Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Noninvasive Technologies for the Diagnosis of Coronary Artery Disease in Women

Amendment Date: 31 May 2011 (see Section VII for details)

I. Background and Objectives for the Systematic Review

Overview

Cardiovascular disease is the leading cause of mortality for women in the United States.\(^1\) Coronary heart disease—which includes coronary artery (or atherosclerotic) disease (CAD), myocardial infarction (MI), acute coronary syndromes, and angina—is the largest subset of this mortality.\(^1\) According to the American Heart Association (AHA), approximately one in three female adults has some form of cardiovascular disease. Since 1984, the number of deaths attributed to cardiovascular disease in women has exceeded that in men, reaching 454,613 in 2005, more than deaths from all forms of cancer combined.\(^2\) It is estimated that 8.1 million women alive today have a history of heart attack, angina pectoris (chest pain or discomfort caused by reduced blood supply to the heart muscle), or both, and experts predict that this year alone an estimated 370,000 women will have a new or recurrent MI. Overall, women who have had an acute MI—particularly those older than 55 years of age—have a worse prognosis than men, with a greater recurrence of MI and higher mortality.\(^1\) More women (5.5 million) than men (4.3 million) have angina in total numbers. Among women older than 20 years of age, non-Hispanic black women have the highest incidence of angina (6.7%) when compared to non-Hispanic whites (4.3%) and Mexican Americans (4.5%).\(^2\) However, the prevalence of CAD in women with chest pain is about 50 percent, as compared with 80 percent in men, which complicates diagnosis in women.\(^3\)

The AHA suggests that there is evidence showing that women at risk for CAD are less often referred for the appropriate diagnostic test than are men.\(^1\) Coronary anatomy and pathology have traditionally been defined and identified by catheter x-ray angiography, also referred to as coronary angiography.\(^4\) In this invasive procedure, a catheter is inserted into the femoral, brachial, or radial artery and passed up through the aorta to directly engage the right and left coronary arteries; an iodinated contrast agent is then injected into each artery while digital x-ray images are recorded.\(^4\) The major benefits of invasive coronary angiography over noninvasive techniques are that the use of a catheter makes it possible to see the coronary arteries in greater detail and to combine diagnosis and treatment in a single procedure. The limitations of the procedure include the skill of the interventionist and the inability to provide data on the functional impact of a luminal obstruction. These limitations are generally considered to be minor.
when compared with the benefits of the procedure, and coronary angiography is now the standard for clinical care of patients who have chest pain suggestive of CAD.

Coronary angiography, however, is not risk free. Arterial bleeding can occur at the access site, and manipulation of the catheter within the aorta and coronary arteries may cause an atherosclerotic embolus that, in turn, could result in stroke or heart attack. Separation of material from the inner lining of the artery may also cause a blockage downstream of the catheter tip. The contrast agent used during the procedure to visualize the coronary arteries may cause anaphylaxis or renal impairment or injury, and there is radiation exposure during the digital x-ray imaging. Although it is a rare occurrence, the catheter can puncture an artery and cause internal bleeding.

Coronary angiography is generally indicated in patients who have chest pain and are at high risk for CAD. For intermediate-risk patients, clinicians have a wide range of noninvasive diagnostic modalities to choose from, with wide variability in reported sensitivities and specificities. Noninvasive technologies (NITs) are especially important options for patients who have contraindications to invasive catheterization or for those who would be put at higher risk for complications with invasive screening. Included patients would be those who have a higher risk of an embolic stroke because of extensive vascular disease in the aorta, those with endocarditis involving the aortic valve, and those who are at high risk for developing a pseudoaneurysm at the site of catheter insertion because of underlying vascular disease.4

NITs include:

- Exercise/stress electrocardiogram (ECG)
- Resting ECG technology
- Exercise/stress echocardiography (ECHO) with or without a contrast agent
- Exercise/stress radionuclide myocardial perfusion imaging (including single proton emission computed tomography [SPECT] and positron emission tomography [PET])
- Cardiac perfusion and stress magnetic resonance imaging (CMR)
- Multidetector cardiac computed tomography angiography (CTA)

The AHA and the American College of Cardiology (ACC) recommend that women with suspected CAD should be classified as symptomatic or asymptomatic and further classified as being at low, intermediate, or high risk for the disease to guide the decision about which diagnostic test to use first.1 In 2005, the AHA developed a consensus statement on the role of noninvasive testing in the clinical evaluation of women with suspected CAD. In summary, the AHA recommends that women who are symptomatic and at intermediate to high risk of having CAD should undergo noninvasive diagnostic studies (i.e., exercise electrocardiography and cardiac imaging studies), and that those who are asymptomatic and at low-risk of CAD should not undergo cardiac imaging studies.1

Treadmill testing with exercise ECG is the oldest and most commonly used form of stress testing. It is widely available and has low initial costs. According to joint AHA and ACC guidelines, women should undergo exercise testing if they have an intermediate
risk of CAD on the basis of symptoms and risk factors. Factors that are unique to women (such as hormonal factors) have been reported to induce ECG changes during exercise that diminish the accuracy of the test. ECG changes alone may not provide adequate prognostication. Exercise ECG has been recognized in the literature as being less sensitive and specific for diagnosing obstructive CAD in women than in men. Additional factors may improve the accuracy of the exercise test, such as chronotropic and hemodynamic responses to exercise. Despite sex-specific limitations, existing ACC/AHA guidelines propose that evidence of sex-specific limitations is insufficient to remove the stress exercise ECG test as the initial test for symptomatic women at intermediate risk for CAD who have normal resting ECG results and are capable of exercise. The AHA asserts that integrating other parameters into exercise scores (e.g., the Duke Treadmill Score, the ST/heart rate index) may improve the predictive value in women and that a positive ECG result in women indicates that further diagnostic tests are necessary.

Another ECG-based test is the newly developed Multifunction Cardiogram® (MCG; Cardiac Analytics, Powell, OH). With this resting ECG technology, patients are tested while lying in a supine position. From the MCG machine, five ECG wires with electrodes are attached to the patient at the four standard limb-lead and precordial-lead V5 positions. An automatic simultaneous 2-lead (leads V5 and II) ECG sampling is recorded for 82 seconds with amplification and digitization, and the ECG data are then transmitted to a data center via an encrypted Internet connection. Results are then compiled into a report that can be reviewed on the MCG unit itself or on any computer that has a Web browser. At present, this device is not widely available.

Exercise/stress ECHO is another noninvasive method for diagnosing CAD that provides information on the presence of left ventricular systolic or diastolic dysfunction, valvular heart disease, and the extent of infarction and stress-induced ischemia (defined as new or worsening wall-motion abnormalities). Exercise ECHO can be performed by using a treadmill or an upright bicycle. In patients who cannot exercise, dobutamine is the most commonly used pharmacological stress agent. Vasodilator stress ECHO uses dipyridamole or adenosine. The AHA asserts that exercise/stress ECHO provides significantly higher specificity and accuracy for diagnosing obstructive CAD in women than does standard exercise ECG testing. Exercise/stress ECHO is recommended for women who are symptomatic and are at intermediate to high risk of CAD (women with suspected CAD must also have abnormal results from resting ECG), and dobutamine stress ECHO is recommended for women with a normal or abnormal ECG results who are incapable of exercise. The significant advantages of stress ECHO over ECG are superior diagnostic performance, ability to localize areas of ischemia, and the option of performing stress testing on patients who are unable to exercise. According to a recent review, the overall sensitivities for exercise/stress ECHO are reported to be slightly worse in women than in men, although the specificities appear to be comparable for both.

Exercise/stress myocardial perfusion imaging, which includes SPECT, PET, and scintigraphy, is a nuclear-based technique that uses a combination of test elements to diagnose CAD. Of the imaging modalities, SPECT is the most commonly performed
stress imaging test in the U.S., especially for men and women who are unable to exercise.\textsuperscript{1} Recently, the use of stress PET has increased. Parameters included in this modality are perfusion defects, global and regional left ventricular function, and left ventricular volumes. This modality has been found to have technical limitations in women, including false-positive results because of breast attenuation and a small left ventricular chamber size; however, recent advances have improved its accuracy.\textsuperscript{1} SPECT imaging is recommended for symptomatic women with an intermediate to high risk of CAD.\textsuperscript{1} A higher prevalence of single-vessel CAD among women adversely affects the diagnostic accuracy of this modality (as well as ECHO).\textsuperscript{3}

ECG, ECHO, and perfusion imaging techniques do not provide direct visualization of coronary artery anatomy. They evaluate cardiac electrical activity, 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 need for invasive coronary artery imaging.

Other emerging modalities provide direct visualization of coronary anatomy that is similar to coronary angiography but without invasive catheterization. These include cardiac \textit{computed tomography angiography (CTA)} and \textit{cardiac magnetic resonance imaging (CMR)}.

Recently, the AHA published a scientific statement on CMR and CTA, which is summarized below.\textsuperscript{7} These recommendations are made for the general population and are not specific to women. The AHA states that both tests are suboptimal for patients with atrial fibrillation and other arrhythmias, and image quality may be further reduced by a high body mass index. Overall, the AHA concludes that the potential benefit of noninvasive coronary angiography is likely to be greatest for symptomatic patients who are at intermediate risk for CAD after initial risk stratification, including patients with equivocal stress test results. The AHA does not recommend that CMR or CTA be used to screen for CAD in patients without symptoms; in particular, concerns about the radiation dose limit the use of cardiac CTA in patients who have a very low pretest likelihood of coronary stenoses. At the same time, patients with a high pretest likelihood of coronary stenoses are likely to require intervention and invasive catheter angiography for definitive evaluation. The AHA asserts that the main advantages of CTA, when compared with CMR, are wider availability, higher spatial resolution, and more consistent, shorter examinations with better patient adherence. Advantages associated with CMR include the lack of need for ionizing radiation and an iodinated contrast agent. However, it is not clear whether the diagnostic accuracy or the relative balance of benefits and harms associated with either of these techniques differs between men and women.\textsuperscript{3,8}

Controversies and uncertainties surrounding NIT of CAD for women

Noninvasive diagnosis of CAD in women is particularly challenging for many reasons. Women with chest pain demonstrate a lower prevalence of CAD, and their symptoms are less predictive and more often atypical when compared to those of men.\textsuperscript{3} Additionally, women are often older at the time of initial diagnosis; therefore, age-related
comorbidities limit their tolerance for exercise testing. In summary, many factors affect the accuracy of diagnostic testing for CAD in women, including:

- Lower prevalence of coronary artery disease
- Higher prevalence of nonobstructive CAD (microvascular abnormalities, mitral valve prolapse)
- Less predictive symptomatology
- Limited exercise tolerance because of older age, obesity, and diabetes at initial diagnosis
- Different response to exercise than men
- Lower peak exercise values
- Lesser increase in the left ventricular ejection fraction
- Increase in cardiac output by enhancing end-diastolic volume
- Inappropriate catecholamine release
- Hormonal influences of estrogens mimicking a digitalis-like false-positive ECG response
- Anatomical differences affecting stress test results
- Female breast attenuation artifacts
- Smaller coronary artery size
- Smaller left ventricular chamber size
- Higher prevalence of single-vessel disease
- Poor left ventricular opacification on echocardiography

In addition to all the factors that may affect the accuracy of noninvasive testing in women, there is currently considerable variation in which tests are used and in which order. In the acute care setting, patients are often referred for early invasive coronary angiography as the initial risk stratification test although lower risk patients may be evaluated first with noninvasive testing. After undergoing coronary angiography, some patients may be referred for noninvasive stress testing to define the functional significance of a coronary stenosis (constriction or narrowing) that is borderline in severity or is located such that the risk of treatment is increased. Some cardiovascular experts advocate for a diagnostic strategy that includes both anatomic information (from direct coronary imaging, traditionally performed by using catheter angiography) and functional information collected during exercise or pharmacological stress testing. Currently, there is no reference standard that achieves both of these objectives.

Relevance

The goals of the diagnostic workup for women who have symptoms of chest pain syndrome are to identify CAD with optimal accuracy and establish the basis for instituting preventive and therapeutic interventions. More effective diagnostic strategies are critical for women at risk of CAD because up to 40 percent of initial cardiac events are fatal. The literature suggests that, when compared to men, women are initially diagnosed with more advanced CAD because of the lack of early recognition and management. Therefore, a better understanding of how the accuracy of the many
different noninvasive tests for CAD varies by sex could dramatically improve outcomes for many women.
Nevertheless, the noninvasive testing of women for CAD also raises uncertainty for decisionmakers because invasive coronary angiography has nonnegligible patient risk. It is also costly, requiring expensive equipment and the time and skill of highly trained physicians and support staff. Although the use of noninvasive modalities to minimize the need for invasive procedures offers the possibility of better patient outcomes at less cost, the wide range of diagnostic modalities (each with advantages and disadvantages for their use) make it difficult for clinicians, patients, and payers to determine which test is best or should be covered in a given clinical situation.

II. The Key Questions

The key questions (KQs) were posted on the Effective Health Care Program Web site for public comment from June 15, 2010, to July 13, 2010. Most of the comments received with regard to the strengths and limitations of NIT in women agreed with the content outlined under "Background and Objectives for the Systematic Review." Based on the public comments, the following changes were made to the KQs:

- KQ 1: The use of stress ECHO with or without a contrast agent was added.
- KQ 3: Identification of the treatment option (medical therapy or revascularization) was added.
- KQ 4: Nephrogenic systemic fibrosis was added as an adverse event associated with late-stage chronic kidney disease for patients undergoing CMR.

Other comments were received and considered but not included in the KQs, including the following:

- Add an assessment of the cost-effectiveness of the different NITs. The research team will collect cost-effectiveness data if it is reported, but the scope of this review does not include a cost-effectiveness analysis.
- Define which NIT is appropriate for individual patients given relevant clinical circumstances. Discerning such a definition would be appropriate for a clinical guideline document but does not fit the objective of a comparative effectiveness review (CER).
- Add imaging of the carotid intima-media thickness as a predictor for KQ 2. Coronary calcium scoring has also been shown to be predictive of cardiovascular risk in women who are asymptomatic. However, neither one of these tests is applicable to the symptomatic population under consideration in this project.
The KQs, revised after public comments, are found in the table below.

<table>
<thead>
<tr>
<th>KQ 1: What is the accuracy of one noninvasive technology (NIT) in diagnosing obstructive and nonobstructive CAD when compared to another NIT or to coronary angiography in women with chest pain syndrome?</th>
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<tr>
<td>• Exercise electrocardiogram (ECG) stress test (including resting ECG technology, such as a multifunctional cardiogram)</td>
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<tr>
<td>• Exercise/stress echocardiography (ECHO) with or without a contrast agent</td>
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<tr>
<td>• Exercise/stress radionuclide myocardial perfusion imaging (including single proton emission computed tomography [SPECT] and positron emission tomography [PET])</td>
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<tr>
<td>• Cardiac perfusion and stress magnetic resonance imaging (CMR)</td>
</tr>
<tr>
<td>• Multidetector cardiac computed tomography angiography (CTA)</td>
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</table>

| KQ 2: What are the predictors of diagnostic accuracy (age, race/ethnicity, body size, heart size, menopausal status, functional status, stress modality) of different NITs in women? |

<table>
<thead>
<tr>
<th>KQ 3: Is there evidence that the use of NITs (when compared to other NITs or to diagnostic cardiac catheterization) in women improves:</th>
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</thead>
<tbody>
<tr>
<td>a. Risk stratification/prognostic information?</td>
</tr>
<tr>
<td>b. Decisionmaking regarding treatment options (e.g., revascularization, optimal medical therapy)?</td>
</tr>
<tr>
<td>c. Clinical outcomes (e.g., death, myocardial infarction, unstable angina, hospitalization, revascularization, angina relief, quality of life)?</td>
</tr>
</tbody>
</table>

| KQ 4: Are there significant safety concerns/risks (i.e., radiation exposure, access site complications, contrast agent-induced nephropathy, nephrogenic systemic fibrosis, anaphylaxis, arrhythmias) associated with the use of different NITs to diagnose CAD in women with chest pain syndromes? |

- **Population(s):**
  Adult women (age ≥ 18 years) who present symptoms of chest pain syndrome

- **Interventions:**
  NITs for the diagnosis of obstructive and nonobstructive CAD, including:
  - Exercise ECG stress test
  - Resting ECG technology
  - Exercise/stress ECHO with or without a contrast agent
  - Exercise/stress radionuclide myocardial perfusion imaging (including SPECT and PET)
  - Cardiac perfusion and stress magnetic resonance imaging (CMR)
  - Multidetector cardiac computed tomography angiography (CTA)
• **Comparators**:  
  Another NIT or diagnostic cardiac catheterization

• **Outcomes for each question**:  
  o Primary outcomes—accurate diagnosis of obstructive and nonobstructive CAD  
  o Secondary outcomes:  
    - Risk stratification/prognostic information  
    - Treatment (none, medical therapy, percutaneous coronary intervention, coronary artery bypass surgery)  
    - Clinical outcomes (e.g., death, myocardial infarction, unstable angina, hospitalization, revascularization, angina relief, quality of life)

• **Adverse events**—radiation exposure, access site complications, contrast agent-induced nephropathy, nephrogenic systemic fibrosis, anaphylaxis, and arrhythmias

• **Timing**:  
  Not applicable

• **Setting**:  
  Inpatient or outpatient settings, primarily primary care and cardiology clinics
III. Analytic Framework

Figure 1. Analytic Framework for Noninvasive Technologies for the Diagnosis of CAD in Women

Alternate text: Figure 1 depicts the key questions (KQs) within the context of the PICO (population, interventions, comparators, and outcomes) described elsewhere in this document. In general, the figure shows that the CER will consider the accuracy of one noninvasive diagnostic test (NIT) vs. another or vs. coronary angiography for diagnosing obstructive and nonobstructive coronary artery disease (CAD) in women who have chest pain (KQ 1); various possible predictors of diagnostic accuracy (including age, race/ethnicity, body size, heart size, menopausal status, functional status, and stress modality) of the different NITs in this context (KQ 2); whether the use of NITs improves prognostic information, risk stratification, treatment offered, and clinical outcomes (including myocardial infarction, unstable angina, hospitalization, death, revascularization, angina relief, and quality of life in the population of interest) (KQ 3); and whether there are significant safety concerns or risks (including radiation exposure, access site complications, contrast agent-induced nephropathy, nephrogenic systemic fibrosis, anaphylaxis, and arrhythmias) associated with the use of NITs in this context (KQ 4).
IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

An article will be *included* in the CER if all of the following criteria are met:

- Study population includes women with chest pain syndrome (e.g., exertional dyspnea, shortness of breath, and/or angina) with or without a known diagnosis of CAD; data for women are presented separately from data for men.
- Original data for any of the NITs listed in KQ 1
- Human subjects; adults (age ≥18 years of age)
- English-language articles
- Randomized controlled trials, prospective and retrospective observational studies, or registries
- Study includes a comparison of one NIT to another or to diagnostic cardiac catheterization

An article will be *excluded* if any of the following criteria apply:

- None of the patients have symptomatic chest pain (i.e., an asymptomatic population), or some of the patients have symptomatic chest pain but results are not reported separately for this subgroup
- All patients are known to have CAD and are not being tested for chest pain symptoms (e.g., post-revascularization testing to assess for persistent ischemia)
- All subjects are < 18 years of age, or some subjects are under < 18 years of age but results are not broken down by age
- Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series)
- Study does not include a comparison of one NIT to another, or to diagnostic cardiac catheterization

Given the high volume of English-language publications (including the majority of known important studies), non-English articles will be excluded. It is the opinion of the investigators that the resources required to translate non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.

An article will be identified as a *review* if it is a relevant review article, meta-analysis, or methods article. For all included studies, we will indicate the total number of patients enrolled and longest length (weeks or months) of followup if relevant.
Outcomes of interest

For Key Question 1:
- Sensitivity
- Specificity
- True positive, false negative, true negative, false positive
- Indeterminate or technically inadequate results
- Prevalence

For Key Question 2:
- Predictors include age, race/ethnicity, body size, heart size, menopausal status, functional status, stress modality

For Key Question 3:
- Risk stratification/prognostic information
- Treatment:
  - No treatment needed
  - Medical management
  - Invasive management—revascularization by means of percutaneous coronary intervention or coronary artery bypass graft
- Clinical outcomes:
  - Myocardial infarction
  - Unstable angina
  - Hospitalization
  - Death
  - Revascularization
  - Angina relief
  - Quality of life

For Key Question 4:
- Safety and adverse events—radiation exposure, access site complications, contrast agent-induced nephropathy, nephrogenic systemic fibrosis, anaphylaxis, and arrhythmias—and how these events vary by demographic factors

Sample size

We will not exclude articles based on sample size during the full-text screening but may revisit this decision when performing the full-text abstraction and synthesis.
B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

Our search strategy will use the National Library of Medicine’s medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. In consultation with our research librarians, we will use PubMed, Embase®, and the Cochrane Database of Systematic Reviews for our literature search. Our proposed search strategy for PubMed is included in the Appendix; this strategy will be adapted as necessary to search the other databases. The reference list for identified pivotal articles will be manually hand-searched and cross-referenced against our library, and additional manuscripts will be retrieved. All citations will be imported into an electronic bibliographic database (EndNote® Version X4 or greater; Thomson Reuters, Philadelphia, PA).

In developing this CER, we will apply the rules of evidence and formulation of strength of evidence recommended by the Agency for Healthcare Research and Quality (AHRQ) in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*). In developing this CER, we will apply the rules of evidence and formulation of strength of evidence recommended by the Agency for Healthcare Research and Quality (AHRQ) in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*).9 We will solicit feedback from the Task Order Officer and the Technical Expert Panel throughout our evidence review and will follow the recommended methodology for literature search strategies, inclusion/exclusion of studies in our review, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each key question.

C. Data Abstraction and Data Management

The Duke research team will create data abstraction forms and evidence table templates for abstracting data for the KQs. Based on their clinical and methodological expertise, a pair of researchers will be assigned to abstract data from the eligible articles based on the research questions. One researcher will abstract the data, and the second will read the article and the accompanying abstraction to check for accuracy and completeness. Disagreements will be resolved by consensus, or by obtaining a third reviewer’s opinion if consensus cannot be reached between the first two researchers. Guidance documents will be drafted and given to the researchers as reference material to perform this task, thus aiding in both reproducibility and standardization of data collection.

We will design the data abstraction forms for this project to collect the data required to evaluate the specified eligibility criteria for inclusion in this review as well as collect demographics and data needed to determine outcomes (intermediate outcomes, health outcomes, and safety outcomes). The safety outcomes will be framed to help identify radiation exposure, contrast agent-induced nephropathy, nephrogenic systemic fibrosis, anaphylaxis, and arrhythmias, which are the more common adverse events resulting from the different NITs. Before use, the abstraction form templates will be pilot tested with a sample of included articles to ensure that all relevant data elements are captured and that there is consistency/reproducibility between abstractors. The abstraction forms will be revised as necessary before all of the included studies are abstracted.
D. Assessment of Methodological Quality of Individual Studies

The included studies will be assessed on the basis of the quality of their reporting of relevant data. We will evaluate the quality of individual studies using the approach described in the *Methods Guide*. To assess study quality, we will: (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) make a summary judgment of the study’s quality. To evaluate methodological quality, we will apply criteria for each study type that are derived from the core elements described in the *Methods Guide* and within QUADAS, a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. To indicate the summary judgment of the quality of the individual studies, we will use the summary ratings of good, fair, and poor based on the study’s adherence to well-accepted standard methodologies (such as QUADAS) and adequate reporting standards.

Grading will be outcome-specific; thus, a given study may be graded to be of different quality for two individual outcomes reported within that study. Study design will be considered when grading quality. Randomized controlled trials will be graded as good, fair, or poor. Observational studies will graded separately, also as good, fair, or poor. We anticipate any retrospective studies that are included would be graded as fair or poor.

We will use data abstracted on the population studied, the intervention and comparator, the outcomes measured, settings, and timing of assessments to identify specific issues that may limit the applicability of individual studies or a body of evidence as recommended in the *Methods Guide*. We will use these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison to the target population, the intervention used in comparison with technologies currently in use, and clinical relevance and timing of the outcome measures. We will summarize issues of applicability qualitatively.

E. Data Synthesis

We will summarize the primary literature by abstracting relevant continuous data (e.g., age, sensitivity, specificity, event rates) and categorical data (e.g., race, presence of CAD [yes/no]). Data for patients with no known diagnosis of CAD will be collected and analyzed separately from data for mixed CAD populations including patients with and without known CAD. We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis). The feasibility of a meta-analysis will depend on the volume of relevant literature, the conceptual homogeneity of the studies, and the completeness of the results reporting. When a meta-analysis is appropriate, we will run separate analyses of the accuracy of each NIT modality compared to cardiac catheterization on the no known CAD and mixed CAD populations using random-effects models to quantitatively synthesize the available evidence. We will test for heterogeneity while recognizing that the ability of statistical methods to detect heterogeneity may be limited. For comparison, we will also perform a fixed-effects meta-analysis. We will present summary estimates, standard errors, and confidence intervals.
Most outcomes that we will analyze in this CER are expected to be binary or categorical, and we will therefore summarize these outcomes by proportions. We will summarize inherently continuous variables, such as age, by mean, median, and standard deviation.

We also plan to evaluate the potential of verification bias and other potential limitations of our synthesized analyses based on the underlying clinical domain and diagnostic testing practices. For example, angiography is often administered only to a subset of patients who are undergoing diagnostic tests within a studied population. This subset of patients is not a completely random sample because angiography-based verification of disease is often driven by previous test results and/or other considerations. Verification bias-corrected values of sensitivity and specificity may be computed if predictive values are assumed to be the same in the verified and unverified groups. However, to perform this correction, the proportion of positive tests in the population of interest must be known. Hence, we will record the proportion of positive tests within tested groups if this information is available in the studies reviewed.

To explore additional sources of potential bias, we will also record whether the diagnostic tests were interpreted in a blinded fashion; that is, without knowledge of results of other diagnostic tests or clinical history and risk factors, if such information is available in the reviewed studies.

F. Grading the Evidence for Each Key Question

The strength of evidence for each key question will be assessed by using the approach described in the Methods Guide. The evidence will be evaluated by using the four required domains: risk of bias (low, medium, or high), consistency (consistent, inconsistent, or unknown/not applicable), directness (direct or indirect), and precision (precise or imprecise). Additionally, when appropriate, the studies will be evaluated for the presence of confounders that would diminish an observed effect, the strength of association (magnitude of effect), and publication bias. The strength of evidence will also be assigned an overall grade of high, moderate, low, or insufficient according to the following four-level scale:

**High:** High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate:** Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

**Low:** Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.

**Insufficient:** Evidence either is unavailable or does not permit estimation of effect.
V. References


VI. Definition of Terms

Not applicable.
VII. Summary of Protocol Amendments

Amendment 1, 31 May 2011:

This amendment modifies the literature inclusion/exclusion criteria in Section IV A to clarify that data must be presented for female subjects as a subgroup if the population includes both genders, and to allow inclusion of articles that present pooled data from patient populations with and without a known diagnosis of CAD. The original exclusion criterion required data to be presented for patients without a known diagnosis of CAD. Articles presenting data from populations in which all patients are known to have CAD remain excluded.

The original exclusion criterion that required data to be reported for patients without known CAD limited the literature base in such a way that few studies addressing prognostic/risk stratification, predictors of accuracy, cardiovascular outcomes, and harms met the standards for inclusion. This amendment broadens the body of evidence to allow a more thorough consideration of these elements.

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness Reviews (CERs) the key questions will be posted for public comment and finalized after review of the comments.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report, and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical Briefs, be published three months after the publication of the Evidence Report.

It is our policy not to release the names of the peer reviewers or TEP panel members until
Appendix. Proposed Search Strategy

Patient Problem/Population:

Chest pain OR dyspnea OR shortness of breath OR angina

OR

(CAD[tiab]) OR (coronary artery disease[mesh] OR "coronary artery disease"[tiab] OR coronary disease[mesh] OR "coronary disease"[tiab] OR "coronary heart disease"[tiab])

+ Comparisons:

6 groups of terms. Strategy involves ANDing each with any of the other 5 to require comparison, then ORing all resulting sets together to include articles about any of the resulting comparisons.

Echo = (echocardiography OR echo OR cardiogram)

Exercise ECG = (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill)

Nuclear (SPECT and/or PET) = (single photon emission computed tomography OR SPECT OR positron emission tomography OR “PET” OR myocardial perfusion imaging OR “nuclear scan” or radionuclide imaging)

CTA – ((cardio* OR heart OR coronary OR cardiac) AND "Tomography, X-Ray Computed"[Mesh]) OR ("CT angiography" OR CTA OR "Cardiac Computed Tomography" OR MSCT OR Multislice computed tomography OR Multi-slice computed tomography OR MDCT OR multidetector computed tomography OR multi-detector computed tomography OR "cardiac CT" OR "Cardiovascular CT")

MRI/MRA = ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA))

Cath – (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR “X-ray angiography” OR “Xray angiography”)

+ Female:

women OR woman OR female OR females OR sex factors

+ Diagnosis:

/diagnosis OR diagnos* OR predict* OR predictive value of tests OR sensitivity OR specificity OR (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *
Limits:
NOT Editorials, letters, case reports
NOT Animals [mesh:noexp]
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