Effective Health Care Program

Noninvasive Technologies for the Diagnosis of Coronary Artery Disease in Women

Executive Summary

Background

Cardiovascular disease is the leading cause of mortality for women in the United States.[1] Coronary heart disease— which includes coronary artery (or atherosclerotic) disease (CAD), myocardial infarction (MI), acute coronary syndromes, and angina—is the largest subset of this mortality.[1] According to the American Heart Association (AHA), approximately one in three female adults has some form of cardiovascular disease. Since 1984, the number of deaths attributed to cardiovascular disease in women has exceeded that in men, reaching 454,613 in 2005—more than deaths from all forms of cancer combined.[2] It is estimated that 8.1 million women alive today have a history of heart attack, angina pectoris (chest pain or discomfort caused by reduced blood supply to the heart muscle), or both, and experts predict that in 2010 alone an estimated 370,000 women will have a new or recurrent MI. Overall, women who have had an acute MI— particularly those older than 55 years of age—have a worse prognosis than men, with a greater recurrence of MI and higher mortality.[1] More women (5.5 million) than men (4.3 million) have angina in total numbers. However, the prevalence of CAD in women with chest pain is about 50

percent, compared with 80 percent in men, which complicates diagnosis in women.[3]

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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

Coronary angiography, however, is not risk-free.[4] Arterial bleeding can occur at the access site, and manipulation of the catheter within the aorta and coronary arteries may cause an atherosclerotic embolus that, in turn, could result in stroke or heart attack. Separation of material from the inner lining of the artery may also cause a blockage downstream of the catheter tip. The contrast agent used during the procedure to visualize the coronary arteries may cause anaphylaxis, renal impairment, or injury, and there is radiation exposure during the digital x-ray imaging. Although it is a rare occurrence, the catheter can puncture an artery and cause internal bleeding.

Coronary angiography is generally indicated in patients who have chest pain and are at high risk for CAD. For intermediate-risk patients, clinicians have a wide range of noninvasive diagnostic modalities to choose from, with wide variability in reported sensitivities and specificities. Noninvasive technologies (NITs) are especially important options for patients who have contraindications to invasive catheterization, or for those who would be put at higher risk for complications with invasive screening.[4]

Types of Noninvasive Technologies

NITs can assess functional status (i.e., ischemia or no ischemia) or visualize anatomic abnormalities (i.e., no CAD, nonobstructive CAD, or obstructive CAD). Types of NITs include the following:

- Functional modalities:
  – Exercise/stress electrocardiography (ECG) exercise/ stress or resting
  – Exercise/stress echocardiography (ECHO) with or without a contrast agent
  – Exercise/stress radionuclide myocardial perfusion imaging, including single proton emission computed tomography (SPECT) and positron emission tomography (PET)
- Anatomic modalities:
  – Stress myocardial perfusion and wall motion magnetic resonance imaging (CMR)
  – Coronary computed tomography angiography (coronary CTA)

The AHA and the American College of Cardiology (ACC) recommend that women with suspected CAD should be classified as either symptomatic or asymptomatic and further classified as being at low, intermediate, or high risk for the disease to guide the decision about which diagnostic test to use first.[1] In 2005, the AHA developed a consensus statement on the role of noninvasive testing in the clinical evaluation of women with suspected CAD. In this statement, the AHA recommended that women who are symptomatic and at intermediate to high risk of having CAD should undergo noninvasive diagnostic studies (i.e., exercise electrocardiography and cardiac imaging studies) and that those who are asymptomatic and at low risk of CAD should not undergo cardiac imaging studies.[1] The AHA consensus statement was a thorough synopsis of the extant literature regarding the diagnosis of CAD in women with expert-guided recommendations for the workup of symptomatic women but did not include a comparative effectiveness review of the accuracy of the various NIT modalities in women.

Objectives

The goal of this comparative effectiveness report was to conduct a systematic review of the peer-reviewed medical literature assessing (1) the accuracy of different NITs for diagnosing CAD in women with symptoms suspicious of CAD, (2) the predictors affecting test accuracy, (3) the ability to provide risk stratification and prognostic information, inform decisionmaking about treatment options, and affect clinical outcomes, and (4) the safety concerns and risks to women undergoing these tests. The following Key Questions (KQs) were considered in this comparative effectiveness review:

- 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?

Analytic Framework

Figure A shows the analytic framework for the systematic review of NITs for the diagnosis of CAD in women.

Figure A. Analytic framework
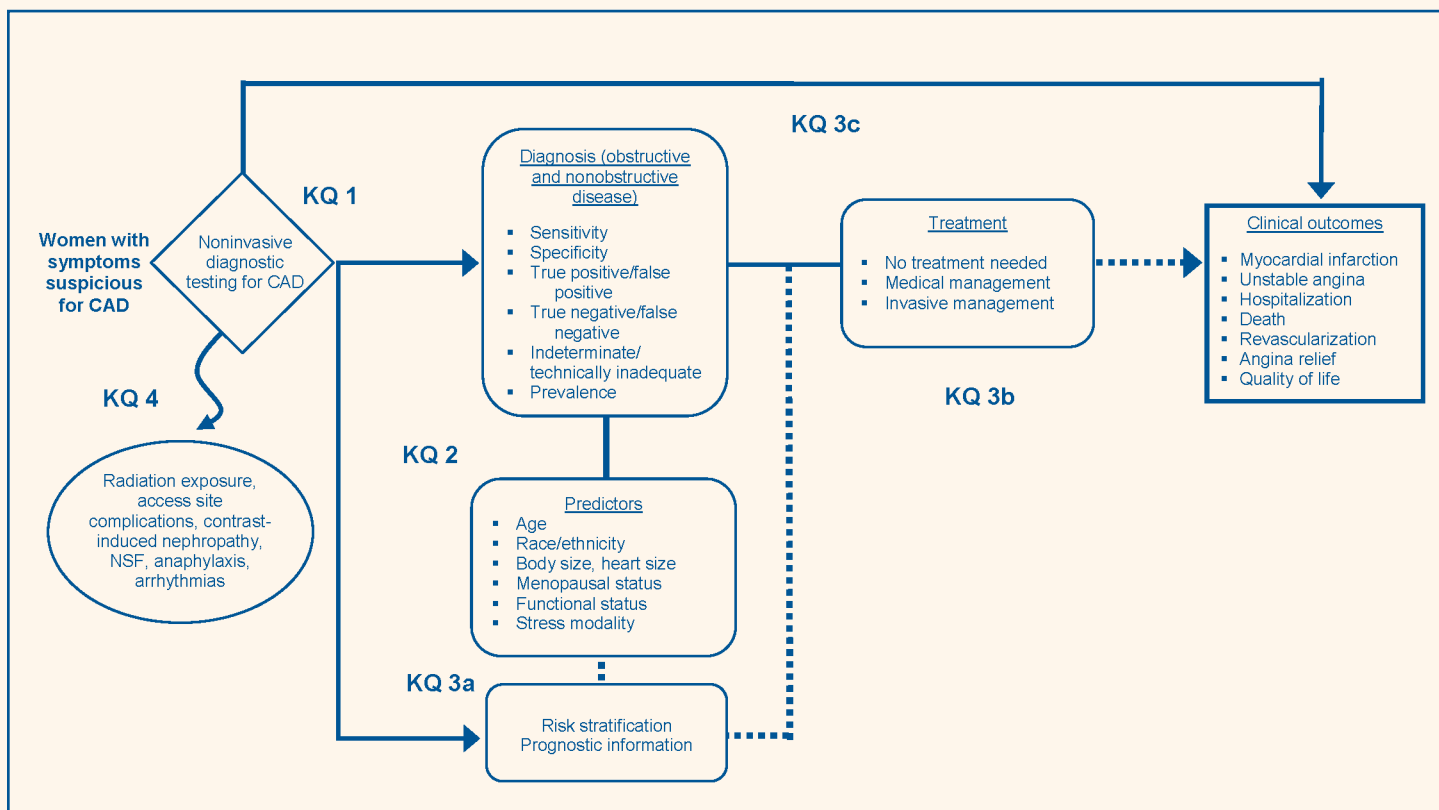
Abbreviations: CAD = coronary artery disease; KQ = Key Question; NSF = nephrogenic systemic fibrosis

Methods

Input From Stakeholders

The Evidence-based Practice Center (EPC) followed AHRQ's recommended methodology, described in Methods Guide for Effectiveness and Comparative Effectiveness Reviews,[5] for literature search strategies, inclusion/exclusion of studies, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each KQ.

During the topic refinement stage, we solicited input from Key Informants, representing clinicians (cardiology, primary care, cardiac imaging), patients, scientific experts, and Federal agencies to help define the KQs. The KQs were then posted for public comment for 30 days, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP), comprising clinical, content, and methodological experts, to provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP did analysis of any kind and did not contribute to the writing of the report.

Data Sources and Selection

We included studies published in English from January 1, 2000, through September 12, 2011. Search strategies were specific to each database in order to retrieve the articles most relevant to the KQs. Our search strategy used the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. We used PubMed®, Embase®, the Cochrane Database of Systematic Reviews, and the Cochrane Central Registry of Controlled Trials for our literature search. We also searched the grey literature of study registries and conference abstracts for relevant articles from completed trials, including Clinicaltrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; WHO: International Clinical Trials Registry Platform Search Portal; CSA Conference Papers Index; and Scopus. The exact search strings used in our strategy are given in Appendix A of the full report. Reference lists of articles applicable to the relevant KQs of previous AHRQ reports on this topic[6,7] and from identified systematic reviews and meta-analyses were manually hand-searched and cross-referenced against our library, and additional manuscripts were retrieved. All citations were imported into an electronic bibliographic database (EndNote® Version X4; Thomson Reuters, Philadelphia, PA).

We developed a list of article inclusion and exclusion criteria for the KQs (Table A). Using the prespecified inclusion and exclusion criteria, titles and abstracts were examined independently by two reviewers for potential relevance to the KQs. Articles included by any reviewer underwent full-text screening. At the full-text screening stage, two independent reviewers read each article to determine if it met eligibility criteria. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to "include" or "exclude" the article for data abstraction. When the paired reviewers arrived at different decisions about whether to include or exclude an article, we reconciled the difference through a third-party arbitrator. Articles meeting our eligibility criteria were included for data abstraction. Relevant systematic review articles, meta-analyses, and methods articles were flagged for hand-searching and cross-referencing against the library of citations identified through electronic database searching.

Table A. Summary of inclusion and exclusion criteria		
Study Characteristic	**Inclusion Criteria**	**Exclusion Criteria**
Study design	An article was included if the following two criteria were met: • Original data or related methodology paper of an included article • Randomized controlled trial, prospective or retrospective observational study, or registry	• Not a systematic review • Letter to editor • Case series • Review article, meta-analysis, or methods paper of an excluded article • Not peer reviewed
Population	Study included adult women (age ≥ 18 years of age) who present symptoms of symptoms suspicious for CAD (e.g., exertional dyspnea, shortness of breath, and/or angina) with or without a known diagnosis of CAD; data for women must be presented separately from data for men	• All subjects were < 18 years of age, or some subjects were under < 18 but results were not broken down by age • No patients had symptomatic chest pain (i.e., an asymptomatic population), or some of the patients had symptomatic chest pain but results were not reported separately for this subgroup • All patients were known to have CAD and were not being tested for chest pain symptoms (e.g., postrevascularization testing to assess for persistent ischemia)
Interventions	NITs for the diagnosis of obstructive and nonobstructive CAD included: • Exercise electrocardiogram stress test • Resting electrocardiogram technology • Exercise/stress echocardiography with or without a contrast agent • Exercise/stress radionuclide myocardial perfusion imaging, including single proton emission computed tomography and positron emission tomography • Stress myocardial perfusion and wall motion magnetic resonance imaging • Coronary computed tomography angiography	Coronary artery calcium scoring by electron beam computed tomography since this modality is often used to screen asymptomatic patients for CAD
Comparators	Another NIT or coronary angiography	Study did not compare one NIT with another, or with coronary angiography

Table A. Summary of inclusion and exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Outcomes	Primary outcome—accurate diagnosis of obstructive and nonobstructive CAD	Outcomes not related to diagnostic accuracy for detecting CAD
	KQ 1 patient-level outcomes: • Sensitivity • Specificity • True positive, false negative, true negative, false positive • Indeterminate or technically inadequate results • Prevalence	• Vessel-based outcomes • Outcomes of women not reported separately from total population
	KQ 2 outcomes: Predictors of diagnostic accuracy—age, race/ethnicity, body size, heart size, menopausal status, functional status, stress modality	Outcomes of women not reported separately from total population
	KQ 3 outcomes: • Risk stratification/prognostic information • Treatment —none, medical therapy, percutaneous coronary intervention, or coronary artery bypass surgery • Clinical outcomes—death, myocardial infarction, unstable angina, hospitalization, revascularization, angina relief, quality of life	Outcomes of women not reported separately from total population
	KQ 4 outcomes: Safety and adverse events—radiation exposure, access site complications, contrast agent-induced nephropathy, nephrogenic systemic fibrosis, anaphylaxis, arrhythmias—and how these events varied by demographic factors	Outcomes of women not reported separately from total population
Setting	Inpatient or outpatient settings, primarily primary care and cardiology clinics	None
Publication languages	English only	Given the high volume of English-language publications (including the majority of known important studies), non-English articles were excluded

Abbreviations: CAD = coronary artery disease; KQ = Key Question; NIT = noninvasive technology

Data Extraction and Quality Assessment

The investigative team created forms for abstracting the data elements for the KQs. Based on their clinical and methodological expertise, two researchers were assigned to abstract data from the eligible articles pertaining to the research questions. One researcher abstracted the data, and the second overread the article and the accompanying abstraction form to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus was not reached by the first two researchers. To aid in both reproducibility and standardization of data collection, researchers received data abstraction instructions directly on each form created specifically for this project with the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada). We designed these forms to collect the data required to evaluate the specified eligibility criteria for inclusion in this review as well as to collect demographics and data needed to determine outcomes (intermediate outcomes, health outcomes, and safety outcomes). Appendix B of the full report lists the elements used in the data abstraction forms.

Appendix C of the full report contains a bibliography of all studies included in this review, organized alphabetically by author. When appropriate, methods articles providing additional detail were considered when abstracting data for an included study.

The studies included in this comparative effectiveness review were assessed on the basis of the quality of their reporting of relevant data. We evaluated the quality of individual studies using the approach described in AHRQ's Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter referred to as the Methods Guide).[5] To assess study quality, we (1) classified the study design, (2) applied predefined criteria for quality and critical appraisal, and (3) made a summary judgment of the study's quality. To evaluate methodological quality, we applied criteria for each study type that were derived from the core elements described in the Methods Guide[5] and from QUADAS,[8] a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of Good, Fair, and Poor based on the study's adherence to well-accepted standard methodologies (such as QUADAS) and adequate reporting standards.

We used data abstracted on the population studied, the intervention and comparator, the outcomes measured, settings, and timing of assessments to identify specific issues that may have limited the applicability of individual studies or a body of evidence as recommended in the Methods Guide.[5,9] We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison with the target population, the intervention used in comparison with technologies currently in use, and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively. Appendix D of the full report summarizes our assessment of the quality and applicability for each included study as well as the assessed QUADAS quality scores for diagnostic accuracy.

Data Synthesis and Analysis

We summarized the primary literature by abstracting relevant continuous data (e.g., age, sensitivity, specificity, event rates) and categorical data (e.g., race/ethnicity, presence of CAD). Data for patients with no known diagnosis of CAD were collected and analyzed separately from data for mixed CAD populations that included patients with and without known CAD. We then determined the feasibility of completing a quantitative synthesis (i.e., summary receiver operating characteristic [SROC] curves for diagnostic accuracy or meta-analysis for other outcomes). The feasibility of a meta-analysis or SROC curve depended on the volume of relevant literature, the homogeneity of the studies in terms of the populations studied, the interventions included or the outcomes assessed, and the completeness of the results reporting. For each SROC calculation, we ran separate analyses of the accuracy of each NIT modality compared with coronary angiography on the no-known CAD and mixed CAD populations using random-effects models to quantitatively synthesize the available evidence. In our primary analyses, we evaluated these performance characteristics in the population of women who had no previously known CAD. In secondary analyses, we explored a broader patient population by including those studies that had women from mixed populations of known and no known CAD. We also assessed the impact on our findings if, in each population, we restricted our analyses to those studies that were assessed to be good quality. We then compared the performance characteristics of the NIT modalities with each other in a generalized linear mixed model. In a final exploratory analysis, we evaluated the test performance of the modalities in women compared with men in a similar generalized linear model with sex as a covariate. We presented summary estimates and confidence intervals (CIs).

For synthesizing the accuracy data for studies included in our assessment of KQ 1, we used the following approach as advocated by Leeflang et al.[10] This approach allows the paired nature of sensitivity and specificity and randomness between studies to be taken into account. The analyses are based on true positive (TP), false negative (FN), false positive (FP), and true negative (TN) frequencies abstracted from relevant publications. Estimated study specific sensitivity (TP/[TP+FN]) and specificity (TN/[TN+FP]) values are displayed in paired forest plots together with exact 95% CIs.[11] The fixed-effects estimates and their variance–covariance matrix provided (after reverse logit transformation) summary sensitivity and specificity values and a joint confidence region (dotted oval shape on figures) as well as separate CIs for summary sensitivity and specificity as presented on figures and forest plots in the report. We used the Rutter and Gatsonis[12] SROC curve as described by Arends et al.,[13] and it is presented in figures as a solid line over the range of the available data.

Grading the Body of Evidence

The strength of evidence for each Key Question was assessed using the approach described in AHRQ's Methods Guide on Medical Test Reviews for grading the evidence related to the diagnostic accuracy of the NITs (KQ 1),[14] and the Methods Guide for Effectiveness and Comparative Effectiveness Reviews for grading the evidence related to the other Key Questions (KQs 2–4).[5,15] The evidence was evaluated using the four required domains: risk of bias (low, medium, or high), consistency (consistent, inconsistent, or unknown/not applicable), directness (direct or indirect), and precision (precise or imprecise). Additionally, when appropriate, the studies were evaluated for the presence of confounders that would diminish an observed effect, the strength of association (magnitude of effect), and publication bias. The strength of evidence was assigned an overall grade of High, Moderate, Low, or Insufficient according to the following four-level scale:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
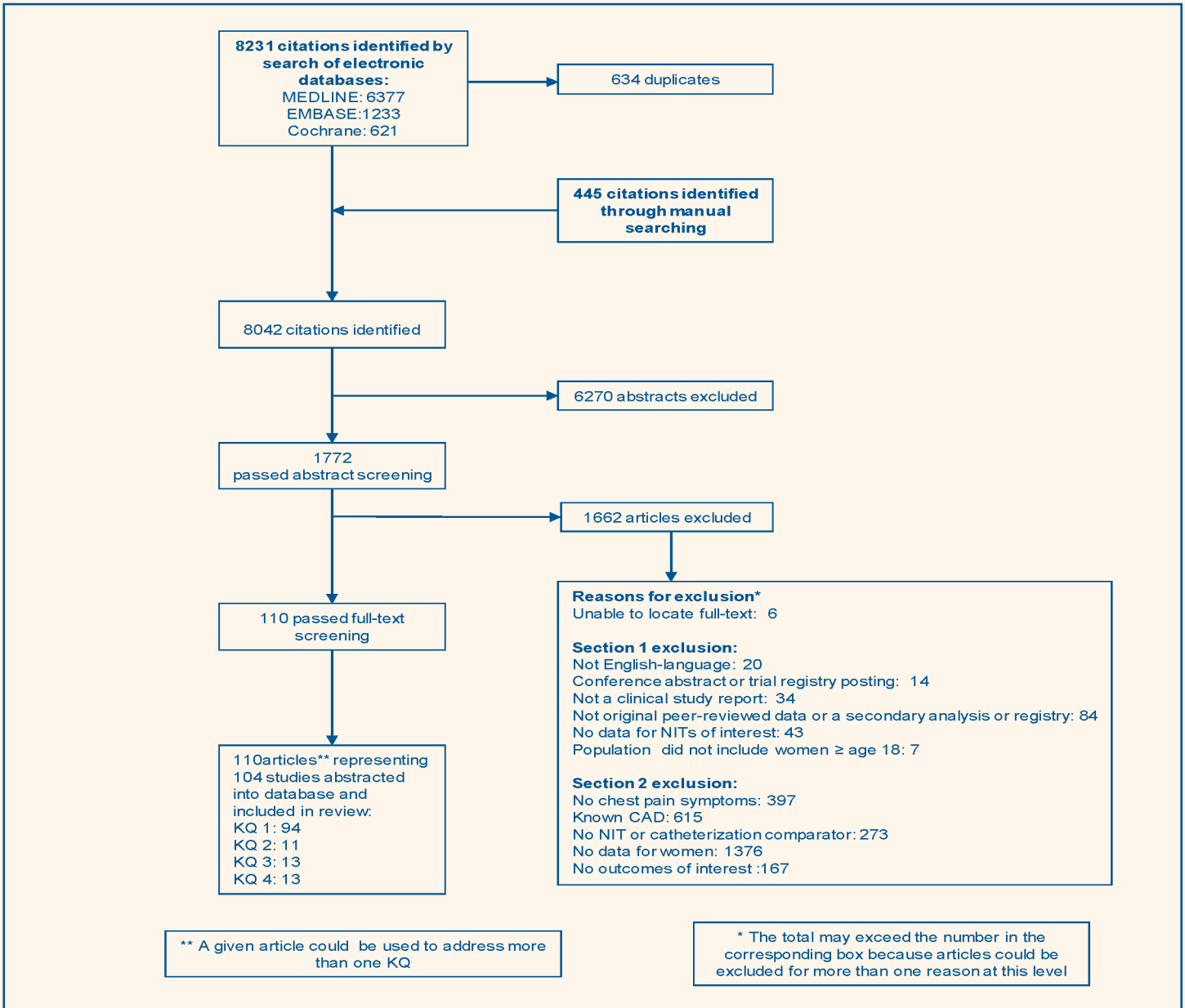
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

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

- Insufficient—Evidence either is unavailable or does not permit estimation of effect.

Results

The flow of articles through the literature search and screening process is depicted in Figure B. Of the 8,231 citations identified by our searches, 634 were duplicates. A manual search identified an additional 445 citations for a total of 8,042 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 1,772 full-text articles were retrieved and screened. Of these, 1,662 articles were excluded at the full-text screening stage. Of these, we excluded 1,376 (83 percent) for not reporting data on women and 615 (37 percent) for looking only at a population with known CAD. (Note that an article may have been excluded for more than one reason.) The final set comprised 110 articles representing 104 studies.

Of the 104 studies, 1 was an RCT, 79 were prospective observational, and 24 were retrospective observational with study cohorts comprising individuals who presented for NIT testing and received diagnostic coronary angiography (100 studies) or another NIT modality only (4 studies). The four studies without coronary angiography compared ECHO with ECG[16,17] or ECG with SPECT.[18,19] Three of these studies were applicable to KQ 3,[16-18] and one was applicable to KQ 2.[19] Of the 94 studies included in the KQ 1 results, 5 reported NIT versus NIT comparisons in addition to coronary angiography.[20-24]

Figure B. Literature flow diagram

8231 citations identified by search of electronic databases:
MEDLINE: 6377
EMBASE: 1233
Cochrane: 621

→ 634 duplicates

445 citations identified through manual searching

8042 citations identified

→ 6270 abstracts excluded

1772 passed abstract screening

→ 1662 articles excluded

110 passed full-text screening

110 articles** representing 104 studies abstracted into database and included in review:
KQ 1: 94
KQ 2: 11
KQ 3: 13
KQ 4: 13

Reasons for exclusion*
Unable to locate full-text: 6

Section 1 exclusion:
Not English-language: 20
Conference abstract or trial registry posting: 14
Not a clinical study report: 34
Not original peer-reviewed data or a secondary analysis or registry: 84
No data for NITs of interest: 43
Population did not include women ≥ age 18: 7

Section 2 exclusion:
No chest pain symptoms: 397
Known CAD: 615
No NIT or catheterization comparator: 273
No data for women: 1376
No outcomes of interest: 167

** A given article could be used to address more than one KQ

* The total may exceed the number in the corresponding box because articles could be excluded for more than one reason at this level

Abbreviations: CAD = coronary artery disease; KQ = Key Question; NIT = noninvasive technology; SR = systematic review

Summary of Key Findings

We analyzed the results by study population (no known CAD and mixed CAD populations) and by study quality (good quality rating). Table B and Figure C show the summary sensitivities and specificities for each NIT modality. Table C summarizes our key findings.

Modality	Population	Quality of Included Studies	Number of Studies	Number of Women	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)
ECG	No known CAD	All	29	3,392	62% (55%–68%)	68% (63%–73%)
		Good	10	1,410	70% (58%–79%)	62% (53%–69%)
	Mixed population	All	41	4,879	61% (54%–67%)	65% (58%–72%)
		Good	13	1679	65% (52%–76%)	60% (52%–68%)
ECHO	No known CAD	All	14	1,286	79% (74%–83%)	83% (74%–89%)
		Good	5	561	79% (69%–87%)	85% (68%–94%)
	Mixed population	All	22	1,873	78% (73%–83%)	86% (79%–91%)
		Good	8	807	77% (65%–85%)	89% (76%–95%)
SPECT	No known CAD	All	14	1,000	81% (76%–86%)	78% (69%–84%)
		Good	4	394	83% (52%–95%)	72% (37%–92%)
	Mixed population	All	30	2,146	82% (77%–87%)	81% (74%–86%)
		Good	10	982	82% (72%–88%)	79% (66%–87%)
CMR	No known CAD	All	5	501	72% (55%–85%)	72% (55%–85%)
		Good	5	501	84% (69%–93%)	84% (69%–93%)
	Mixed population	All	6	778	78% (61%–89%)	84% (74%–90%)
		Good	5	610	76% (55%–89%)	84% (72%–91%)
Coronary CTA	No known CAD	All	5	474	93% (69%–99%)	77% (54%–91%)
		Good	3	124	85% (26%–99%)	73% (17%–97%)
	Mixed population	All	8	690	94% (81%-98%)	87% (68%–96%)
		Good	4	201	83% (58%–94%)	77%% (40%–94%)

Abbreviations: CAD = coronary artery disease; CI = confidence interval; CMR = cardiac magnetic resonance; CTA = computed tomography angiography; ECG = exercise/stress electrocardiogram; ECHO = echocardiogram; SPECT = single proton emission computed tomography

Figure C. Summary of accuracy of NITs compared with coronary angiography for diagnosing CAD in women with no known CAD (all studies)
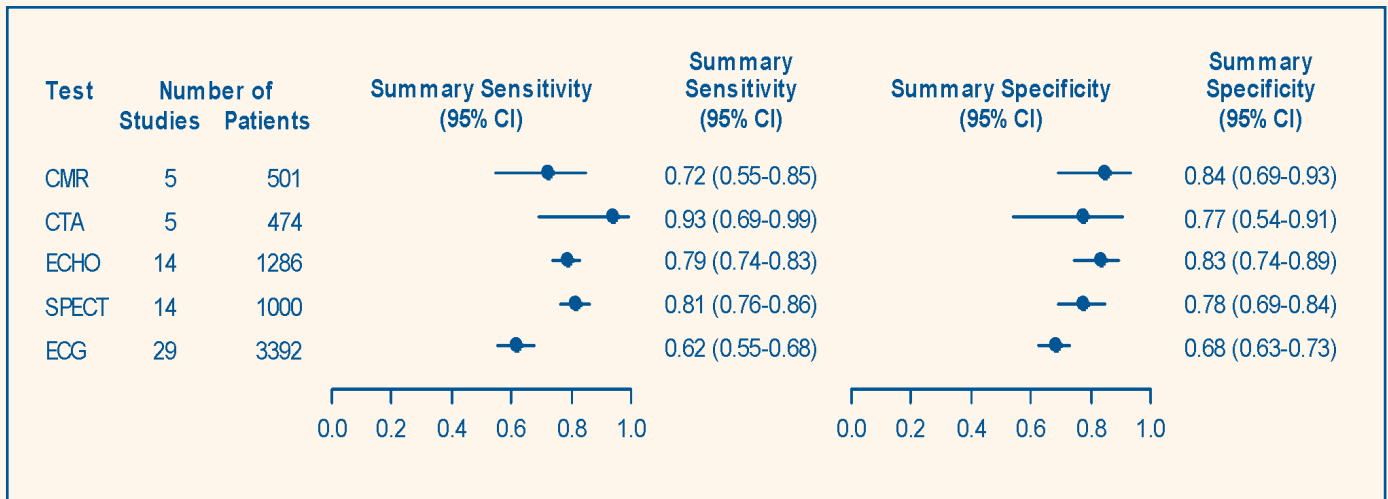
Test	Number of Studies	Patients	Summary Sensitivity (95% CI)	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)	Summary Specificity (95% CI)
CMR	5	501		0.72 (0.55-0.85)		0.84 (0.69-0.93)
CTA	5	474		0.93 (0.69-0.99)		0.77 (0.54-0.91)
ECHO	14	1286		0.79 (0.74-0.83)		0.83 (0.74-0.89)
SPECT	14	1000		0.81 (0.76-0.86)		0.78 (0.69-0.84)
ECG	29	3392		0.62 (0.55-0.68)		0.68 (0.63-0.73)

0.0 0.2 0.4 0.6 0.8 1.0   0.0 0.2 0.4 0.6 0.8 1.0

Table C. 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) or 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 C. 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.

Table C. Summary of key findings (continued)		
Key Question	**Strength of Evidence**	**Conclusions**
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.

Discussion

In summary, the findings of this comparative effectiveness review provide evidence for the accuracy of exercise/stress ECG, ECHO, SPECT, CMR, and coronary CTA compared with coronary angiography used for diagnosing CAD in women. The diagnostic accuracy appears to be consistent over time except for the sensitivity of CMR, which appears to be increasing over time (although the large confidence intervals reflect the underlying uncertainty in this measure). We are confident that the summary statistics for ECG, ECHO, and SPECT are robust and unlikely to change with the addition of new studies based on both the number of good-quality trials comparing these modalities with coronary angiography and the tight confidence intervals. More good-quality studies comparing CMR or coronary CTA with coronary angiography in the no-known CAD population and reporting sex-based results are needed to strengthen the summary statistics for those modalities.

Decisions around performing tests (either noninvasive or invasive) in patients with symptoms suspicious for CAD revolve around first understanding the pretest probability and testing/action thresholds for patients from the AHA/ACC stable angina guidelines and appropriate use criteria for the various NIT modalities.[25-28] Specifically, clinicians faced with patients who have a guideline-defined low-to-intermediate pretest probability of CAD may decide to obtain a noninvasive test, ideally with a high negative predictive value in this population and low risk of adverse events, in order to "rule out" disease. These may be patients with atypical chest pain (e.g., reflux or musculoskeletal disease) who are concerned about a heart problem and who require reassurance that their symptoms are not cardiac in origin. In contrast, in patients with high pretest probability of CAD (greater than 90 percent chance), a test with very high positive predictive value in this population and potentially more risk may be chosen since the disease of interest is thought to be present; in these cases, invasive angiography—the gold standard—is recommended by the current clinical practice guidelines. Finally, it is the spectrum of intermediate probability between 10 and 90 percent for which the clinicians must choose noninvasive tests that provide the right balance of sensitivity, specificity, and clinical risk to warrant testing. The choice of NIT may differ by clinician preference, availability, or setting (outpatient vs. chest pain unit of an emergency department).

It is in this context that the findings of this report on the effectiveness of NITs in women must be considered. First, women are thought to be at lower pretest probability of CAD when evaluated in comparison with men of the same age. When comorbidities or risk factors are taken into account, the pretest likelihood increases with a higher number of comorbidities. Second, women susceptible to

some of the adverse effects of testing may have poor test performance or have higher rates of complication from invasive arterial access. Third, because of body shape and limited functional capacity, women may not obtain the same test performance that men do from noninvasive testing. Finally, because of the lack of full representation of women across the spectrum of disease, the available literature may not provide data on performance at the ends of the probability spectrum. Spectrum bias may be present since the studies we evaluated had potentially varied populations and varied disease definitions.

While readers may assume that requiring coronary angiography as the comparator would bias this report toward a higher risk CAD population, we found that the mean CAD prevalence ranged from 0.26 to 0.44; thus there was a broad spectrum of CAD prevalence in these studies. In fact, the range of CAD prevalence in this review is similar to a recent analysis of a large administrative database of patients referred for coronary angiography in which the prevalence of significant obstructive disease was 38 to 40 percent.[29] The patient population that does not require coronary angiography can be characterized as having symptoms with low suspicion for CAD or pretest probability of less than 10 percent (note that all included studies enrolled patients with "suspected CAD"). Thus, results from this review would not apply to patients with low pretest probability of disease (e.g., gastroesophageal reflux, musculoskeletal pain, or panic attacks) where an NIT may be performed for clinical reassurance that their symptoms are noncardiac in origin.

In general, because there are few patients with high pretest probability, most clinicians would prefer to have patients undergo one NIT prior to determining a treatment choice or referral to coronary angiography. More than one NIT test is often required when the initial test results are equivocal. Our review did not identify studies that discussed the order in which different NITs were used for evaluating CAD. In fact, multiple testing or layered-testing strategies are areas where significant research is needed.

The current data suggest that NITs with higher sensitivity include coronary CTA and SPECT, and stress ECHO may represent an NIT with higher specificity. Stress CMR shows emerging data that may be in the upper range for both sensitivity and specificity. Additionally, the findings also demonstrate that NIT performance in women is not as good as in men, likely due to the reasons addressed above. The accuracy may also be location or operator dependent, and thus the results of published studies conducted at highly specialized centers may not uniformly

apply to those seen in routine practice. Choice of NIT—and whether to use exercise or pharmacological stress imaging—may be influenced by functional capacity, which tends to be lower in women compared with men. Of note, the accuracy data for NIT modalities in men appeared a little higher than expected given previous meta-analyses of diagnostic accuracy data in the total population, which is likely because the published literature combined the accuracy data for men and women. Taken in context, these findings give support to the current ACC/AHA recommendations and studies on noninvasive testing in women.

Women are more likely than men to have false-positive stress tests; i.e., abnormal stress imaging with nonobstructive CAD on coronary angiography. In fact, up to 9 percent of women presenting with acute coronary syndrome will not have obstructive CAD when they undergo coronary angiography for potential PCI.[30] Some experts suggest that these phenomena are due to the presence of microvascular obstruction, the incidence of which is hard to determine since there is no clear diagnostic test used to establish the diagnosis.

Currently, there is debate on whether NITs that measure heart function abnormalities (ECG abnormalities, wall motion abnormality, ischemia), including exercise ECG, stress ECHO, and cardiac nuclear imaging, are equivalent or inferior to NITs that measure anatomic abnormalities (detection of CAD) by CMR or coronary CTA. Will knowing the coronary anatomy (nonobstructive or obstructive) in symptomatic patients lead to better implementation of secondary measures—control of blood pressure, diabetes, and hyperlipidemia—to reduce future cardiac events? Or is it more important to intervene with medications and/or revascularization when ischemia is present? Though this review does not answer these important questions, we describe this evidence gap in the Future Research section.

Limitations of This Review

Despite identifying 104 studies (110 articles) that met the inclusion criteria, this systematic review has several limitations. First, our search focused on comparator studies of the various NITs with a gold standard of coronary angiography for establishing the diagnosis of CAD in symptomatic patients. While this focus was adequate for identifying studies to assess the diagnostic accuracy of the NIT modalities in women, we found very few comparative studies that reported the influence of clinical characteristics or patient demographics on diagnostic accuracy. Few comparative studies (NIT vs. coronary angiography, or

NIT vs. NIT) provided information on incremental risk stratification, prognostic information, or meaningful information regarding decisionmaking, and few reported the significant risks in women. Study results on these issues were reported for the total patient population and did not separate the effects by sex. Many of the included studies were single-sex (women) studies and limited our ability to fully evaluate sex differences. Also, by focusing on symptomatic patients, this report did not review the use of coronary artery calcium scoring for asymptomatic, high-risk populations.

We are aware that there are several noncomparator studies of each of the NIT modalities that address these issues in women since routine clinical care does not require two NIT modalities or an NIT modality plus coronary angiography for the diagnostic workup of suspected CAD. Given the focus on comparative effectiveness, we did not include these noncomparator studies in our review. By focusing the review on comparative studies, however, we are reducing the bias that is inherent in noncomparative studies. Noncomparative studies have selection, spectrum, and intervention biases for the following reasons: The choice of NIT is determined by the treating provider; only a subset of patients with indeterminate or positive results are referred for further NIT testing or coronary angiography; and the clinical outcomes may be influenced by the medical treatments or revascularization options that are offered. Second, the sample size and low representation of women in most of the comparator studies may affect the authors' ability to analyze the results by sex, therefore reducing the number of studies reporting these findings separately. Third, most studies lacked long-term followup of the patient population, which affected our ability to find studies that reported prognostic information on how the different NITs influenced clinical outcomes. Finally, our summary of the harms and risks of NITs is limited by the lack of disclosure of periprocedural and postprocedural complications in most of the studies.

Conclusions

This systematic review has provided evidence for the summary sensitivities and specificities of exercise/stress ECG, ECHO, SPECT, CMR, and coronary CTA compared with coronary angiography in women. There was limited or insufficient evidence on the influence of clinical and demographic factors on comparative diagnostic accuracy, risk stratification, prognostic information, treatment decisions, clinical outcomes, and harms from different NITs specifically in women. Modifying the search criteria to include noncomparator studies of NIT modalities may increase the number of studies that address this limitation.

Future Research

This comprehensive review of the comparative effectiveness of NIT modalities for diagnosing women with suspected CAD identified numerous gaps in evidence that would be suitable for future research and for improving the reporting of findings of NIT studies in the published literature.

Randomized trials comparing functional versus anatomic modalities. Almost all the studies reviewed were prospective observational studies where patients already scheduled for coronary angiography also underwent one or two NIT modalities to assess the diagnostic accuracy of the NITs. In routine clinical practice, clinicians order one type of NIT modality based on a patient's ability to exercise, test availability, and clinician preference. Exercise ECG, stress ECHO, and nuclear imaging all measure functional parameters to assess for ischemia and obstructive CAD. Newer technologies such as coronary CTA and CMR offer clinicians the ability to evaluate anatomic parameters to assess both nonobstructive and obstructive CAD. A comparison of a functional testing strategy to an anatomic testing strategy for patients with symptomatic chest pain is currently being done in two large clinical trials (PROMISE [NCT001174550] and RESCUE [NCT01262625]). The information from these clinical trials could inform how the choice of an NIT modality affects prognosis, treatment decisions, and clinical outcomes.

Studies assessing outcomes beyond diagnostic accuracy. Our review found very few comparative NIT studies that looked at risk stratification, prognostic information, treatment decisions, and clinical outcomes. Future studies, whether observational or controlled clinical trials, should have long-term followup of patient cohorts to assess these factors. This is important because a positive NIT result could lead to further testing to establish the diagnosis of CAD as well as lead to more attention to secondary prevention for CAD. As stated previously, multiple testing or layered-testing strategies, plus the influence on risk-factor modification (e.g., medication prescriptions and adherence), are areas where significant research is needed.

Studies of sufficient sample size and representation of women. Many studies assessing the comparative diagnostic accuracy of an NIT modality with another NIT modality or with coronary angiography did not present a sample size calculation for the numbers needed per group. In addition, after excluding the women-only studies, the studies with both sexes had low representation of women. In order to assess sex differences in NIT diagnostic accuracy or the impact on clinical outcomes, a sufficient

sample size is required to have adequate statistical power for subgroup analyses.

Reporting sex and CAD population subgroups separately. From 1,662 citations, we excluded 1,376 (83 percent) for not reporting data on women and 615 (37 percent) for looking only at a population with known CAD. Since publication of the AHRQ report on the use of NITs in women,[6,7] there has been an increase in the number of studies reporting sex-based differences. We encourage more reporting of women's results as well as separating the results from no known CAD and known CAD populations. One challenge we encountered in this review was that the primary data representing the numbers of TP, TN, FP, and FN were not presented in most studies and often needed to be back-calculated based on reported sensitivities and specificities and underlying disease prevalence for our quantitative synthesis. It would aid future comparisons of modalities if study authors were to report the primary data for women and men separately either within the article itself or within an online supplementary appendix.

Assessing clinical and demographic factors that influence diagnostic accuracy. Clinicians are taught that clinical factors such as weight, heart size, functional status, race/ethnicity, sex, age, and menopausal status can influence the diagnostic accuracy of various NIT modalities. However, we found very few comparative studies that looked at the impact of these clinical and demographic factors on the sensitivity and specificity of NIT results. More evidence about predictors affecting diagnostic cardiac testing is needed to support or dispel these long-held notions. Additional studies of the NIT modalities to assess differing symptomatology and timing at presentation, racial differences, various risk profiles, and different settings (outpatient, inpatient, emergency room) would be help to build the evidence base needed for clinical decisionmaking.

Reporting of risk, harms, and/or safety outcomes. Diagnostic procedures to screen for heart disease can result in harmful clinical events (nephropathy, radiation exposure, access site complications). Systematic reporting of adverse events in publications—in total and by sex—should continue to clarify which NIT modalities are safe after they are approved for use in clinical practice.

Glossary

AHA	American Heart Association
ACC	American College of Cardiology
CAD	coronary artery disease
CMR	cardiac magnetic resonance imaging
CTA	coronary computed tomography angiography
ECG	electrocardiogram, electrocardiography
ECHO	echocardiogram, echocardiography
KQ	Key Question
MeSH	Medical Subject Heading
NIT	noninvasive technology
NSF	nephrogenic systemic fibrosis
PET	positron emission tomography
MI	myocardial infarction
SPECT	single proton emission computed tomography
TEP	Technical Expert Panel

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