis
Aviram G, 2005[40]	22	57	Y	N	Y	CT16 (Phillips)	S	All segs included	A – 100%	S	86% (all segs)	98% (all segs)	Did include info on anomalous vessel course	14 of 22 patients had CAD, only vessels > 1.5 mm
Bogaert J, 2003[41]	21	62	N	Y	Y	MRA – 1.5T (Phillips)	V	2 patients 29% segs excluded	A – 100%	V	55.5% (eval segs)	83.7% (eval segs)	N	Limited number of visible segments, navigator – free breathing
Burgstahler C, 2005[20]	117	72 and 57	Y	R	Y	CT16 (Siemens)	N	6-B10% of segments not visualized, 11-18% stented or severe calcification, 17% only able to tell if presence or absence of vessel occlusion	A-100%	S	80-89% (eval seg)	96-98% (eval seg)	N	Two groups with mean age of 72 vs 57. Calcium score higher in older age cohort. Sensitivity decreased with age, but no sign difference in specificity. 3 patients overall excluded from lower age group due to technical problems with scan.
Cademartiri F, 2005[42]	126	59	N	R	Y	CT16 (Siemens)	N	Not clear, only > 2 mm segs	A – 100%	B	90% (low Ca) 92% (high Ca)	97% (low Ca) 91% (high Ca)	R – estimated 8 mSv men 13 mSv women	Only > 2 mm segs, cut group into 60 low Ca,60 high Ca without accuracy difference
Cury RC, 2005[43]	29	58	Y	N	Y	CT16 (Siemens)	S	16% of known stenosis from Angio excluded on MDCT	A – 100%	S	Not reports – linear comparison to angio QCA	Not reports – linear comparison to angio QCA	R – do mention dose modulation and reduction in radiation	Evaluation of MDCT to QCA on angio from minor to significant stenosis. 16% known stenosis excluded for calcium/motion artifact
Fine JJ, 2004[44]	50	58	Y	Y	Y	CT16 (Siemens)*	N	2% segments	A – 100%	V	87% (eval segs)	97% (eval segs)	N	Vessels > 1.5 mm only
Fine JJ, 2006[23]	66	62	Y	N	Y	CT64 (Siemens)	N	No exclusions, vessel only analysis	A – 100%	V	95% (by vessel)	96% (by vessel)	N	> 1.5 mm vessels,
Ghersin E, 2006[45]	66	57	Y	Y	Y	CT16 (Phillips)	V	11% pts then 20% segs non-eval	A – 100%	S	80% (eval segs)	89% (eval segs)	N	No beta-blockers, acute chest pain patients, 60% with AMI, prior stents in population
Gulati GS, 2005[46]	31	53	N	R	Y	CT16 (Siemens)*	V	14% segments non-eval.	A – 100%	S	85% (eval seg)	94% (eval seg)	N	> 1.5 mm vessels only, 5 patients with coronary anomalies
Heuschmid M, 2005[47]	37	56	N	N	Y	CT16 (Siemens)*	S	22.1% of segs non-eval	A – 100%	B	59% (eval segs)	87% (eval seg)	N	Sensitivity rose to 93% in patients with lower Ca score (<1000)

Evidence Table

Article #	N=	Age mean	Population Consecutive Y or N(no or not stated)	Prospective (Y) or Retrospective (R) or Not Stated (N)	Blinded read (Y) or N (no or not stated	Imaging Technology Scanner Type (CT16, CT64, MRA)*	Image Reconstruction Vendor (V) and/or (S) Standardized or N (Not Stated)	% Images non-diagnostic or N (Not stated)	Gold Standard and % receiving X-Ray Angio (A)	Analysis method: Patient (P) Vessel (V) segment (S) or Both (B)	Reported Sensitivity	Reported Spec.	Reported Harm: Radiation (R), Nephrotoxicity (K), (O) Other or Not Stated (N)	Comment:
Hoffmann U, 2004[14]	33	57	Y	Y	Y	CT16 (Siemens)	S	17% with restricted quality	A – 100%	B	63% (segs)	96% (segs)	N	Calcification accounted for 94% of False +
Hoffmann MHK, 2005[17]	103	61.5	Y	Y	Y	CT-16 (Phillips)	S	6.4% segments 27% patients with only partial coronary tree coverage	A – 100%	B	95% (segs) 97% (pts)	98% (segs) 87% (all pts)	R – 8.3 mSv ave	Pts sinus rhythm able to breath hold 25 secs; stent segs excluded
Ikonen AEJ, 2003[48]	69	58	N	N	Y	MRA – 1.5T (Siemens)	N	16% segs excluded	A – 100%	V	75% (eval segs)	62% (eval segs)	N	
Kaiser C, 2005[19]	149	63.9	Y	Y	Y	CT16 (Siemens)	N	23% segments poor quality	A – 100%	S	30% (all segs) 86% (all pts)	91% (all segs) 49% (all pts)	N	Large study – analysis in all segs and pts, 34% segs with Calcium, motion artifacts 24% pts
Kefer J, 2005[49]	56	65	N	Y	Y	CT16 (Phillips) and MRA 1.5T (Phillips)	S	6 patients (10%) did not undergo all three tests	A – 100%	B	75% MRA 82% MDCT	77% MRA 79% MDCT	N	Study evaluating both MDCT and MRA to angiogram all in same patients.
Kim WY, 2001[28]	109	59	Y	Y	Y	MRA – 1.5T (Phillips)	N	16% segs excluded	A – 100%	V	100% (eval segs)	85% (eval segs)		Prospective, Multicenter, free-breathing, LM and prox-mid coronaries only
Kuettner A, 2004[50]	60	58	Y	Y	Y	CT16 (Siemens)*	S,V	21% poor image quality	A – 100%	B	72% (all segs)	97% (all segs)	N	Accuracy goes up as high calcium patients excluded
Kuettner A, 2005[51]	72	64	Y	N	Y	CT16 (Siemens)	N	6.6% segs	A – 100%	B	82% (segs)	98% (segs)	N	Mean calcium mass 86
Kuettner A, 2005[21]	124	64.1	Y	Y	Y	CT16 (Siemens)	S	4 patients excluded, 19% poor image quality	A – 100%	S	85% (per patient)	98% (per patient)	N	All segments, analysis only by patient, but for distal vessel segments did not perform well
Leber AW, 2005[25]	59	64	Y	Y	Y	CT64 (Siemens)	V	4/59 (7%) patients non-evaluable images	A – 100%	B	73% (eval segs)	97% (eval segs)	N	Entire tree seen in 55 of 59 patients and used for analysis
Leschka S, 2005[22]	67	60.1	Y	N	Y	CT64 (Siemens)	S	No segs excluded	A – 100%	B	94% (all segs)	97% (all segs)	N	Sinus rhythm, > 1.5 mm vessels
Manning WJ, 1993[52]	39	54	N – only when MRA available	Y	Y	MRA – 1.5T (Siemens)	N	7 vessels excluded	A – 100%	V	90% (eval vessels)	92% (eval vessels)	N	MRI contraindications, two Left coronary systems not evaluated due to time constraints
Martuscelli E, 2004[53]	64	58	N	N	Y	CT16 (GE)	N	16% segs 3 pts excluded	A – 100%	B	89% (evaluable segs) 78% (all segs)	98% (evaluable segs) Not reports all segs	N	All patients B-Blocker, only vessesl >1.5 mm included, 3 pts excluded 1 - HR.70, 2-breath hold

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Mollet NR, 2004[18]	128	58.9	N	Y	Y	CT16 (Siemens)	S	1 pt excluded and stented segs excluded	A – 100%	B	92% (segs) 100% (pt)	95% (segs) 86% (pt)	N	Only vessels > 2 mm, sinus rhythm, pts can hold breath 20sec prior to enrollment, 60% beta-blocker, stented segs excluded
Mollet NR, 2005[54]	51	58.9	N	Y	Y	CT16 (Siemens)	N	All evaluated	A – 100%	B	95% (segs) 100% (pt)	98 (segs) 85% (pt)	N	Only vessels > 2 mm, sinus rhythm, pts can hold breath 20sec prior to enrollment
Mollet NR, 2005[26]	51	59.6	Y	Y	Y	CT64 (Siemens)	S	I patient scan not evaluable	A – 100%	B	99% (eval segs) 100% (eval pt.	95% (eval segs) 92%(eval pts)	N	75% of patients with disease, multivessel in 45% patients, Ca+ agaston >400 in 18 pts
Moon J-Y, 2005[55]	61	59.3	N	Y	Y	CT16 (Siemens)*	N	3 pts (5%) not evaluable	A – 100%	B	85.7% (eval - pts) 80.6% (eval – segs)	91.3% (eval-pts) 93.4% (eval-segs)	N	All got B-Blocker, only Vessels > 2.0 mm,
Morgan-Hughes GJ, 2005[56]	58	61	Y	Y	Y	CT16 (GE)	S,V	1 pt excluded	A – 100%	S	83% (all segs)	97% (all segs)	N	
Muller MF, 1997[57]	35	61	N	Y	Y	MRA – 1.5T (Siemens)	S	5 pts excluded (14%)	A – 100%	S	83% (eval pts)	94% (eval pts)	N	
Muller MF, 2004[58]	30	60	N	N	Y (but not blinded to PTCA location)	MRA – 1.5T (Siemens)	N	15% poor image quality	A – 100%	S	82% (all segs)	85% (all segs)	N	LM and coronaries in 3 segments (prox,mid,dis), all pts with previous PTCA
Nieman K, 2002[59]	59	58	N	N	Y	CT16 (Siemens)*	N	Only looked at main vessel and 2 mm sidebranches	A – 100%	V	95% (vess)	86% (vess)	N	34 patients given additional B-blocker
Raff GL, 2005[24]	70	59	Y	Y	Y	CT64 (Siemens)	N	12% segs not evaluable	A – 100%	B	86% (eval segs) 95% (eval pts)	95% (eval segs) 90% (eval pts)	N	All segments including < 1.5 mm vessels, 26% with Ca+ agaston > 400, BMI>30 reduced accuracy
Regenfus M, 2000[60]	50	60.7	N	N	Y	MRA – 1.5T (Siemens)	V	24.4% segs excluded	A – 100%	P and V	94.4% (eval.pts)	57.1% (eval pts)	N	Only 82% of patients could breath hold for 32-heartbeat sequence
Ropers D, 2003[61]	77	58	Y	N	N	CT16 (Siemens)*	S	12% segs all arteries evaluable in 74% pts	A – 100%	B	85% (pt)	78% (pt)	N	All got B-Blocker, only Vessels > 1.5 mm,
Ropers D, 2006[27]	84	58	N	N	Y	CT64 (Siemens)	V	4% patients and segs non-eval.	A – 100%	B	93% (eval seg) 96% (eval pt)	97% (eval seg) 91% (eval pt)	R Ave. 7.45 mSv men and 10.24 mSv women	> 1.5 mm vessels only

Evidence Table

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Sakuma H, 2005[62]	39	63.9	N	N	N	MRA – 1.5T (Phillips)	S	13% patients non-eval	A – 51%	V	82% (eval pts getting angio)	91% (eval pts getting angio)	N	Only 51% of patients got gold standard angiogram
Sandstede JJ, 1999[63]	30	NA	N	N	Y	MRA – 1.5T (Siemens)	N	23% pts excluded	A – 100%	V	81% (eval pts)	89% (eval pts)	N	Navigator sequence, vessel analysis, no branches, not clear total # excluded
Schuijf JD, 2005[64]	45	63	N	N	Y	CT16 (Toshiba)	S	6% of segs	A – 100%	S	85% (eval-segs)	89% (eval-segs)	N	Study includes grafts and stents along with native coronaries
So NM, 2005[65]	29	60.2	N	Y	Y	MRA – 1.5T (Siemens)	N	19% segs non-eval	A – 100%	V,P	92.8% (eval pt)	95.3% (eval pt)	N	
Van Geuns RJ, 2000[66]	38	(43-72)	N	N	Y	MRA – 1.5T (Siemens)	V	31% segs excluded 4 patients excluded	A – 100%	V	68% (eval pts)	97% (eval pts)	N	Only proximal and mid coronary sections included
Watanabe Y, 2002[67]	12	NA	N	N	Y	MRA – 1.5T (Phillips)	S,V	30% segs poor quality	A – 100%	V	96% (eval segs/pts)	88% (eval seg/pts)	N	Navigator, large number of segs excluded, vessel analysis
Wittlinger T, 2002[68]	25	62.2	N	N	Y	MRA – 1.5T (Siemens)	N	5 pts (20%) excluded then 15% segs poor quality	A – 100%	V	75% (eval segs/pts)	100% (eval segs/pts)	N	Only prox/mid vessel assessment

*= Used a 16 MDCT with a 12x0.75 configuration.