Effective Health Care Program

Future Research Needs Paper
Number 41

Noninvasive Technologies for the Diagnosis of Coronary Artery Disease in Women: Future Research Needs

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Number 41

Noninvasive Technologies for the Diagnosis of Coronary Artery Disease in Women: Future Research Needs

Identification of Future Research Needs From Comparative Effectiveness Review No. 58

Prepared for:
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This report is based on research conducted by the Duke Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10066-I). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

An important part of evidence reports is to not only synthesize the evidence, but also to identify the gaps in evidence that limited the ability to answer the systematic review questions. AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that is needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

We welcome comments on this Future Research Needs document. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Executive Summary

Background

Cardiovascular disease is the leading cause of mortality for women in the United States.[1] According to the American Heart Association (AHA), approximately one in three female adults have some form of cardiovascular disease. AHA suggests there is evidence showing that women at risk for coronary artery disease (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 coronary angiography, a procedure that is 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 technologies (NITs) to choose from that can assess functional status (i.e., ischemia or no ischemia) or visualize anatomic abnormalities (i.e., no CAD, nonobstructive CAD, or obstructive CAD). Functional modalities include stress electrocardiography (ECG); stress echocardiography (ECHO); and stress radionuclide myocardial perfusion imaging, including single-proton emission computed tomography (SPECT) and positron emission tomography (PET). Anatomic modalities include stress myocardial perfusion and wall-motion cardiac magnetic resonance (CMR) imaging and coronary computed tomography angiography (coronary CTA). The comparative safety and accuracy of these NITs in women was uncertain, although substantial data exists for populations combining men and women, and for mixed populations of known and no known CAD.

In 2012, a Comparative Effectiveness Review (CER), "Noninvasive Technologies for the Diagnosis of Coronary Artery Disease in Women," evaluated the diagnostic accuracy and risks of NITs in women with symptoms suspicious for CAD, including assessing predictors affecting test accuracy, and the ability of NITs to provide risk stratification and prognostic information, inform decisionmaking about treatment options, and affect clinical outcomes.[2]

A total of 104 comparative studies (110 articles) were included. For women with no known CAD, the summary of accuracy for each NIT modality compared with coronary angiography was ECG (29 studies): sensitivity 62 percent, specificity 68 percent; ECHO (14 studies): sensitivity 79 percent, specificity 83 percent; SPECT (14 studies): sensitivity 81 percent, specificity 78 percent; CMR (5 studies): sensitivity 72 percent, specificity 84 percent; and CTA (5 studies): sensitivity 94 percent, specificity 87 percent. Compared with men evaluated in the same studies, in women ECG and coronary CTA modalities were both less sensitive and less specific. The ECHO and SPECT modalities, although less sensitive, appeared to be more specific in women. The lower specificity of the ECG modality in women was the only statistically significant difference. Strength of evidence was high for ECG, ECHO, and SPECT, and was low for CMR and coronary CTA compared with coronary angiography in women. Eleven comparative studies examined predictors of diagnostic accuracy in women such as postmenopausal status, race/ethnicity, heart size, beta blocker use, and pretest probability; insufficient evidence was available to draw conclusions about predictors that affect accuracy. Eight studies assessed risk stratification and prognostic factors, two studies assessed treatment decisionmaking, and four studies provided comparative clinical outcomes but provided insufficient evidence on the comparative effectiveness of NITs to provide risk stratification, prognostic information, treatment decisionmaking, or impact on clinical outcomes in women. Thirteen comparative studies reported risks. Of these, four studies of coronary CTA showed a higher mean effective radiation dose and attributable risk of cancer incidence in women compared with men; however, radiation safety issues were not discussed in other NIT modalities with radiation exposure. Thus,

there was insufficient evidence regarding the comparative risks of various NIT modalities in women.

Given the clinical and economic importance of noninvasive testing for CAD in women, the ongoing investment in NIT research, and the remaining areas of uncertainty, we sought to create a prioritized research agenda that would represent the interests of diverse stakeholders and allow the remaining areas of uncertainty to be addressed.

Analytic Framework

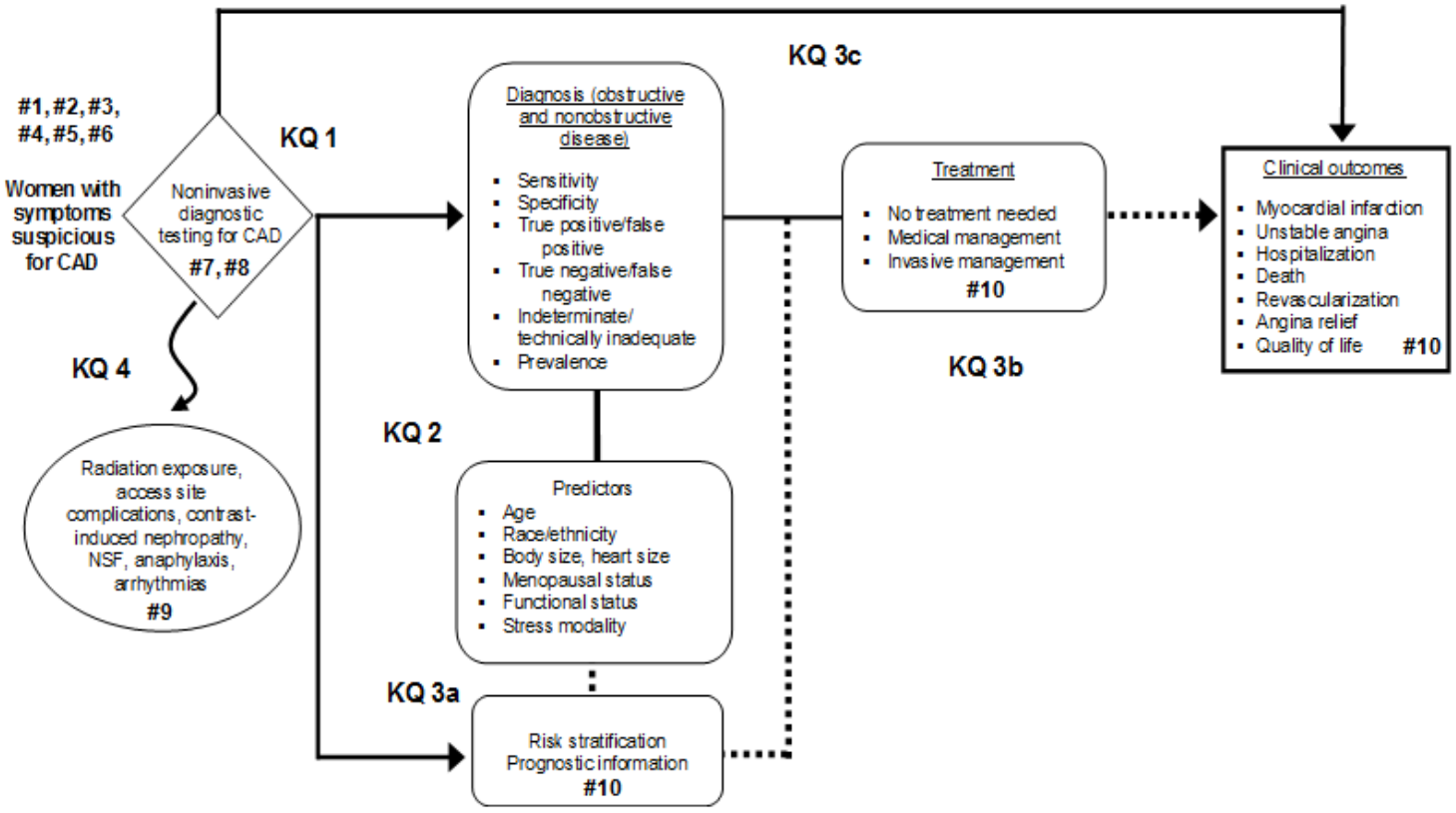
We mapped the initial list of research needs developed by the CER study authors (Table A) into an analytic framework as depicted in Figure A. The Key Questions from the CER are organized within the context of the population, interventions, comparators of interest, and outcomes (PICO) and are displayed accordingly in the analytic framework.

Table A. Initial list of evidence gaps

PICO Element	Evidence Gaps
Population	1. Does the comparative accuracy of NITs in women vary based on the pretest probability of CAD of the women undergoing the test? How does the pretest probability of CAD impact the findings on clinical decisionmaking? 2. Does the comparative accuracy of NITs in women vary based on differing symptomology and timing at presentation? 3. Does the comparative accuracy of NITs in women vary based on racial/ethnicity differences? 4. Does the comparative accuracy of NITs in women vary based on patient risk profiles? 5. Does the comparative accuracy of NITs in women vary based on different settings (outpatient, inpatient, emergency room)? 6. Does the comparative accuracy of NITs in women vary based on age?
Intervention and comparator	7. What is the comparative safety and accuracy of functional vs. anatomic NIT modalities? 8. What is the comparative safety and accuracy of functional NIT testing strategies with and without imaging?
Outcome	9. What are the potential harms of NITs? 10. What is the impact of NIT modalities on outcomes beyond diagnostic accuracy (risk stratification, prognostic information, treatment decisions, and clinical outcomes)?

CAD = coronary artery disease; NIT = noninvasive technology

Figure A. Analytic framework



CAD = coronary artery disease; KQ = Key Question; NSF = nephrogenic systemic fibrosis
Note: #1 to #10 represent the evidence gaps outlined in Table A.

Methods

Our approach to identifying evidence gaps, prioritizing future research, and developing recommendations for stakeholders is outlined in the following steps:

1. Develop an analytic framework from the original CER in order to understand the clinical and policy context of the review and its initial list of Future Research Needs.
2. Create an initial list of evidence gaps based on the CER organized according to the population, interventions, comparators, and outcomes (PICO) framework.[3]
3. Form a stakeholder group representing appropriate clinician, policymaker, and patient perspectives.
4. Expand the list of evidence gaps based on stakeholder input.
5. Perform an updated review of published literature since the last CER (search last updated in September 2011) and a horizon scan for recently published and ongoing studies that may address the evidence gaps, but which are not included in the current CER.
6. Solicit stakeholder prioritization of the identified research gaps based on the updated literature review.
7. Determine the most appropriate study designs for the highest priority research areas.

Stakeholders were selected to include a broad range of stakeholder perspectives, including researchers involved in some of the primary randomized controlled trials (RCTs) included in the

CER, other clinical experts and researchers in the content area, representatives from Federal and nongovernmental funding agencies, representatives from relevant professional societies, health care decision- and policymakers, and representatives from related consumer and patient advocacy groups. We started with the research priorities identified in the original CER and then, based on input from the stakeholder workgroup during the first call, we ultimately expanded the list of research priorities from a list of 10 to a total of 19.

We performed three database searches to identify ongoing and recently published studies relevant to the identified evidence gaps. These included a search of ClinicalTrials.gov, an update of the PubMed, Embase, and Cochrane searches used in the original CER, and a search of PubMed® for relevant systematic reviews that may address the evidence gaps considered out of scope in the original review. Based on these searches, a document was created listing all included articles and clinical trials that might pertain to the 19 listed evidence gaps.

The stakeholders were provided with the AHRQ Effective Health Care Program "Framework for Considering Study Designs for Future Research Needs,"[4] and were instructed to use these criteria as the basis for their decisions regarding research prioritization. The stakeholders performed two online rankings of the identified research priorities (including the additional priorities identified by the stakeholder team). This ranking utilized a forced-ranking prioritization method, whereby participants were given 7 votes to allocate to any of the 19 research priorities, with a maximum of 3 votes per item.

For the top-tier Future Research Needs, we considered potential study designs and their advantages and disadvantages.[4] While these proposed methods to address each area are not intended to be restrictive of potential study designs, we comment on each design's potential benefits or limitations for answering these questions.

Results

Based on the Comparative Effectiveness Review "Noninvasive Technologies for the Diagnosis of Coronary Artery Disease in Women,"[2] and our discussion with stakeholders, we identified 19 potential research areas. The stakeholder voting identified the seven highest priority areas for future research, and these results were consistent over two separate prioritization exercises. The research priorities are shown in Table B.

Table B. Final ranking of Future Research Needs for noninvasive technologies for the diagnosis of CAD in women

Tier	Question	Score
Top Tier	What is the impact of NIT modalities on outcomes beyond diagnostic accuracy (risk stratification, prognostic information, treatment decisions, and clinical outcomes)?	14
	*Are women getting the same diagnostic testing as men? Are men over-tested and/or women under-tested?**	10
	What is the comparative accuracy in real-world settings? (most of the studies were single center, best-quality/high expertise centers)	8
	Does the comparative accuracy of NITs in women vary based on the pretest probability of CAD of the women undergoing the test? How does the pretest probability of CAD impact the findings on clinical decisionmaking?	7
	*What is the comparative effect of NIT modalities on utilization, further testing, and impact on cost?**	6
	Does the comparative accuracy of NITs in women vary based on patient risk profiles?	5
	*Is there a sequential order in which NITs should be used for evaluating CAD (i.e., multiple testing or layered-testing strategies)?**	5
Middle Tier	What is the comparative safety and accuracy of functional vs. anatomic NIT modalities?	4
	What is the comparative safety and accuracy of functional NIT testing strategies with and without imaging?	4
	*How would a better understanding of provider diagnostic ordering patterns and understanding of appropriate use guidelines to support evidence-based decisionmaking impact the use of NITs?**	3
	Does the comparative accuracy of NITs in women vary based on differing symptomology and timing at presentation?	2
	Does the comparative accuracy of NITs in women vary based on racial/ethnicity differences?	2
	*What is the value of performing a specific NIT test for the diagnosis of CAD in women, compared with no testing?**	2
	Does clinician preference, availability, or setting (outpatient vs. *chest pain unit of an emergency department) impact NIT use?**	2
Lower Tier	*Does the comparative accuracy of NITs in women vary based on different settings (outpatient, inpatient, emergency room)?**	1
	Does the comparative accuracy of NITs in women vary based on: body size, heart size, menopausal status, functional status, stress modality?	1
	*How does patient preference of testing factor into decisionmaking?**	1
	Does the comparative accuracy of NITs in women vary based on age?	0
	What are the potential harms of NITs?	0

CAD = coronary artery disease; NIT = noninvasive technology
*Out-of-scope research topics are highlighted in italics.

Discussion

The recommendations for future research prioritization of NITs in this report represents the perspectives of a broad range of stakeholders, including researchers involved in some of the primary RCTs included in the CER, other clinical experts and researchers in the content area, representatives from Federal and nongovernmental funding agencies, representatives from relevant professional societies, health care decision- and policymakers, and representatives from related consumer and patient advocacy groups. The top tier of seven research priorities remained stable between our first and second prioritization exercise. These areas represent three primary foci: (1) clinical decisionmaking (i.e., risk stratification/profiles, pretest probability, prognostic information, treatment decisions,); (2) long-term clinical outcomes (i.e., revascularization and cardiovascular events); and (3) implementation and generalizability (i.e., accuracy and utilization in real world settings, appropriate test ordering, multiple testing or layer-testing strategies).

The stakeholder group identified and prioritized several topics that were out of the scope of the original review, primarily regarding how these tests are being used in actual practice. This

suggests a need for more descriptive data to complement trial accuracy data. Although our original search strategy could have identified studies that addressed several of these topics, many of the questions represent ones where the outcomes of interest were not specifically targeted within our review or for which the current published literature largely depends on noncomparative studies. As such, our current systematic review did not allow us to summarize the strength of the available evidence for these questions. The expansion of topics promotes consideration of new areas of research that have not been adequately explored. This is evidenced by the literature scan in this report, which was only able to identify articles or trial records for one of the eight out-of-scope topics. Nevertheless, the original CER did not comment on the state of current research in these out-of-scope areas, and they should only be promoted with the caveat that the existing literature may already adequately address these areas.

Conclusions

A workgroup of 11 stakeholders identified the following 7 research areas as the highest priority for future research for the comparative effectiveness of NITs for the diagnosis of CAD in women.

1. What is the impact of NIT modalities on outcomes beyond diagnostic accuracy (risk stratification, prognostic information, treatment decisions, and clinical outcomes)?
    a. Recommended study design: large, long-term clinical trial would be preferable, if not possible then an observational study could be informative
2. *Are women getting the same diagnostic testing as men? Are men overtested and/or women undertested?* (This is an out-of-scope research topic.)
    a. Recommended study design: systematic review of the evidence, potentially followed by either modeling of existing observational studies and administrative datasets to explore whether women with similar characteristics to men are getting tested or development of a new observational study to explore this gap
3. What is the comparative accuracy in real world settings? (most of the studies were single center, best-quality/high-expertise centers)
    a. Recommended study design: systematic review of the evidence, potentially followed by national or broad registry for imaging for common indications exploring findings within real-world settings
4. Does the comparative accuracy of NITs in women vary based on the pretest probability of CAD of the women undergoing the test? How does the pretest probability of CAD impact the findings on clinical decisionmaking?
    a. Recommended study designs: an observational study of patients with varying pretest probabilities of CAD
5. *What is the comparative effect of NIT modalities on utilization, further testing, and impact on cost?* (This is an out-of-scope research topic.)
    a. Recommended study design: systematic review of the evidence, potentially followed by either a new RCT or observational study if systematic review reveals that this information is not available from analysis of existing data sources
6. Does the comparative accuracy of NITs in women vary based on patient risk profiles?
    a. Recommended study design: an observational study of patients with varying patient risk profiles.

7. *Is there a sequential order in which NITs should be used for evaluating CAD, i.e. multiple testing or layered-testing strategies?* (This is an out-of-scope research topic.)
    a. Recommended study design: systematic review of the evidence, potentially followed by either new RCT or observational studies with a focus on sequential ordering of NITs.

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Background

Cardiovascular disease is the leading cause of mortality for women in the United States.[1] According to the American Heart Association (AHA), approximately one in three female adults have some form of cardiovascular disease. AHA suggests there is evidence showing that women at risk for coronary artery disease (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 coronary angiography, a procedure that is 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 technologies (NITs) to choose from that can assess functional status (i.e., ischemia or no ischemia) or visualize anatomic abnormalities (i.e., no CAD, nonobstructive CAD, or obstructive CAD). Functional modalities include stress electrocardiography (ECG); stress echocardiography (ECHO); and stress radionuclide myocardial perfusion imaging, including single-proton emission computed tomography (SPECT) and positron emission tomography (PET). Anatomic modalities include stress myocardial perfusion and wall-motion cardiac magnetic resonance (CMR) imaging and coronary computed tomography angiography (coronary CTA). The comparative safety and accuracy of these NITs in women was uncertain.

In 2012, a Comparative Effectiveness Review, "Noninvasive Technologies for the Diagnosis of Coronary Artery Disease in Women," evaluated the diagnostic accuracy and risks of NITs in women with symptoms suspicious for CAD, including assessing predictors affecting test accuracy, and the ability of NITs to provide risk stratification and prognostic information, inform decisionmaking about treatment options, and affect clinical outcomes.[2] The CER addressed the following four Key Questions (KQs):

KQ 1. What is the accuracy of one NIT in diagnosing obstructive and nonobstructive CAD when compared with another NIT or with coronary angiography in women with symptoms suspicious for CAD?

- Exercise ECG stress test, including resting ECG technology (e.g., multifunctional cardiogram)
- Exercise/stress ECHO with or without a contrast agent
- Exercise/stress radionuclide myocardial perfusion imaging, including SPECT and PET
- CMR imaging
- Coronary CTA

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

KQ 3. Is there evidence that the use of NITs (when compared with other NITs or with coronary angiography) in women improves:

- **KQ 3a.** Risk stratification/prognostic information?
- **KQ 3b.** Decisionmaking regarding treatment options (e.g., revascularization, optimal medical therapy)?
- **KQ 3c.** Clinical outcomes (e.g., death, myocardial infarction, unstable angina, hospitalization, revascularization, angina relief, quality of life)?

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 symptoms suspicious for CAD?

A total of 104 comparative studies (110 articles) were included. For women with no known CAD, the summary of accuracy for each NIT modality compared with coronary angiography was ECG (29 studies): sensitivity 62 percent, specificity 68 percent; ECHO (14 studies): sensitivity 79 percent, specificity 83 percent; SPECT (14 studies): sensitivity 81 percent, specificity 78 percent; CMR (5 studies): sensitivity 72 percent, specificity 84 percent; and CTA (5 studies): sensitivity 94 percent, specificity 87 percent. Compared with men evaluated in the same studies, in women ECG and coronary CTA modalities were both less sensitive and less specific. The ECHO and SPECT modalities, although less sensitive, appeared to be more specific in women. The lower specificity of the ECG modality in women was the only statistically significant difference. Strength of evidence was high for ECG, ECHO, and SPECT, and low for CMR and coronary CTA compared with coronary angiography in women. Eleven comparative studies examined predictors of diagnostic accuracy in women such as postmenopausal status, race/ethnicity, heart size, beta blocker use, and pretest probability; insufficient evidence was available to draw conclusions about predictors that affect accuracy. Eight studies assessed risk stratification and prognostic factors, two studies assessed treatment decisionmaking, and four studies provided comparative clinical outcomes. There is insufficient evidence on the comparative effectiveness of NITs to provide risk stratification, prognostic information, treatment decisionmaking, or impact on clinical outcomes in women. Thirteen comparative studies reported risks. Of these, four studies of coronary CTA showed a higher mean effective radiation dose and attributable risk of cancer incidence in women compared with men; however, radiation safety issues were not discussed in other NIT modalities with radiation exposure. Thus, there was insufficient evidence regarding the comparative risks of various NIT modalities in women. Summary of the evidence and findings are shown in Table 1.

Table 1. Summary of key findings

Key Question	Strength of Evidence	Conclusions
KQ 1. Diagnostic accuracy of NITs in women	ECG: High ECHO: High SPECT: High CMR: Low Coronary CTA: Low	94 studies described the diagnostic accuracy of NITs in comparison to another NIT or coronary angiography in women. Of these 94 studies, 78 studies included sufficient data to estimate the sensitivity and specificity of the NIT compared with coronary angiography. Summary from all studies with no known CAD: • 41 studies (13 good quality, 22 fair, 6 poor) of exercise ECG showed a summary sensitivity of 62% and specificity of 68% • 22 studies (8 good quality, 13 fair, 1 poor) of exercise/stress ECHO showed a summary sensitivity of 79% and specificity of 83% • 30 studies (10 good quality, 15 fair, 5 poor) of exercise/stress radionuclide perfusion imaging (SPECT, PET) showed a summary sensitivity of 81% and specificity of 78% • 6 studies (5 good quality, 1 fair) of CMR imaging showed a summary sensitivity of 72% and specificity of 84% • 8 studies (4 good quality, 4 fair) of coronary CTA showed a summary sensitivity of 93% and specificity 77% Overall, within a given modality, the summary sensitivities and specificities were similar for both types of populations (unknown CAD and mixed known and no known CAD) and for all studies when compared with good-quality studies. For the newer technologies (i.e., coronary CTA and CMR), more studies in women would be needed to support these findings since the 95% CIs were quite wide. In testing for a statistically significant difference between the diagnostic accuracy of testing modalities in women, our analyses determined that for women with no previously known CAD, there were differences between the performance of the available modalities ($p < 0.001$). The sensitivity of ECHO and SPECT was significantly higher than that of ECG. Specificity of ECG was less than that of CMR (borderline) and of ECHO. In the subset of studies that were good-quality and where there was no known CAD in the included population, our analyses again demonstrated differences between performance of tests ($p = 0.006$) with the specificity of ECG being less than that of CMR and ECHO. Sensitivity analyses exploring mixed populations of women with known and no known CAD showed no statistically significant difference in the sensitivities and specificities from our primary analysis. An analysis exploring the prevalence of CAD across the different NIT modality studies also showed no statistically significant difference. In addition, there were very few studies (1 SPECT, 1 ECHO, and 3 ECG) that did not complete a coronary angiography in all patients who underwent the NIT; therefore the results are minimized for verification bias. Finally we found no evidence of publication bias across the different modalities in our 4 populations of interest (studies of women with no known CAD, good quality studies of women with no known CAD, studies of women from mixed populations, and good quality studies of women from mixed populations).

Table 1. Summary of key findings (continued)

Key Question	Strength of Evidence	Conclusions
KQ 2. Predictors of diagnostic accuracy in women	Insufficient	11 studies (4 good quality, 5 fair, 2 poor) described diagnostic accuracy, and 9 of these examined predictors of diagnostic accuracy of different NITs in women. Summary: • The predictors assessed included (1) postmenopausal women ages 55 to 64 (1 study), (2) race/ethnicity (2 studies), (3) heart size (4 studies), (4) pretest probability (3 studies), and (5) use of beta blocker medications (1 study). • We identified no studies examining the influence of age alone, functional status, or body size on diagnostic accuracy in women. • In terms of the NIT modality, we found four studies of stress ECHO, six studies of stress ECG, two studies of CMR, and four studies of SPECT that reported these predictors. • Insufficient evidence was available to draw definitive conclusions about predictors given the small number of studies for each predictor and for each modality, as well as the combination of predictor by modality.
KQ 3. Improving risk stratification, decisionmaking, and outcomes in women	Insufficient	13 studies (3 good quality, 9 fair, 1 poor) reported prognostic, outcome, or decisionmaking data comparing one NIT with another NIT or with coronary angiography in women with symptoms suspicious for CAD. Summary: • We found 8 studies assessing risk stratification and prognostic information, 2 studies assessing decisionmaking for treatment options, and 4 studies that provided comparative clinical outcomes. • There were insufficient data to demonstrate that the use of specific NITs (compared with coronary angiography) routinely provided incremental risk stratification, prognostic information, or other meaningful information to improve decisionmaking and improve patient outcomes. • Most findings reported in the literature would require significant confirmation and replication in larger studies with women.
KQ 4. Safety concerns	Insufficient	13 studies (9 good quality, 4 fair) reported data pertinent to safety concerns or risks associated with the use of NITs to diagnose CAD in women with symptoms suspicious for CAD. Summary: • Safety data were reported on the following modalities: (1) stress ECG (4 studies), (2) ECHO (6 studies), (3) SPECT (3 studies), (4) CMR (2 studies), and (5) coronary CTA (4 studies). • Data specific to women on access site complications, contrast agent-induced nephropathy, nephrogenic systemic fibrosis, or anaphylaxis associated with NITs were not reported in any of the studies included in this report. • Other than higher mean effective radiation doses for coronary CTA studies for women compared with men (from 3 out of 4 studies reporting radiation exposure levels), the extant literature does not provide sufficient evidence to conclude whether safety concerns, risks, or radiation exposure associated with different NITs to diagnose CAD in patients with suspected CAD differ significantly between women and men.

CAD = coronary artery disease; CI = confidence interval; CMR = cardiac magnetic resonance; CTA = computed tomography angiography; ECG = exercise/stress electrocardiogram; ECHO = echocardiogram; KQ = Key Question; NIT = noninvasive technology; PET = positron emission tomography; SPECT = single-proton emission computed tomography

The weaknesses and shortcomings of the evidence base identified during the review confirmed that more research is needed. AHRQ supports our Evidence-based Practice Center (EPC) to work with various stakeholders to identify and prioritize the future research that is most needed by decisionmakers. Given the clinical and economic importance of noninvasive testing for CAD in women, the ongoing investment in NIT research, and the remaining areas of uncertainty, we sought to create a prioritized research agenda that would represent the interests of diverse stakeholders and allow the remaining areas of uncertainty to be addressed. This report is a summary of that process and our findings.

Methods

Overview

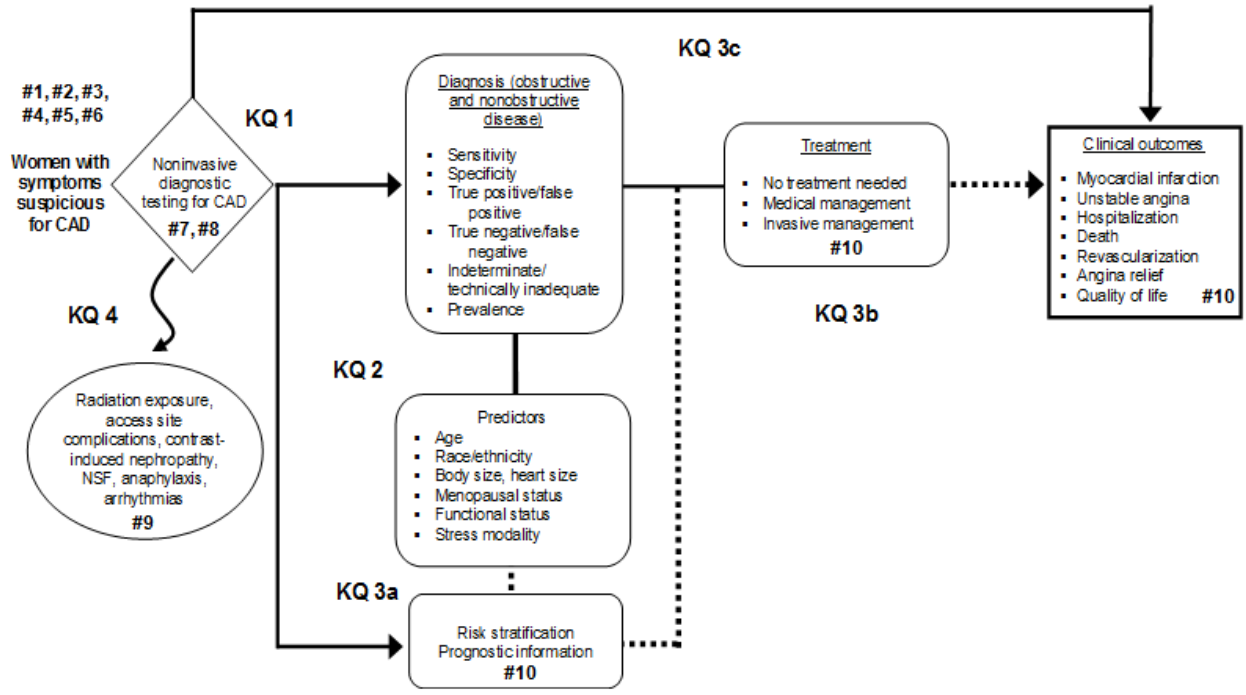
Our approach to identifying evidence gaps, prioritizing future research, and developing recommendations for stakeholders is outlined in the following steps. Further detail is provided below.

1. Develop an analytic framework from the original CER in order to understand the clinical and policy context of the review and its initial list of Future Research Needs.
2. Create an initial list of evidence gaps based on the CER organized according to the population, interventions, comparators, and outcomes (PICO) framework.[3]
3. Form a stakeholder group representing appropriate clinician, policymaker, and patient perspectives.
4. Expand the list of evidence gaps based on stakeholder input.
5. Perform an updated review of published literature since the last CER (search last updated in September 2011) and a horizon scan for recently published and ongoing studies that may address the evidence gaps, but which are not included in the current CER.
6. Solicit stakeholder prioritization of the identified research gaps based on the updated literature review.
7. Determine the most appropriate study designs for the highest priority research areas.[4]

Analytic Framework

Figure 1 depicts the Key Questions within the context of the population, interventions, comparators of interest, outcomes, timing, and settings (PICOTS). In general, the figure shows that the CER considered the accuracy of one noninvasive diagnostic test (NIT) versus another or versus coronary angiography for diagnosing obstructive and nonobstructive coronary artery disease (CAD) in women with symptoms suspicious for CAD (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).

Figure 1. Analytic framework



CAD = coronary artery disease; KQ = Key Question; NSF = nephrogenic systemic fibrosis
Note: #1 to #10 represent the evidence gaps outlined in Table 2.

Initial List of Research Needs

Results from the 2012 report suggest several evidence gaps for future research. These possibilities are neither exhaustive nor prioritized. The initial list generated by the study authors is provided in Table 2, organized according to the PICO format, with the addition of implementation gaps and methods for evidence synthesis.

Table 2. Initial list of evidence gaps

PICO Element	Evidence Gaps
Population	1. Does the comparative accuracy of NITs in women vary based on the pretest probability of CAD of the women undergoing the test? How does the pretest probability of CAD impact the findings on clinical decisionmaking? 2. Does the comparative accuracy of NITs in women vary based on differing symptomology and timing at presentation? 3. Does the comparative accuracy of NITs in women vary based on racial/ethnicity differences? 4. Does the comparative accuracy of NITs in women vary based on patient risk profiles? 5. Does the comparative accuracy of NITs in women vary based on different settings (outpatient, inpatient, emergency room)? 6. Does the comparative accuracy of NITs in women vary based on age?
Intervention and comparator	7. What is the comparative safety and accuracy of functional vs. anatomic NIT modalities? 8. What is the comparative safety and accuracy of functional NIT testing strategies with and without imaging?
Outcome	9. What are the potential harms of NITs? 10. What is the impact of NIT modalities on outcomes beyond diagnostic accuracy (risk stratification, prognostic information, treatment decisions, and clinical outcomes)?

CAD = coronary artery disease; NIT = noninvasive technology

Creation of Stakeholder Group

We selected stakeholders to include researchers involved in some of the primary randomized controlled trials (RCTs) included in the CER, other clinical experts and researchers in the content area, representatives from Federal and nongovernmental funding agencies, representatives from relevant professional societies, health care decisionmakers and policymakers, and representatives from related consumer and patient advocacy groups (Table 3). Within each group, we sought to identify an individual who was either familiar with the clinical area and its current uncertainties, or who brought a specific methodological area of expertise to the workgroup.

Table 3. Stakeholder organizations and roles

Organization	Purpose/Role
National Heart, Lung, and Blood Institute	The National Heart, Lung, and Blood Institute is one of the main funders of potential future studies of the comparative safety and effectiveness of NITs in patients with suspected CAD. It was important to include their perspective in the prioritization of evidence gaps.
American College of Physicians	The American College of Physicians is the largest group representing internal medicine and its subspecialties. A large portion of the care of patients with CAD is managed by generalists or medicine subspecialists in the office setting and the American College of Physicians represents this broad group of stakeholders.
American College of Cardiology	The American College of Cardiology comprises 39,000 cardiovascular specialists, and is a leader in the formulation of health policy, standards, and guidelines for cardiovascular research.
American Heart Association	The American Heart Association funds clinical, outcome, and health services research on cardiovascular disease and stroke. They are also a leading advocacy group for advancing science and improving the quality of cardiovascular care.
Society of Cardiovascular Computed Tomography	The Society of Cardiovascular Computed Tomography is an international society that addresses all issues pertaining to the field of cardiovascular computed tomography, and develops standards, guidelines, and recommendations for the clinical use of cardiovascular CT. As one of the technologies considered in this report, an expert opinion in this field is invaluable.

Table 3. Stakeholder organizations and roles (continued)

Organization	Purpose/Role
Society for Cardiovascular Magnetic Resonance	The Society for Cardiovascular Magnetic Resonance is an international society that provides CMR education, training, standards development, and accreditation. Experts in this field were needed for the CMR testing considered in this report.
American Society of Echocardiography	The American Society of Echocardiography develops guidelines and standards for cardiac ultrasound, one of the noninvasive test modalities considered in this report.
American College of Radiology	The American College of Radiology is committed to making imaging safe, effective and accessible to those who need it. The organization is comprised of radiologists, nuclear medicine physicians, and others; has a strong advocacy component; and provides continuing education for radiology.
Office of Research on Women's Health	The Office of Research on Women's Health establishes the NIH research agenda for women's health, co-funds research projects in partnership with NIH Institutes and Centers, and ensures that the NIH policy to include women and minorities in clinical research is followed. It is important to include their perspective in the prioritization of evidence gaps.
Payor	We sought a representative from a private payor in the health insurance industry. Although these payors are not likely to be funders of future research projects, they will be eventual payors of the treatments recommended by the future research studies; and, therefore, their perspective on the types of studies needed to change their coverage decisions is helpful.
Patient Advocate	We identified a patient advocate to represent the research priorities and issues from the patient's perspective. This person was oriented to the topic and relevant issues in advance of the discussion so he/she would be an active participant.
Centers for Medicare and Medicaid Services (CMS)	We sought a representative from the Centers for Medicare and Medicaid Services. Although the Centers for Medicare and Medicaid Services is not likely to be a funder of future research projects, they will be eventual payors of the treatments recommended by the future research studies; and, therefore, their perspective on the types of studies needed to change their coverage decisions is helpful.

CAD = coronary artery disease; CMR = cardiovascular magnetic resonance; CT = computed tomography; NIH = National Institutes of Health; NIT= noninvasive technology

We were able to recruit representatives from each of these twelve groups. A total of 11 (many representing several of the above perspectives) stakeholders were included in our final panel.

Stakeholder input was solicited and received through Web-based survey techniques, email, and group discussions via teleconference. Group discussions were moderated by the Evidence-based Practice Center (EPC) investigators to avoid domination of the discussion by any particular group and to ensure that all participants had an equal opportunity to ask questions and express their views. The AHRQ Task Order Officer was a participant in all group teleconferences and was included on all electronic communication with the stakeholder group.

Each potential stakeholder completed a statement of disclosure, was screened for apparent conflicts of interest, and approved by AHRQ prior to the first stakeholder call. Efforts were made to assemble a balanced group of individuals representing a wide range of perspectives.

Expansion of Research Gaps

We used the research priorities identified in the CER and input from the stakeholder workgroup during the first call to ultimately expand the list of research priorities to include 19 potential evidence gaps (Table 4).

While many of these research areas were within the scope of the initial review, several raised by the stakeholder group were outside the scope of this review. These areas may represent important gaps in the knowledge base; however, we are less confident about the current state of the evidence since they were not included in the original report. These "out-of-scope" topics

were included in our list, but were specifically noted so that the stakeholders were aware that these areas had not undergone the same level of systematic review and we, therefore, could not provide the same level of detail on the state of current evidence.

We have organized these gaps according to the PICO format and listed them in the table below. The areas determined to be out of scope from the original review are italicized in Table 4.

Table 4. Potential Future Research Needs based on the Comparative Effectiveness Review and stakeholder input

PICO Element	Potential Future Research Need
Population	1. Does the comparative accuracy of NITs in women vary based on the pretest probability of CAD of the women undergoing the test? How does the pretest probability of CAD impact the findings on clinical decisionmaking? 2. Does the comparative accuracy of NITs in women vary based on differing symptomology and timing at presentation? 3. Does the comparative accuracy of NITs in women vary based on racial/ethnicity differences? 4. Does the comparative accuracy of NITs in women vary based on patient risk profiles? 5. Does the comparative accuracy of NITs in women vary based on different settings (outpatient, inpatient, emergency room)?* 6. Does the comparative accuracy of NITs in women vary based on age? 7. Does the comparative accuracy of NITs in women vary based on: body size, heart size, menopausal status, functional status, stress modality?
Intervention and comparator	8. What is the comparative safety and accuracy of functional vs. anatomic NIT modalities? 9. What is the comparative safety and accuracy of functional NIT testing strategies with and without imaging? 10. *Is there a sequential order in which NITs should be used for evaluating CAD (i.e., multiple testing or layered-testing strategies)?**
Outcome	11. What are the potential harms of NITs? 12. What is the impact of NIT modalities on outcomes beyond diagnostic accuracy (risk stratification, prognostic information, treatment decisions, and clinical outcomes)? 13. *What is the comparative effect of NIT modalities on utilization, further testing, and impact on cost?** 14. *Are women getting the same diagnostic testing as men? Are men over-tested and/or women under-tested?** 15. What is the comparative accuracy in real world settings? (most of the studies were single center, best-quality/high expertise centers) 16. *How does patient preference of testing factor into decisionmaking?** 17. *What is the value of performing a specific NIT test for the diagnosis of CAD in women, compared with no testing?**
Implementation gaps	18. *Does clinician preference, availability, or setting (outpatient vs. chest pain unit of an emergency department) impact NIT use?** 19. *How would a better understanding of provider diagnostic ordering patterns and understanding of appropriate use guidelines to support evidence-based decisionmaking impact the use of NITs?**

CAD = coronary artery disease; NIT = noninvasive technology

*Out-of-scope research topics are in italics.

Review of Current Literature

We performed three database searches to identify ongoing and recently published studies relevant to the identified evidence gaps. These searches included the following:

1. A search of ClinicalTrials.gov for ongoing studies. This search included the key words "noninvasive" and "coronary artery disease" and NOT "Male" and was limited to open studies received from 12/2010 to 3/2012.

2. An update of the PubMed®, Embase, Cochrane Central Registry of Controlled Trials and Cochrane Database of Systematic Reviews searches used in the original CER to identify relevant literature published since the last search date (9/12/2011).
3. A search of PubMed for relevant systematic reviews and meta-analyses included in our original search and in the update which might address the out of scope evidence gaps.

The exact search strategies used are provided in Appendix A.

Search results were reviewed for applicability to the identified research gaps listed in Table 4. We included articles from each search if they met the following criteria: (1) presents original data or secondary analysis of data from an RCT, prospective or retrospective observational study, or registry (2) includes data for an NIT of interest (ECG, ECHO, SPECT/PET, CMR, or CTA); (3) population includes women with chest pain syndrome; results are reported separately for symptomatic group; (4) population includes women not known to have CAD; (5) includes comparison of an NIT to another NIT, or of an NIT to diagnostic cardiac catheterization; (6) data for women are reported as a subgroup; and (7) included outcomes that could be categorized according to our identified list of research priorities. The goal for this literature search was to provide the stakeholders an idea of which research areas had recent or ongoing literature to address these gaps. Since we did not intend to synthesize this data with the existing report, these articles did not undergo full article abstraction or reconciliation of differences between article reviewers. We did however review the full-text of the relevant articles as the reporting of gender-specific outcomes was often not clear at the abstract level.

The search of each database yielded the following list of articles:

ClinicalTrials.gov:

- 21 active protocols submitted since 12/2010
- 5 included as potentially relevant based on screening
- 3 RCTs, 1 observational study, 1 nonrandomized intervention trial
- Sample size: 210 to 1,350 patients

Updated PubMed search and search of systematic reviews on out of scope topics>

- 520 articles found in original search
- 112 included as potentially relevant based on abstract screening
- 8 included as relevant based on full-text screening

Based on these searches, we created a list of articles and clinical trials pertaining to the 19 identified evidence gaps. This document was provided to the stakeholders prior to their final prioritization and is reproduced in Appendix B.

Research Prioritization

Process Used

The stakeholders were provided with the AHRQ Effective Health Care Program's prioritization criteria for Future Research Needs and were instructed to use these criteria (potential value [for significant health impact] for addressing the evidence gaps of knowledge, translation, and implementation, and probability of success) as the basis for their decisions regarding research prioritization.

Potential Value Criteria

- Potential for new knowledge: (research would not be redundant; question not sufficiently researched, including completed and in-process research; utility of available evidence limited by changes in practice, e.g., disease detection or evolution in technology)
- Potential for significant health impact on the current and future health status of people with respect to burden of the disease and health outcomes: mortality, morbidity, and quality of life
- Potential to reduce important inappropriate (or unexplained) variation in clinical practices known to relate to quality of care; potential to resolve controversy or dilemmas in what constitutes appropriate health care; potential to improve decisionmaking for patient or provider by decreasing uncertainty
- Potential for significant (nontrivial) economic impact related to the costs of health service: to reduce unnecessary or excessive costs; to reduce high costs due to high volume use; to reduce high costs due to high unit cost or aggregate cost. Costs may impact consumers, patients, health care systems, or payers.
- Potential risk from inaction: unintended harms from lack of prioritization of proposed research; opportunity cost of inaction
- Addresses inequities and vulnerable and diverse populations (including issues for patient subgroups); potential to reduce health inequities
- Potential to allow assessment of ethical, legal, and social issues pertaining to the condition

Probability of Success Criteria

Feasibility

- Feasibility of proposed study duration
- Feasibility of proposed study costs; are costs of study reasonable, given overall resource constraints?

Likelihood

- Likelihood that the study would fill an identified evidence gap
- Likelihood that the study would fill an implementation gap (likely to improve translation of research findings or existing recommendations into clinical practice or identify improved strategies for research translation)
- Likelihood that the study question would be answered by a study with a low risk of bias
- Likelihood that the needed result could be produced in a timely manner (efficiency)
- Likelihood that study would provide evidence about both health benefits and potential harms
- Likelihood of change (proposed topic exists within a clinical, consumer, or policymaking context that is likely amenable to evidence-based change)

Capacity

- Sufficient research capability and capacity so that the issue can be addressed with confidence
- Utilizes existing resources or builds desired research capacity or decisional support

- Effectively utilizes existing research and knowledge by considering where there is other research planned or in progress that will answer the research question (nonduplicative)

Participants in our stakeholder group participated in two conference calls, each of which was followed by an online prioritization exercise. The first call (March 2012) was used to introduce the stakeholder group to the project's objective and to describe the key clinical questions, the original CER report and its findings, and the proposed methods for the prioritization process. During this meeting, the identified research priorities were introduced to the stakeholders, and the group was invited to share feedback regarding additional research priorities. Following this conference call (March 2012), the stakeholders were invited to perform an initial online ranking of the identified research priorities (including the additional priorities identified by the stakeholder team). This ranking utilized a forced-ranking prioritization method, whereby participants were given 7 votes, which could be allocated to any of the 19 research priorities, with a maximum of 3 votes per item.

Stakeholders then participated in a second conference call (April 2012), during which the Duke EPC team shared the search results for relevant ongoing and recently published studies, as well as the stakeholders' initial ranking of research priorities results. During this conference call, the majority of the time was dedicated to discussing prioritization. Following this second call, a final online ranking exercise was distributed to the stakeholder group. This exercise utilized the same prioritization method as the first ranking exercise, and produced the final ranked list of research priorities. Research needs were ranked into tiers; only those in the top tier moved on to the final stage of study design development.

Research Question Development and Research Design Considerations

For the top-tier Future Research Needs, we considered advantages and disadvantages of various potential study designs. We adapted a conceptual framework for recommending study designs based on our prior report "Future Research Needs for Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease."[5] Our overall approach to recommending study designs for addressing specific evidence gaps was to emphasize the study design with the least risk of bias, but the greatest likelihood of completion. For areas outside of the original CER scope, we suggested specific study designs that may be appropriate, while remaining cognizant that without a comprehensive systematic review, one cannot determine with certainty the degree to which those evidence gaps have already been addressed. A thorough systematic review may be the most appropriate initial step before further original research is undertaken for the priorities out of scope from the CER. The figure depicting this framework and a discussion of different designs is included in Appendix C.

Results

Based on the 2012 CER and our discussion with stakeholders, we identified the 19 potential research areas listed in Table 4. Not all areas were considered within the scope of the 2012 CER; these out-of-scope areas are highlighted in italics. Since these areas were out of scope for the original review, it is unclear whether large evidence gaps exist for these areas; however, they were identified and deemed potentially important by the stakeholder panel. With regard to the final stakeholder ranking, all 11 stakeholders participated and ranked the research priorities. The final ranking is listed below in Table 5 and is divided into a top, middle, and lower tier, based on the overall score.

Table 5. Final ranking of Future Research Needs for noninvasive technologies for the diagnosis of CAD in women

Tier	Question	Score
Top Tier	What is the impact of NIT modalities on outcomes beyond diagnostic accuracy (risk stratification, prognostic information, treatment decisions, and clinical outcomes)?	14
	*Are women getting the same diagnostic testing as men? Are men over-tested and/or women under-tested?**	10
	What is the comparative accuracy in real world settings? (most of the studies were single center, best-quality/high expertise centers)	8
	Does the comparative accuracy of NITs in women vary based on the pretest probability of CAD of the women undergoing the test? How does the pretest probability of CAD impact the findings on clinical decisionmaking?	7
	*What is the comparative effect of NIT modalities on utilization, further testing, and impact on cost?**	6
	Does the comparative accuracy of NITs in women vary based on patient risk profiles?	5
	*Is there a sequential order in which NITs should be used for evaluating CAD, i.e. multiple testing or layered-testing strategies?**	5
Middle Tier	What is the comparative safety and accuracy of functional vs. anatomic NIT modalities?	4
	What is the comparative safety and accuracy of functional NIT testing strategies with and without imaging?	4
	How would a better understanding of provider diagnostic ordering patterns and understanding of appropriate use guidelines to support evidence-based decisionmaking *impact the use of NITs?**	3
	Does the comparative accuracy of NITs in women vary based on differing symptomology and timing at presentation?	2
	Does the comparative accuracy of NITs in women vary based on racial/ethnicity differences?	2
	*What is the value of performing a specific NIT test for the diagnosis of CAD in women, compared with no testing?**	2
	Does clinician preference, availability, or setting (outpatient vs. *chest pain unit of an emergency department) impact NIT use?**	2
Lower Tier	*Does the comparative accuracy of NITs in women vary based on different settings (outpatient, inpatient, emergency room)?**	1
	Does the comparative accuracy of NITs in women vary based on: body size, heart size, menopausal status, functional status, stress modality?	1
	*How does patient preference of testing factor into decisionmaking?**	1
	Does the comparative accuracy of NITs in women vary based on age?	0
	What are the potential harms of NITs?	0

CAD = coronary artery disease; NIT = noninvasive technology

*Out-of-scope research topics are highlighted in italics.

These final rankings were not significantly changed from the preliminary rankings provided by the stakeholders prior to the second call, although the two evidence gaps related to functional NIT modalities dropped to the middle tier while the gaps related to patient risk profiles and pretest probabilities were raised in priority. Based on the stakeholder-identified top tier, the EPC team discussed potential study designs for each research area—these are listed in Table 6. While the proposed methods to address each area are not intended to be restrictive of potential study designs, this section is intended to discuss the benefits or limitations for each study design for answering these questions.

Table 6. High priority research areas and possible study designs

Research Area	RCT?	Meta-Analysis or Individual Patient Data Analysis Across RCTs?	Meta-Analysis of Observational Studies?	New Observational Study?	Analysis of Existing Data?	Model?
What is the impact of NIT modalities on outcomes beyond diagnostic accuracy (risk stratification, prognostic information, treatment decisions, and clinical outcomes)?	**Yes:** either need an RCT with long term followup with strategy of NIT's or need observational study where the test and treatment are tied together. RCT would provide most informative evidence	**Maybe:** may be appropriate if sufficient studies available, although not identified in initial review	**Yes:** if the individual patient data is available from the observational studies and the long term outcomes are ascertained the same way for the NITs	**Maybe:** if RCT is not feasible, then an observational study could explore the evidence gap though without the same fidelity	**No:** unlikely to help for comparative NIT data as very few comparative studies currently exist with long term clinical outcome findings	**Maybe:** potential role for helping determine clinically important differences
*Are women getting the same diagnostic testing as men? Are men over-tested and/or women under-tested?**	***No:** most likely not feasible (or ethical) to randomize participants to over-testing or under-testing*	***Maybe:** depends on the data source for testing – observational studies mainly from current administrative datasets have limitations*	***Yes:** if patient level data with indications / clinical comorbidities are captured*	***Yes:** this is feasible with a NIT registry or cohort of patients with similar indications (low-intermediate chest pain)*	***Maybe:** but need the existing data to be comparative and have the features of interest included*	***Yes:** from current observational studies and administrative datasets can build a propensity model to see if women with similar characteristics are getting tested*
What is the comparative accuracy in real world settings? (most of the studies were single center, best-quality/high expertise centers)	**Maybe:** depends on enrollment criteria – question may be more efficiently served with prospective observational registry	**No:** not unless existing real world registry data available	**Maybe:** if there is sufficient description of observational studies across broad studies	**Yes:** national or broad registry for imaging for common indications would allow exploration	**Maybe:** if broad observational comparative data includes needed patient characteristics	**Maybe:** potential role for modeling the impact of different rates of outcomes that may be observed outside traditional clinical trials
Does the comparative accuracy of NITs in women vary based on the pretest probability of CAD of the women undergoing the test? How does the pretest probability of CAD impact the findings on clinical decisionmaking?	**No:** unlikely to randomize to testing schemes based on pretest probability unless the test and strategies defined are different	**Maybe:** if enough comparative NIT studies had well defined pretest probability of patients	**Maybe:** if comparative NITs had pretest data, but most don't and usually same test is not done across spectrum	**Yes:** could capture in observational study the patient risk and testing performed	**No:** not enough existing data due to lack of rigorous reporting of symptoms and pretest probability	**Maybe:** potential role for helping determine clinically important differences

Table 6. High priority research areas and possible study designs (continued)

Research Area	RCT?	Meta-Analysis or Individual Patient Data Analysis Across RCTs?	Meta-Analysis of Observational Studies?	New Observational Study?	Analysis of Existing Data?	Model?
*What is the comparative effect of NIT modalities on utilization, further testing, and impact on cost?**	***Yes:** could be captured as downstream primary or secondary endpoints in RCT for NIT strategies.*	***Maybe:** may be appropriate if sufficient studies available, although not identified in initial review*	***Yes:** if existing observational NIT data have these outcomes reported then can be performed*	***Yes:** can have observational study of downstream utilization and testing*	***Yes:** potentially could do analysis in administrative claims data – would not know impact on decisionmaking*	***Maybe:** potential role in defining clinically or economically meaningful differences*
Does the comparative accuracy of NITs in women vary based on patient risk profiles?	**No:** unlikely to randomize to testing schemes based on pretest probability unless the test and strategies defined are different	**Maybe:** if enough comparative NIT studies had well defined pretest probability of patients	**Maybe:** if comparative NITs had pretest data, but most don't and usually same test is not done across spectrum	**Yes:** could capture in observational study the patient risk and testing performed	**No:** not enough existing data due to lack of rigorous reporting of symptoms and pretest probability	**Maybe:** potential role for helping determine clinically important differences
*Is there a sequential order in which NITs should be used for evaluating CAD, i.e. multiple testing or layered-testing strategies?**	***Yes:** RCT with strategies with multiple tests or algorithms would be useful*	***Maybe:** may be appropriate if sufficient studies available, although not identified in initial review*	***No:** unfortunately – variable use of downstream testing so hard to understand the role of sequential data or tests without specific patient and outcome data*	***Yes:** possibly could design a strategy observational study where the strategy a clinician is using for NITs could be captured at start for an indication*	***No:** limited with regards to multiple difference layered testing strategies and outcomes*	***Maybe:** could use existing claims data to model which patients/ characteristics are associated with layered and sequential testing*

CAD = coronary artery disease; NIT= noninvasive technology; RCT = randomized controlled trial

*Out-of-scope research topics are highlighted in italics.

Discussion

The 2012 CER, "Noninvasive Technologies for the Diagnosis of Coronary Artery Disease in Women," provided evidence for the summary sensitivities and specificities of exercise/stress ECG, ECHO, SPECT, CME and coronary CTA compared with coronary angiography. There was limited or insufficient evidence from comparative studies to define the influence of clinical and demographic factors on NIT diagnostic accuracy, risk stratification, prognostic information, treatment decisions, clinical outcomes, and harms in women. The recommendations for future research on NIT found in this report represent a broad range of stakeholder perspectives including those of general physicians, physician specialists, researchers, policymakers, and patients. The prioritized areas represent three primary foci: (1) clinical decisionmaking (i.e. risk stratification/profiles, pretest probability, prognostic information, treatment decisions,); (2) long-term clinical outcomes (i.e. revascularization and cardiovascular events); and (3) implementation and generalizability (i.e. accuracy and utilization in real world settings, appropriate test ordering, multiple testing or layer-testing strategies).

The use of NIT to assist clinicians in decisionmaking is vitally important for determining a woman's risk profile, prognosis, and treatment of cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, tobacco use, physical inactivity). A comparative study of NITs in women in a long-term clinical trial is preferable, but a more feasible approach could be a prospective observational study of women with varying pretest probabilities and/or risk profiles. The impact of NIT on clinical outcomes in women is an understudied area. Important outcomes include: referral for invasive diagnostic testing (i.e. coronary angiography), revascularization (percutaneous coronary intervention or coronary artery bypass grafting), and cardiovascular events (nonfatal and fatal myocardial infarction, cardiovascular death). Again, a large, long-term clinical trial is the preferred approach, but a prospective, comparative observational study measuring these outcomes over the long-term would strengthen the evidence. Finally, the real-world implementation of NIT is relatively unknown. Whether the diagnostic accuracy of NIT in usual care settings is comparable to the published reports from highly specialized centers needs further study. The appropriate use of NIT in women compared with men, the influence on downstream testing (either multiple tests or layered-testing), and impact on cost is important since the cost of modalities differ. The Government Accountability Office reports that $14.1 billion is spent per year on cardiovascular imaging. A systematic review of the implementation, generalizability, and utilization of NIT in real world settings would need to be performed prior to determining whether future research on administrative databases or registries could be recommended. The original CER showed that very few NIT articles are RCTs; thus, future research involving RCTs is recommended.

Given the limited time the stakeholders have to review the existing evidence, it is also possible that their prioritization represents their general research priorities, rather than the state of evidence for this specific topic. Though it is not the aim of this report, the information is still useful as a representation of topics that are of direct interest to researchers in the field. As AHRQ prepares further prioritization reports, it would be interesting to examine recurrent themes that arise in the top tier of research priorities.

The stakeholder group included several topics that were out of scope for the original review. The expansion of topics promotes consideration of new areas of research that have not been adequately explored; however, the original CER did not comment on the state of current research in these out-of-scope areas, and they should only be promoted with the caveat that existing literature may already adequately address these areas. We identified recent publications on these

out-of-scope topics, but we cannot summarize the state of evidence with the same rigor as in-scope topics included in the original CER.

Conclusions

A workgroup of 11 stakeholders identified the following seven research areas as the highest priority for future research for the comparative effectiveness of NITs for the diagnosis of CAD in women.

1. What is the impact of NIT modalities on outcomes beyond diagnostic accuracy (risk stratification, prognostic information, treatment decisions, and clinical outcomes)?
    a. Recommended study design: large long-term clinical trial would be preferable, if not possible then an observational study could be informative
2. *Are women getting the same diagnostic testing as men? Are men over-tested and/or women under-tested?* (This is an out-of-scope research topic.)
    a. Recommended study design: systematic review of the evidence, potentially followed by either modeling of existing observational studies and administrative datasets to explore whether women with similar characteristics to men are getting tested or development of a new observational study to explore this gap
3. What is the comparative accuracy in real world settings? (most of the studies were single center, best-quality/high expertise centers)
    a. Recommended study design: systematic review of the evidence, potentially followed by national or broad registry for imaging for common indications exploring findings within real-world settings
4. Does the comparative accuracy of NITs in women vary based on the pretest probability of CAD of the women undergoing the test? How does the pretest probability of CAD impact the findings on clinical decisionmaking?
    a. Recommended study designs: an observational study of patients with varying pretest probabilities of CAD
5. *What is the comparative effect of NIT modalities on utilization, further testing, and impact on cost?* (This is an out-of-scope research topic.)
    a. Recommended study design: systematic review of the evidence, potentially followed by either a new RCT or observational study if systematic review reveals that this information is not available from analysis of existing data sources
6. Does the comparative accuracy of NITs in women vary based on patient risk profiles?
    a. Recommended study design: an observational study of patients with varying patient risk profiles.
7. *Is there a sequential order in which NITs should be used for evaluating CAD, i.e. multiple testing or layered-testing strategies?* (This is an out-of-scope research topic.)
    a. Recommended study design: systematic review of the evidence, potentially followed by either new RCT or observational studies with a focus on sequential ordering of NITs.

References

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2. Dolor RJ, Patel MR, Melloni C, et al. Noninvasive Technologies for the Diagnosis of Coronary Artery Disease in Women. Comparative Effectiveness Review No. 58 (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 12-EHC034-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2012.www.effectivehealthcare.ahrq.gov/reports/final.cfm.
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Abbreviations

AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
CAD	Coronary artery disease
CER	Comparative Effectiveness Review
CMR	Cardiac magnetic resonance
CTA	Computed tomography angiograph
ECG	Electrocardiography
ECHO	Echocardiography
EPC	Evidence-based Practice Center
KQ	Key Question
NIT	Noninvasive technology
PET	Positron emission tomography
PICO	Population, interventions, comparators, and outcomes
RCT	Randomized controlled trial
SPECT	Single-photon emission computed tomography

Appendix A. Exact Search Strings

The exact search strings used for this project are given below.

Pubmed® Search Strategy (Update of Search Performed for Original CER)

Search date: March 13, 2012
Number of articles: 159

((((/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 *[MeSH:noexp] OR diagnosis, differential[MeSH:noexp] OR diagnosis[Subheading:noexp])) AND ((women OR woman OR female OR females OR sex factors) AND ((((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])) OR (Chest pain OR dyspnea OR shortness of breath OR angina)) AND (((echocardiography OR echo OR cardiogram) AND ((electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR "PET" OR myocardial perfusion imaging OR "nuclear scan" OR radionuclide imaging) OR (((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")) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR "X-ray angiography" OR "Xray angiography"))) OR ((electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) AND ((echocardiography OR echo OR cardiogram) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR "PET" OR myocardial perfusion imaging OR "nuclear scan" OR radionuclide imaging) OR (((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")) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR "X-ray angiography" OR "Xray angiography"))) OR ((single photon emission computed tomography OR SPECT OR positron emission tomography OR "PET" OR myocardial perfusion imaging OR "nuclear scan" OR radionuclide imaging) AND ((echocardiography OR echo OR cardiogram) OR (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction

cardiogram OR exercise test OR treadmill) OR (((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")) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR "X-ray angiography" OR "Xray angiography"))) OR ((((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")) AND ((echocardiography OR echo OR cardiogram) OR (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR "PET" OR myocardial perfusion imaging OR "nuclear scan" OR radionuclide imaging) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR "X-ray angiography" OR "Xray angiography"))) OR (((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) AND ((echocardiography OR echo OR cardiogram) OR (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR "PET" OR myocardial perfusion imaging OR "nuclear scan" OR radionuclide imaging) OR (((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")) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR "X-ray angiography" OR "Xray angiography"))) OR ((cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR "X-ray angiography" OR "Xray angiography") AND ((echocardiography OR echo OR cardiogram) OR (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR "PET" OR myocardial perfusion imaging OR "nuclear scan" OR radionuclide imaging) OR (((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")) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)))))))) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp])) NOT (Animals[Mesh:noexp])
Limits:

Publication Date: September 2011 – present
Language: English

Pubmed® Search Strategy (Search for Systematic Reviews)

Search date: March 26, 2012
Number of articles: 66

((((/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 *[MeSH:noexp] OR diagnosis, differential[MeSH:noexp] OR diagnosis[Subheading:noexp])) AND ((women OR woman OR female OR females OR sex factors) AND ((((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])) OR (Chest pain OR dyspnea OR shortness of breath OR angina)) AND (((echocardiography OR echo OR cardiogram) AND ((electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR "PET" OR myocardial perfusion imaging OR "nuclear scan" OR radionuclide imaging) OR (((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")) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR "X-ray angiography" OR "Xray angiography"))) OR ((electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) AND ((echocardiography OR echo OR cardiogram) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR "PET" OR myocardial perfusion imaging OR "nuclear scan" OR radionuclide imaging) OR (((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")) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR "X-ray angiography" OR "Xray angiography"))) OR ((single photon emission computed tomography OR SPECT OR positron emission tomography OR "PET" OR myocardial perfusion imaging OR "nuclear scan" OR radionuclide imaging) AND ((echocardiography OR echo OR cardiogram) OR (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (((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")) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR "X-ray angiography" OR "Xray angiography"))) OR ((((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")) AND ((echocardiography OR echo OR cardiogram) OR (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR "PET" OR myocardial perfusion imaging OR "nuclear scan" OR radionuclide imaging) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR "X-ray angiography" OR "Xray angiography"))) OR (((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) AND ((echocardiography OR echo OR cardiogram) OR (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR "PET" OR myocardial perfusion imaging OR "nuclear scan" OR radionuclide imaging) OR (((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")) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR "X-ray angiography" OR "Xray angiography"))) OR ((cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR "X-ray angiography" OR "Xray angiography") AND ((echocardiography OR echo OR cardiogram) OR (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR "PET" OR myocardial perfusion imaging OR "nuclear scan" OR radionuclide imaging) OR (((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")) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)))))))) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp])) NOT (Animals[Mesh:noexp])
Limits:
Reviews and Meta-analyses
Publication Date: September 2011 – present
Language: English

Embase® Search Strategy (Update of Search Performed for Original CER)

Search date: March 13, 2012
Number of articles: 145

'echocardiography'/exp OR echo OR echocardiogram AND ('electrocardiography'/exp OR 'electrocardiogram'/exp OR electrocardiography OR ecg OR ekg OR electrocardio* OR mcg OR 'multifunction cardiogram' OR ('cardiopulmonary exercise test'/exp AND 'exercise test'/exp OR exercise AND test) OR treadmill) OR ('echocardiography'/exp OR echo OR echocardiogram AND ('single photon emission computer tomography'/exp OR 'computer assisted emission tomography'/exp OR 'myocardial perfusion imaging'/exp OR 'single photon emission computed tomography' OR spect OR 'positron emission tomography' OR pet OR 'myocardial perfusion imaging' OR 'nuclear scan' OR 'radionuclide imaging' OR 'heart scintiscanning'/exp)) OR ('echocardiography'/exp OR echo OR echocardiogram AND (cardio* OR heart OR coronary OR cardiac) AND ('computer assisted tomography'/exp OR 'computed tomographic angiography'/exp OR 'multidetector computed tomography'/exp 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')) OR ('echocardiography'/exp OR echo OR echocardiogram AND (cardio* OR heart OR coronary OR cardiac) AND ('nuclear magnetic resonance imaging'/exp OR 'magnetic resonance angiography'/exp OR 'magnetic resonance imaging' OR mri OR 'magnetic resonance angiography' OR mra)) OR ('electrocardiography'/exp OR 'electrocardiogram'/exp OR electrocardiography OR ecg OR ekg OR electrocardio* OR mcg OR 'multifunction cardiogram' OR ('cardiopulmonary exercise test'/exp AND 'exercise test'/exp OR exercise AND test) OR treadmill AND ('single photon emission computer tomography'/exp OR 'computer assisted emission tomography'/exp OR 'myocardial perfusion imaging'/exp OR 'single photon emission computed tomography' OR spect OR 'positron emission tomography' OR pet OR 'myocardial perfusion imaging' OR 'nuclear scan' OR 'radionuclide imaging' OR 'heart scintiscanning'/exp)) OR ('electrocardiography'/exp OR 'electrocardiogram'/exp OR electrocardiography OR ecg OR ekg OR electrocardio* OR mcg OR 'multifunction cardiogram' OR ('cardiopulmonary exercise test'/exp AND 'exercise test'/exp OR exercise AND test) OR treadmill AND (cardio* OR heart OR coronary OR cardiac) AND ('computer assisted tomography'/exp OR 'computed tomographic angiography'/exp OR 'multidetector computed tomography'/exp 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')) OR ('electrocardiography'/exp OR 'electrocardiogram'/exp OR electrocardiography OR ecg OR ekg OR electrocardio* OR mcg OR 'multifunction cardiogram' OR ('cardiopulmonary exercise test'/exp AND 'exercise test'/exp OR exercise AND test) OR treadmill AND (cardio* OR heart OR coronary OR cardiac) AND ('nuclear magnetic resonance imaging'/exp OR 'magnetic resonance angiography'/exp OR 'magnetic resonance imaging' OR mri OR 'magnetic resonance angiography' OR mra)) OR ('single photon emission computer tomography'/exp OR 'computer assisted emission tomography'/exp OR 'myocardial perfusion imaging'/exp OR 'single photon emission computed tomography' OR spect OR 'positron emission tomography' OR pet OR 'myocardial perfusion imaging' OR 'nuclear scan' OR 'radionuclide imaging' OR 'heart scintiscanning'/exp AND (cardio* OR heart OR coronary OR

cardiac) AND ('computer assisted tomography'/exp OR 'computed tomographic angiography'/exp OR 'multidetector computed tomography'/exp 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')) OR ('computer assisted tomography'/exp OR 'computed tomographic angiography'/exp OR 'multidetector computed tomography'/exp 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' AND (cardio* OR heart OR coronary OR cardiac) AND ('nuclear magnetic resonance imaging'/exp OR 'magnetic resonance angiography'/exp OR 'magnetic resonance imaging' OR mri OR 'magnetic resonance angiography' OR mra)) OR ('single photon emission computer tomography'/exp OR 'computer assisted emission tomography'/exp OR 'myocardial perfusion imaging'/exp OR 'single photon emission computed tomography' OR spect OR 'positron emission tomography' OR pet OR 'myocardial perfusion imaging' OR 'nuclear scan' OR 'radionuclide imaging' OR 'heart scintiscanning'/exp AND (cardio* OR heart OR coronary OR cardiac) AND ('nuclear magnetic resonance imaging'/exp OR 'magnetic resonance angiography'/exp OR 'magnetic resonance imaging' OR mri OR 'magnetic resonance angiography' OR mra)) OR (cardio* OR heart OR coronary OR cardiac AND ('nuclear magnetic resonance imaging'/exp OR 'magnetic resonance angiography'/exp OR 'magnetic resonance imaging' OR mri OR 'magnetic resonance angiography' OR mra) AND ('heart catheterization'/exp OR 'cardiac catheterization' OR angiography OR 'invasive coronary angiography' OR 'heart catheterization' OR 'coronary angiography' OR 'x-ray angiography' OR 'xray angiography')) OR ('heart catheterization'/exp OR 'cardiac catheterization' OR angiography OR 'invasive coronary angiography' OR 'heart catheterization' OR 'coronary angiography' OR 'x-ray angiography' OR 'xray angiography' AND ('echocardiography'/exp OR echo OR echocardiogram)) OR ('heart catheterization'/exp OR 'cardiac catheterization' OR angiography OR 'invasive coronary angiography' OR 'heart catheterization' OR 'coronary angiography' OR 'x-ray angiography' OR 'xray angiography' AND ('electrocardiography'/exp OR 'electrocardiogram'/exp OR electrocardiography OR ecg OR ekg OR electrocardio* OR mcg OR 'multifunction cardiogram' OR ('cardiopulmonary exercise test'/exp AND 'exercise test'/exp OR exercise AND test) OR treadmill)) OR ('single photon emission computer tomography'/exp OR 'computer assisted emission tomography'/exp OR 'myocardial perfusion imaging'/exp OR 'single photon emission computed tomography' OR spect OR 'positron emission tomography' OR pet OR 'myocardial perfusion imaging' OR 'nuclear scan' OR 'radionuclide imaging' OR 'heart scintiscanning'/exp AND ('heart catheterization'/exp OR 'cardiac catheterization' OR angiography OR 'invasive coronary angiography' OR 'heart catheterization' OR 'coronary angiography' OR 'x-ray angiography' OR 'xray angiography')) OR (cardio* OR heart OR coronary OR cardiac AND ('computer assisted tomography'/exp OR 'computed tomographic angiography'/exp OR 'multidetector computed tomography'/exp 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') AND ('heart catheterization'/exp OR 'cardiac catheterization' OR angiography OR 'invasive coronary angiography' OR 'heart catheterization' OR 'coronary angiography' OR 'x-ray angiography' OR 'xray angiography')) AND ('thorax pain'/exp OR 'dyspnea'/exp OR 'angina pectoris'/exp OR 'chest pain' OR 'shortness of breath' OR

angina OR dsypnea OR 'coronary artery disease'/exp OR 'ischemic heart disease'/exp OR cad OR 'coronary artery disease' OR 'coronary disease' OR 'coronary heart disease') AND ('female'/exp OR female OR women OR woman OR females OR 'sex difference'/exp) AND (predict OR specificity OR diagnosis:lnk) AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [english]/lim AND [2000-2011]/py NOT ('case report'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
Limits:
Publication Date: September 2011 – present

Cochrane Search Strategy (Update of Search Performed for Original CER)

Search date: March 13, 2012
Number of articles: 167
[Cochrane Central Registry of Controlled Trials and Cochrane Database of Systematic Reviews]
Chest pain OR dyspnea OR shortness of breath OR angina OR CAD OR coronary artery disease OR coronary disease OR coronary heart disease
AND
((echocardiography OR echo OR cardiogram) AND ((electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR PET OR myocardial perfusion imaging OR nuclear scan OR radionuclide imaging) OR (((cardio* OR heart OR coronary OR cardiac) AND X-Ray computed Tomography) 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)) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR X-ray angiography OR Xray angiography))) OR ((electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) AND ((echocardiography OR echo OR cardiogram) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR PET OR myocardial perfusion imaging OR nuclear scan OR radionuclide imaging) OR (((cardio* OR heart OR coronary OR cardiac) AND X-Ray computed Tomography) 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)) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR X-ray angiography OR Xray angiography))) OR ((single photon emission computed tomography OR SPECT OR positron emission tomography OR PET OR myocardial perfusion imaging OR nuclear scan OR radionuclide imaging) AND ((echocardiography OR echo OR cardiogram) OR (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (((cardio* OR heart OR coronary OR cardiac)

AND X-Ray computed Tomography) 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)) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR X-ray angiography OR Xray angiography))) OR ((((cardio* OR heart OR coronary OR cardiac) AND X-Ray computed Tomography) 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)) AND ((echocardiography OR echo OR cardiogram) OR (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR PET OR myocardial perfusion imaging OR nuclear scan OR radionuclide imaging) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR X-ray angiography OR Xray angiography))) OR (((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA)) AND ((echocardiography OR echo OR cardiogram) OR (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR PET OR myocardial perfusion imaging OR nuclear scan OR radionuclide imaging) OR (((cardio* OR heart OR coronary OR cardiac) AND X-Ray computed Tomography) 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)) OR (cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR X-ray angiography OR Xray angiography))) OR ((cardiac catheterization OR angiography OR invasive coronary angiography OR heart catheterization OR coronary angiography OR X-ray angiography OR Xray angiography) AND ((echocardiography OR echo OR cardiogram) OR (electrocardiography OR ECG OR EKG OR electrocardio* OR MCG OR multifunction cardiogram OR exercise test OR treadmill) OR (single photon emission computed tomography OR SPECT OR positron emission tomography OR PET OR myocardial perfusion imaging OR nuclear scan OR radionuclide imaging) OR (((cardio* OR heart OR coronary OR cardiac) AND X-Ray computed Tomography) 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)) OR ((cardiac OR heart OR coronary OR cardio*) AND (magnetic resonance imaging OR MRI OR Magnetic resonance angiography OR MRA))))
AND
women OR woman OR female OR females OR sex factors
AND

diagnosis OR diagnos* OR predict* OR predictive value of tests OR sensitivity OR specificity OR sensitive OR diagnostic OR differential diagnosis

Limits:
Publication Date: September 2011 – present

Clinicaltrials.gov (Update of Search Performed for Original CER)

Search date: March 13, 2012
Number of trials: 21
noninvasive [ALL-FIELDS] AND coronary artery disease [DISEASE] AND (NOT "Male") [GENDER] AND "completed" [SUMMARY-STATUS]

Limits:
Publication Date: September 2011 – present

Appendix B. Table of Research Priorities Linked to Recent Publications and Ongoing Studies

Priority	Details
1	**What is the impact of NIT modalities on outcomes beyond diagnostic accuracy (risk stratification, prognostic information, treatment decisions, and clinical outcomes)?** **MEDLINE/EMBASE/Cochrane:** Shaw LJ, Mieres JH, Hendel RH, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. Circulation 2011;124(11):1239-49. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. JAMA 2011;306(19):2128-36. **ClinicalTrials.gov:** No relevant citations found
2	**Are women getting the same diagnostic testing as men? Are men over-tested and/or women under-tested?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
3	**What is the comparative accuracy in real world settings? (most of the studies were single center, best-quality/high expertise centers)** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
4	**Does the comparative accuracy of NITs in women vary based on the pre-test probability of CAD of the women undergoing the test? How does the pre-test probability of CAD impact the findings on clinical decisionmaking?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** Comparison of Cardiac Imaging Techniques for Diagnosing Coronary Artery Disease, NCT01521468, Observational study of 210 patients.
5	**What is the comparative effect of NIT modalities on utilization, further testing, and impact on cost?** **MEDLINE/EMBASE/Cochrane:** Shaw LJ, Mieres JH, Hendel RH, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. Circulation 2011;124(11):1239-49.

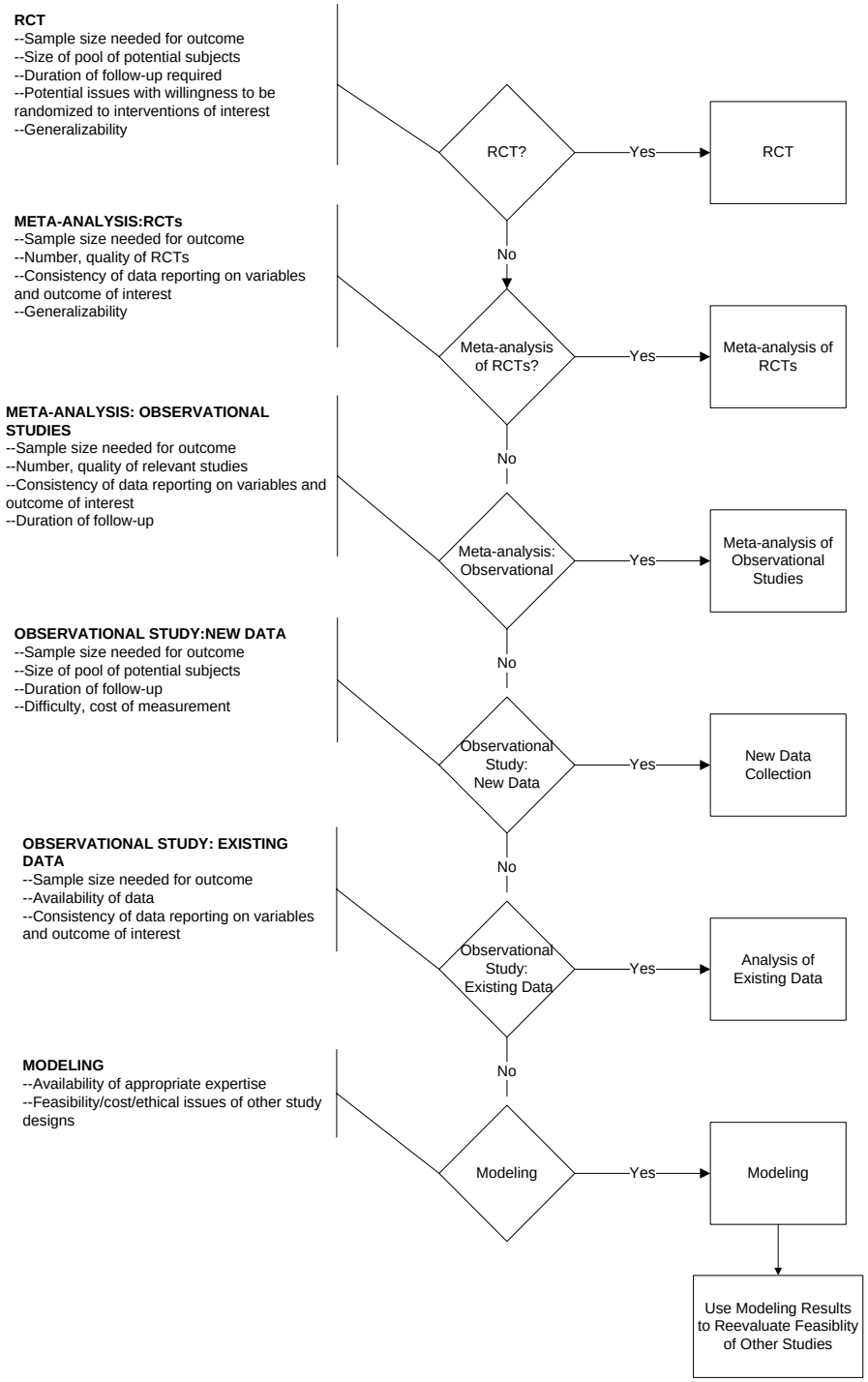
Priority	Details
	Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. JAMA 2011;306(19):2128-36. **ClinicalTrials.gov:** Computed Tomography Versus Exercise Testing in Suspected Coronary Artery Disease, NCT01393028, RCT of 1350 patients. Role of Cardiac CT in Rapid Access Chest Pain Clinics (RADICAL), NCT01464203, RCT of 600 patients.
6	**Does the comparative accuracy of NITs in women vary based on patient risk profiles?** **MEDLINE/EMBASE/Cochrane:** Becker MM, Zwicker C, Altiok E, et al. Accuracy of different stress modalities for evaluation of postmenopausal women with suspected coronary artery disease. European Heart Journal 2011;32 SUPPL. 1:164. Doyle M, Pohost GM, Shaw LJ, et al. Decisions informed by computing entities (DICE) to improve prognostic value of myocardial perfusion imaging: The NHLBI-sponsored women's ischemia syndrome evaluation (WISE) study. Circulation 2011;124(21):2011-11. **ClinicalTrials.gov:** No relevant citations found **Systematic reviews:** Hlatky MA, Pryor DB, Harrell FE, Jr., et al. Factors affecting sensitivity and specificity of exercise electrocardiography. Multivariable analysis. Am J Med 1984;77(1):64-71.
7	**Is there a sequential order in which NITs should be used for evaluating CAD – i.e. multiple testing or layered-testing strategies?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
8	**What is the comparative safety and accuracy of functional versus anatomic NIT modalities?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** Comparison of Cardiac Imaging Techniques for Diagnosing Coronary Artery Disease, NCT01521468, Observational study of 210 patients. Stress Testing Compared to Coronary Computed Tomographic Angiography in Patients With Suspected Coronary Artery Disease, NCT01368770, RCT of 500 patients. Computed Tomography Versus Exercise Testing in Suspected Coronary Artery Disease, NCT01393028, RCT of 1350 patients.

Priority	Details
9	**What is the comparative safety and accuracy of functional NIT testing strategies with and without imaging?** **MEDLINE/EMBASE/Cochrane:** Shaw LJ, Mieres JH, Hendel RH, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. Circulation 2011;124(11):1239-49. Pubul V, Garrido M, Argibay S, et al. Gender differences and prognostic value in the exercise capacity and gated SPECT in patients with suspected coronary artery disease (CAD). European journal of nuclear medicine and molecular imaging 2011;38 SUPPL. 2:S311. **ClinicalTrials.gov:** Comparison of Low-radiation Dose CT Angiography With Invasive Coronary Angiography in Stable Coronary Disease, NCT01476579, Non-Randomized Interventional study of 800 patients. **Systematic reviews:** Kwok Y, Kim C, Grady D, et al. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1999;83(5):660-6.
10	**How would a better understanding of provider diagnostic ordering patterns and understanding of appropriate use guidelines to support evidence-based decision making impact the use of NITs?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
11	**Does the comparative accuracy of NITs in women vary based on differing symptomology and timing at presentation?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
12	**Does the comparative accuracy of NITs in women vary based on racial/ethnicity differences?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
13	**What is the value of performing a specific NIT test for the diagnosis of CAD in women, compared with no testing?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found

Priority	Details
14	**Does clinician preference, availability, or setting (outpatient versus chest pain unit of an emergency department) impact NIT use?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
15	**Does the comparative accuracy of NITs in women vary based on different settings (outpatient, inpatient, emergency room)?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
16	**Does the comparative accuracy of NITs in women vary based on: body size, heart size, menopausal status, functional status, stress modality?** **MEDLINE/EMBASE/Cochrane:** Becker MM, Zwicker C, Altiok E, et al. Accuracy of different stress modalities for evaluation of postmenopausal women with suspected coronary artery disease. European Heart Journal 2011;32 SUPPL. 1:164. Siegler JC, Rehman S, Bhumireddy GP, et al. The accuracy of the electrocardiogram during exercise stress test based on heart size. PLoS One 2011;6(8):e23044. **ClinicalTrials.gov:** No relevant citations found
17	**How does patient preference of testing factor into decision making?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
18	**Does the comparative accuracy of NITs in women vary based on age?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** No relevant citations found
19	**What are the potential harms of NITs?** **MEDLINE/EMBASE/Cochrane:** No relevant citations found **ClinicalTrials.gov:** Comparison of Low-radiation Dose CT Angiography With Invasive Coronary Angiography in Stable Coronary Disease, NCT01476579, Non-Randomized Interventional study of 800 patients.

Appendix C. Criteria for Research Prioritization

Figure C-1. Framework for suggesting study designs for Future Research Needs



We explore below in more detail the potential study designs represented in the Figure above and their specific considerations:

Randomized Controlled Trials (RCTs)

Ideally, all evidence gaps would be filled by conducting effectiveness RCTs that specifically address the area of interest; however, especially for many questions of interest for comparative effectiveness research, RCTs are rarely the most practical option. Considerations include:

- Sample size required for a particular outcome and to include a representative sample of patients: Many outcomes of interest, particularly those involving safety, are relatively uncommon, requiring an inordinately large sample size to achieve adequate power.
- Size of the pool of potential subjects: Some conditions may be relatively uncommon, or the subpopulation of interest relatively small, adversely affecting the sample size.
- Alternatively, comorbidities may be common among patients with the condition in question, creating potential difficulties with inclusion/exclusion criteria for an RCT.
- Duration of followup required: Minimizing loss to followup within the context of a trial, particularly if blinding must be maintained, is both expensive and difficult the longer the duration of followup, but for some outcomes lengthy followup is required.
- Issues with willingness to be randomized: Patient and provider beliefs about effectiveness, side effects, or other factors can make it difficult to recruit subjects into trials for some interventions.
- Generalizability: Inclusion/exclusion criteria often mean that subjects who participate in RCTs rarely reflect the full spectrum of either disease severity or co-morbidity that exists in the real world.

Meta-Analysis of RCTs

If a new RCT is not feasible, then a meta-analysis of existing RCTs may provide the next most valid answer to the question if studies are available; however, all of the potential difficulties with a new RCT are potential problems with existing RCTs. Given sufficient numbers and quality of existing RCTs, some questions may be addressable through meta-analysis. The main issue is whether data on the variables and outcomes of interest have been collected and reported consistently by enough RCTs to warrant a meta-analysis.

Meta-analysis of RCTs may be particularly appropriate for research gaps outside the scope of the initial CER; however, as highlighted by the authors of the original CER in their discussion of future research needs, this method may also be able answer key questions included in the original CER. Depending on the volume of ongoing research, existing reviews may quickly become out of date, particularly in cardiovascular research. In addition, when insufficient evidence exists for particular key questions, modifying the study inclusion/exclusion criteria from the initial review may allow broader inclusion of studies that can address these research gaps. This may be particularly true when a specific clinical condition, such as hypertension, has significant clinical overlap with related conditions such as ischemic heart disease, peripheral vascular disease, diabetes, chronic kidney disease, or congestive heart failure. When the outcomes of interest are common to all conditions (e.g., medication side effects, quality of life) then meta-analysis across clinical conditions may provide additional useful information. In meta-analyses of clinical trials, clinicians are often interested in examining subset effects, yet study-level analyses can lead to biased assessments and have some limitations in explaining heterogeneity. A meta-analysis of individual patient data offers several advantages for this purpose, but may not always be feasible given the multiple different sources of data and the proprietary nature of industry-sponsored research.

Meta-Analysis of Observational Studies

If a meta-analysis of RCTs is not feasible, the next most valid and feasible alternative would be a meta-analysis of observational studies. Many of the same issues inherent in meta-analyses of RCTs (both study-level and patient-level data) are also present, including:

- Heterogeneity in study design, inclusion, and exclusion criteria;
- Consistency in variable definitions and collection; and
- Varying duration of followup.

In addition, control of confounding can be especially challenging at the study level. Here, patient-level meta-analysis may be particularly appropriate, since it facilitates adjustment. The main challenge here is accessibility to the appropriate data, which may be difficult, especially with industry-sponsored studies.

Observational Study – Collection of New Data

If there is not sufficient literature available for a meta-analysis of observational data, then design of a new study would be the next most valid and feasible study design. Ideally, a prospective study with subject recruitment, data collection, and data analysis specifically intended to address the question of interest would be designed and carried out. Challenges to feasibility of a new observational study include:

- Duration of followup and retention: Many of the most important evidence gaps may require data on outcomes over a longer period of time. Subject retention is crucial both to maximize study power and minimize bias to differential dropout, but the resources required to maintain high retention over a long study period are substantial.
- Recruitment: Depending on the outcomes being assessed, participation in an ongoing observational study may be burdensome. Especially for patients treated with already approved treatments and whose clinical care is not affected by participation in a study, assuring maximal recruitment can be difficult. This may be a special problem in some populations with historically low levels of participation in research.

Observational Study – Analysis of Existing Data

If a new observational study is not feasible, there may be existing data available that address the relevant question. Major issues here include:

- Ease of access to data, particularly proprietary data from industry-sponsored trials or private health plans
- Extracting useful data from administrative or clinical records. ICD-9 (*International Classification of Diseases, Ninth Revision*) and CPT (*Current Procedural Terminology*) codes are not sensitive to many relevant factors in a patient's clinical history, or to disease severity within conditions. Paper records are difficult to abstract because of issues relating to legibility, consistency in diagnostic language, and the human resources required to convert clinical records into useful analytic data. Electronic medical records are more useful, but are not universally used, and systems may not be compatible. For any of these sources, data on the variables of greatest interest may not have been consistently collected.

- Generalizability: Patients enrolled in Medicare, Medicaid, or private health plans may differ in a number of respects, such as income and employment history, that may be relevant, but which may be difficult to adjust for given the available data.

Modeling

Finally, if none of the above options is feasible, simulation modeling may be able to address some questions. Modeling is particularly helpful for addressing questions that involve very long durations of followup, or options that cannot feasibly be included in an RCT, such as the comparative impact of different screening frequencies on cancer incidence, mortality, and life expectancy. The main limitation here is the availability of appropriate expertise in both modeling and the clinical conditions being studied.