Effective Health Care Program

Comparative Effectiveness Review
Number 171

Noninvasive Testing for Coronary Artery Disease

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Noninvasive Testing for Coronary Artery Disease

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Preface

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Noninvasive Testing for Coronary Artery Disease

Structured Abstract

Objectives. This report evaluates the current state of evidence regarding effectiveness and harms of noninvasive technologies for the diagnosis of coronary artery disease (CAD) or dysfunction that results in symptoms attributable to myocardial ischemia in stable symptomatic patients who have no known history of CAD.

Data sources. Systematic searches of the following databases were conducted through July 2015: Ovid MEDLINE®, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, and Evidence-Based Medicine Reviews–Health Technology Assessment. Bibliographies of relevant articles were also reviewed.

Review methods. Using predefined criteria, randomized controlled trials (RCTs) and observational studies comparing the effectiveness or safety of noninvasive cardiac testing—stress electrocardiography (ECG), stress echocardiography, single-photon emission computed tomography (SPECT), positron emission tomography, coronary computed tomography angiography (CCTA), and calcium scoring via computed tomography—with other noninvasive tests, usual care, or no testing were included. Analyses were stratified by pretest risk of CAD as reported by the authors. The quality of included studies was assessed, data extracted, and results summarized qualitatively and using meta-analysis where feasible. The strength of the evidence was assessed for primary outcomes to reflect the confidence in effect estimates: high strength of evidence (greatest confidence), moderate (moderate confidence), low (low confidence), and insufficient (no evidence or no confidence in the estimate).

Results. From 17,146 citations identified, 46 studies were included. Definition of pretest risk across studies varied. There was no clear difference in myocardial infarction (MI) or in all-cause mortality between different testing strategies across settings or pretest risk groups that included patients with intermediate pretest risk, based on low- to moderate-strength evidence from nine trials. Across studies, the frequency was low for all-cause mortality (0%–1.5% in outpatient settings, 0%–1.1% in emergency department [ED] settings past the initial visit) and for MI (0%–0.8% in outpatients, 0%–3% in ED settings). Invasive coronary angiography (ICA) was more common following CCTA than following various functional tests, with a large trial of CCTA versus functional testing providing high-strength evidence. Revascularization referral was more common following CCTA versus functional testing in general (high strength of evidence) and versus exercise ECG (low strength of evidence) but was similar compared with SPECT and usual care (low strength of evidence). In ED settings, additional testing was more common following CCTA than following SPECT (high strength of evidence) but less common versus usual care (moderate strength of evidence). Hospitalization was less common following CCTA than following usual care at the initial ED visit (moderate evidence for intermediate pretest risk; low evidence for low to intermediate pretest risk), but similar for CCTA and functional testing in outpatient settings (moderate strength of evidence). Few studies compared functional tests, and findings were inconsistent for ICA and revascularization referral; however, additional noninvasive testing was less common with SPECT than with exercise ECG (low strength of evidence for all outcomes). The impact of testing on post-test probability of CAD and

subsequent clinical decisions regarding treatment or further testing was not described in RCTs. Harms were rarely reported, and limited information regarding radiation exposure was provided.

Conclusions. A review of current studies found no clear differences between testing strategies across settings with regard to clinical or management outcomes on which to base recommendations for one strategy over another for any given pretest risk group that included patients with intermediate pretest risk. No conclusions regarding low-risk patients or high-risk patients without ACS are possible. Limited evidence from RCTs found no clear differences between CCTA and other strategies in clinical outcomes across risk groups, although anatomic testing may result in a higher frequency of referral for ICA and revascularization. The frequency of all-cause mortality and MI was low across studies in all settings. The absence of information on post-test risk stratification and subsequent decisionmaking precluded evaluation of the impact of testing on patient management or outcomes. Testing strategies vary in radiation exposure; there is inadequate comparative evidence to make judgments regarding exposure for the initial test or downstream testing. Assessment of harms was limited. Future research using more refined evidence-based definitions of pretest risk, coupled with information on post-test risk stratification, its impact on clinical management (treatment and referral for additional testing), and longer term followup to assess clinical outcomes, is needed to determine optimal testing strategies and roles of tests in different pretest risk groups.

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Executive Summary

Background

Nature and Burden of Coronary Artery Disease

The public health and economic burdens of coronary artery disease (CAD) are substantial. CAD causes one in six deaths in the United States and is the leading cause of death globally.[1] Annually, approximately 635,000 Americans experience a new coronary event, 280,000 have a recurrent ischemic event, and an additional 150,000 have a silent first myocardial infarction (MI).[2] A large proportion of ambulatory health care visits are for evaluation of patients with suspected CAD, with an estimated 1.5 percent of the population presenting to health care providers with chest pain every year.[3] An estimated $108.9 billion are spent annually on CAD treatment.[4] Optimizing the process for assessing these patients presents an opportunity to improve patient outcomes and target health resources to where they can have the most impact.

The most common underlying cause of CAD is atherosclerosis, a disease process in which plaque builds up on artery walls and can lead to the partial or complete blockage of coronary arteries. As a result, the heart cannot receive adequate blood, oxygen, and vital nutrients. Plaque causes blockage by two mechanisms: (1) progressive narrowing of the artery because plaque compromises the vessel lumen and (2) thrombotic occlusion of the artery, which occurs when the hard surface of a plaque tears or breaks off and exposes the inner fatty prothrombotic and platelet-attracting components to the site, resulting in enlargement of the blockage. The resulting reduction in blood flow can be either acute or chronic and leads to an imbalance in the blood supply to the myocardium, thus increasing the requirements of the myocardium for oxygenated blood either at rest or during exertion.[5,6]

The most common symptom of obstructive CAD is chest pain (angina), which is the first presenting symptom in at least 50 percent of patients with CAD.[7] Other common symptoms include the angina equivalents dyspnea, early fatigue with exertion, indigestion, palpitations, tightness in the throat, and neck or arm pain. However, because these symptoms are also seen in many common noncardiac conditions, such as gastroesophageal reflux, esophageal spasm, and cervical disc disease, they are much less reliable predictors of CAD. Women and people with diabetes are less likely to experience classic angina, making early diagnosis of CAD challenging in these populations. The onset of symptoms and clinical impact of CAD depend on a variety of factors, including plaque distribution and degree of vessel narrowing; however, lesion severity does not necessarily correlate well with symptoms. Further, CAD may remain asymptomatic for many years.

Diagnosis of CAD

Accurate early diagnosis of CAD in symptomatic patients is important for initiation of appropriate treatment and reduction of CAD-related morbidity and mortality. Diagnosis of CAD begins with a thorough clinical workup, including a physical examination, patient history, and possibly resting electrocardiography (ECG), followed by noninvasive testing if in an outpatient clinic. In addition to physical examination and patient history for people presenting with chest pain to the emergency department (ED), some combination of a resting ECG, chest x ray, and/or serum biomarkers such as cardiac troponins is generally done. If the presentation is not acute, the ECG is nonspecific, and cardiac troponins are normal, then the stable patient may be discharged

or receive further testing to help determine the etiology of chest pain and the appropriate management. Patients with a high suspicion for a noncardiac etiology of chest pain may forgo evaluation for occlusive CAD or ischemia in favor of pursuing other testing for such causes (e.g., pulmonary embolism).

A diagnosis of CAD can be made by looking for evidence of the pathophysiologic processes of disease, including anatomic changes of the arterial wall, impaired myocardial perfusion, or consequences of impaired perfusion, such as myocardial contractile dysfunction. Historically, invasive coronary angiography (ICA) has been considered the standard reference diagnostic test for anatomic CAD, defined here as any obstructive lesion that is consistent with symptoms or that may carry an increased risk of acute coronary syndrome (ACS), although its invasive nature makes it less ideal in many patients because of its associated risks and costs. Noninvasive tests are another option, and provide diagnostic and prognostic information that can improve risk stratification, thus guiding subsequent testing and interventions. Noninvasive diagnostic tests can be broadly divided into two categories: functional tests and anatomic tests. Functional tests provide information not provided by standard ICA, such as whether symptoms are correlated with areas of ischemia. Functional tests include exercise ECG, exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single-photon emission computed tomography (SPECT) or positron emission tomography (PET), pharmacologic stress magnetic resonance imaging (MRI), computed tomography (CT), and Doppler ultrasound–derived flow reserve measurements. Noninvasive anatomic tests include coronary CT angiography (CCTA) and coronary artery calcium scoring (CACS). American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Appropriate Use Criteria suggest that, as a general rule, functional testing is more informative than noninvasive anatomic evaluation and exercise testing is more informative than pharmacologic testing.[8]

Deciding which test to use for diagnosis of CAD in stable symptomatic patients is not a simple matter. A patient's pretest CAD risk can be informative as to the test or procedure most appropriate as a first step toward diagnosing CAD. While there are a number of standard risk-assessment tools, these are rarely documented in clinical practice, and the clinician's overall assessment of sociodemographic characteristics (e.g., sex, age) and characteristics of the chest pain (typical or atypical) is the most common assessment of pretest likelihood of CAD. Pretest risk of CAD is frequently based on the ACCF/AHA Guideline and defined as low (<10% pretest probability of CAD), intermediate (10%–90% pretest probability of CAD), or high (>90% pretest probability of CAD).[9] Patients at low pretest risk may undergo noninvasive testing to further delineate their risk and to provide a basis for clinical decisionmaking, although in some cases, an alternative explanation for the symptoms (such as heartburn, costochondritis, or pulmonary disease) may be evaluated first. Patients at intermediate risk commonly undergo noninvasive testing, followed by appropriate treatment for comorbidities and risk factors. The ACCF/AHA intermediate range is intentionally broad, reflecting the availability of noninvasive tests that have been viewed as both safe and effective to further stratify risk in the intermediate pretest risk category. In other words, the low end of the intermediate range is extended irrespective of cost because of the important health consequences of missing disease, but this also results in a situation in which testing is performed in a very large number of individuals who do not have disease.[10] The high end is extended because of the combination of the somewhat high cost and risk of ICA and reasonably high sensitivity of testing to detect high-risk obstructive disease. Patients at high risk may undergo noninvasive testing, although at times clinicians may appropriately decide to bypass noninvasive stress testing and proceed directly to ICA.[8] This is

more frequently done in patients who present to the ED with typical symptoms. In patients for whom clinical judgment remains equivocal, an additional test to further identify risk may be pursued.

The 2012 ACCF/AHA Guideline states that diagnostic testing is most valuable when the pretest probability of ischemic heart diseases is intermediate (10%–90%) and provides a range of options for tests that may be used in a given scenario. However, the effectiveness of different modalities with regard to impact on clinical outcomes is not compared.[9] There remains uncertainty regarding which tests, if any, may be most suitable and most beneficial for specific scenarios in patients who present with symptoms suggestive of CAD. Specifically—

- In patients with low pretest probability of CAD (<10%), are clinical outcomes improved by use of stress testing with or without imaging or with no further testing? It is not clear whether imaging may be necessary in this group of patients, or if there are specific subgroups of low-risk patients who might benefit more from one type of testing than another or who should have no further testing.
- How do tests compare with regard to improvement in clinical outcomes (e.g., MI, premature mortality, and congestive heart failure) in patients whose risk is very low (<5%) or in patients with intermediate to high risk? How do tests differ in their ability to reclassify patient risk after the test and to influence appropriate patient management?
- Are there differences in clinical outcomes following anatomic versus functional testing in either the low-risk group or the group with intermediate to high risk?

Scope and Key Questions

The objective of this review is to assess the effectiveness of noninvasive technologies for the diagnosis of CAD or dysfunction that results in symptoms attributable to myocardial ischemia in patients who present with signs or symptoms suggestive of CAD, whose condition is considered to be stable, and who have no known history of CAD. The intended focus is on clinical outcomes and clinical pathways following the first diagnostic test performed as a result of initial risk assessment, which includes clinical presentation and physical exam, family history of CAD, and findings on resting ECG. Further, this report focuses on established tests for diagnosing CAD. Harms related to both the initial test and subsequent testing are evaluated. Information on the traditional measures of accuracy (e.g., sensitivity and specificity) of noninvasive tests versus the historically accepted gold standard of ICA comprises the majority of the literature and is presented for context. Increasingly, experts in cardiovascular health indicate that evidence on the value of noninvasive diagnostic cardiovascular testing needs to expand beyond traditional measures of test performance, such as sensitivity and specificity compared with a given reference standard, and focus on evaluating the impact of such testing on hard cardiovascular outcomes and downstream harms. Thus, while diagnostic accuracy measures provide important information on test performance, the primary focus of this report is to determine whether noninvasive tests improve clinical health outcomes and impact patient management.

The analytic framework (Figure A) shows the target population, interventions, and outcomes that were examined.

The Key Questions for this Comparative Effectiveness Review are as follows.

In stable symptomatic patients with suspected CAD who do not have previously diagnosed CAD and who have had a resting ECG—

For patients considered to be at ***very low or low risk*** for CAD, what is the comparative effectiveness of **anatomic tests (compared with each other, usual care, or no testing)?**

For patients considered to be at ***very low or low risk*** for CAD, what is the comparative effectiveness of **functional tests (compared with each other, usual care, or no testing)?**

For patients considered to be at ***intermediate to high risk*** for CAD, what is the comparative effectiveness of **anatomic tests (compared with each other, usual care, or no testing)?**

For patients considered to be at ***intermediate to high risk*** for CAD, what is the comparative effectiveness of **functional tests (compared with each other, usual care, or no testing)?**

What is the comparative effectiveness of **anatomic tests versus functional tests** in those who are at ***very low or low risk*** for CAD?

What is the comparative effectiveness of **anatomic tests versus functional tests** in those who are at ***intermediate to high risk*** for CAD?

For each Key Question, the following subquestions were explored:

a. What is the effectiveness of the compared tests for improving primary clinical health outcomes (e.g., quality of life, avoiding MI)?

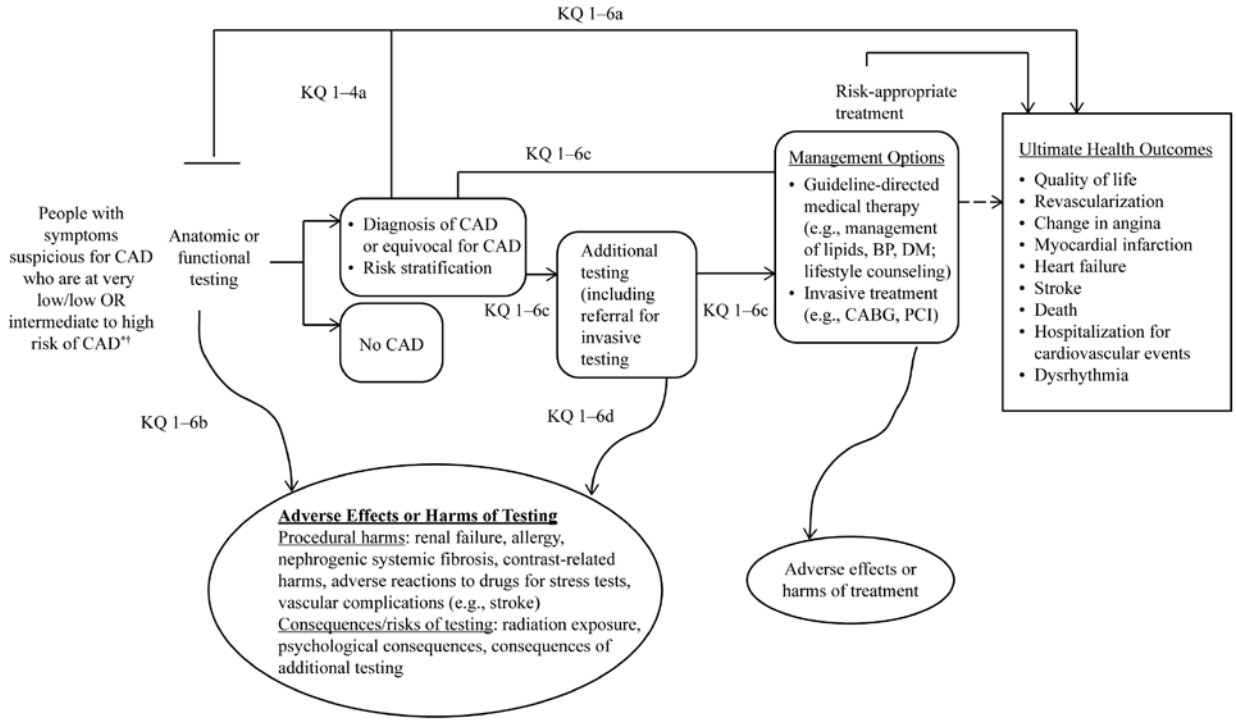
b. What are the adverse effects, consequences, or harms of testing?

c. How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?

d. What harms are associated with additional testing following anatomic tests?

e. Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities) or the patient's ability to exercise?

Figure A. Analytic framework for noninvasive testing for coronary artery disease



BP = blood pressure; CABG = coronary artery bypass graft; CAD = coronary artery disease; DM = diabetes mellitus; KQ = Key Question; PCI = percutaneous coronary intervention
*People at very low or low risk are evaluated separately from those at intermediate to high risk when possible.
†KQ 1–6e: Potential modifiers related to differential efficacy and/or safety include patient factors (e.g., age, sex), comorbidities, and ability to exercise.

Methods

The methods for this Comparative Effectiveness Review follow the guidance in the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (Methods Guide).[11]

Topic Refinement and Review Protocol

The topic for this Comparative Effectiveness Review was ranked as a priority topic by a panel of stakeholders convened through the Duke Evidence-based Practice Center's Cardiovascular Topic Identification project. The preliminary Key Questions were posted on AHRQ's Web site for public comment for 4 weeks. Public comments and input from the Technical Expert Panel (TEP) were used to develop the final Key Questions and protocol. The TEP, convened to provide high-level content and methodological guidance to the review process, consisted of experts in cardiology and cardiac diagnostic testing, radiology, internal medicine, and health services research, as well as professional organizations and policymakers. TEP members disclosed all financial or other conflicts of interest prior to participation. The AHRQ Task Order Officer and the investigators reviewed the disclosures and determined that the TEP members had no conflicts of interest that precluded participation.

Both the final topic-refinement document and the systematic review protocol, developed prior to initiation of the review, can be found on the AHRQ Web site at

www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/. The protocol is also registered with the PROSPERO international database of prospectively registered systematic reviews (CRD42015022081).

Literature Search Strategy

A research librarian conducted searches for primary studies in the following databases through July 2015: Ovid MEDLINE®, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Evidence-Based Medicine Reviews–Health Technology Assessment. A search strategy was developed based on an analysis of the medical subject heading (MeSH) terms and text words of key articles identified a priori. (The full search strategy is available in Appendix A of the full report.) Search start dates were not restricted. The reference lists of included articles and relevant review articles were also reviewed. All citations were downloaded and imported into an electronic database (EndNote® X7, Thomson Reuters, Philadelphia, PA). A list of relevant drugs and manufacturers was provided to the Scientific Resource Center, which requested Scientific Information Packets, and relevant published and unpublished studies were assessed for inclusion in the final report. Additional details regarding handling of citations are found in the full report and in Appendix A of the full report.

Literature searches were updated during the public comment and peer review period in order to ensure that any new publications that met our inclusion criteria were incorporated into the final report.

Inclusion and Exclusion Criteria

Criteria for inclusion and exclusion of studies were based on the Key Questions and the PICOTS (populations, interventions, comparators, outcomes, timing, and setting) approach. Studies of stable symptomatic adult patients undergoing their first noninvasive diagnostic test for suspected CAD were sought. Studies of patients with known CAD (prior MI or prior revascularization) were excluded. In keeping with the review protocol, studies of patients with definite ACS, non–ST-elevation acute coronary syndromes, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) were excluded (or were included only if these patients did not comprise >20% of the study population), as were studies of patients with unstable angina and elevated serum cardiac biomarkers or ECG changes. For all Key Questions, the focus was on evidence from comparative studies with the least potential for bias. Noncomparative studies of predictive accuracy were considered if there was a lack of comparative data for a specific diagnostic modality. Interventions of interest included anatomic imaging (i.e., CCTA, coronary calcium scoring via electron beam or multidetector CT) and functional tests (i.e., stress ECG, stress echocardiography, stress nuclear imaging [SPECT, PET], and stress MRI). Comparators included other noninvasive tests included in the interventions, usual care (as defined by the authors), or no testing. Studies that included technologies that are not widely available, are no longer used, or have not been established for the diagnosis of CAD were excluded.

The primary outcomes (see “Rating the Body of Evidence” section) were considered to be the most clinically important and were the focus of reporting, decisions for data pooling, and determination of overall strength of evidence. Additional outcomes are reported in the detailed evidence synthesis sections of the Results chapter of the full report, organized by the Key Questions, with a focus on outcomes common across studies. Where applicable and where data were available, results from the index visit and the followup period were reported separately. For

studies of predictive accuracy, only hard clinical outcomes (i.e., MI, death, composite cardiac outcome, heart failure) were evaluated. For both the initial test and any subsequent downstream testing, the primary safety outcomes were related to harms of testing (e.g., adverse reaction or allergy to contrast or stress agents) and risks and consequences of testing (e.g., radiation exposure). Studies focused on "per-vessel" or "per-segment" analysis without per-patient findings were excluded, and treatments and outcomes of treatments were beyond the scope of this report. Studies published only as conference abstracts, non–English-language articles, and studies of nonhuman subjects were excluded. Studies had to report original data to be included.

Study Selection

Abstracts for all citations from the literature searches were independently reviewed by two team members and results were recorded in EndNote. All citations that either reviewer found to be potentially appropriate for inclusion underwent full-text review. Two investigators independently evaluated each full-text article for final inclusion. For inclusion, both reviewers had to agree that inclusion criteria were met. Differences between reviewers were resolved through consensus and discussion. A record of studies excluded at the full-text level with reasons for exclusion is included in Appendix C of the full report.

Data Extraction

The investigative team created a form in Microsoft® Excel for abstracting the data elements for the Key Questions. Two staff members and five experienced team members entered data. After data extraction, at least one other staff member and one investigator verified the accuracy and completeness of abstraction. Discrepancies were resolved by discussion and consensus. Specific information included in the data extraction forms is outlined in Appendix D of the full report.

Quality (Risk-of-Bias) Assessment of Individual Studies

Predefined criteria were used to assess the quality (risk of bias) of included randomized controlled trials (RCTs) and observational studies by using clearly defined templates and criteria as appropriate and following guidance from the AHRQ Methods Guide.[11] Assessment of RCTs followed appropriate criteria and methods established in the *Cochrane Handbook for Systematic Reviews of Interventions*.[12] Comparative observational studies were assessed for study design features and sources of potential bias. These criteria and methods were used in concordance with the AHRQ schema, and each study was rated as being "good," "fair," or "poor" quality.[13]

Studies rated "good" are considered to have the least risk of bias, and their results are considered valid. Studies rated "fair" are susceptible to some bias, although not enough to invalidate the results. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses. Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. Studies rated as being poor in quality a priori were not excluded but considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies were present.

Each study evaluated was independently reviewed for quality by two team members. Any disagreements were resolved by consensus. The final quality assessments are described in detail in Appendix I of the full report.

Data Synthesis

When adequate data were reported in at least two studies, meta-analysis was conducted in order to provide more precise estimates for outcomes. To determine the appropriateness of conducting meta-analysis, clinical and methodological diversity and assessed statistical heterogeneity were considered. Given the multiple interventions included in this report, a network meta-analysis was planned to estimate the relative effects of interventions that were not directly compared, and to make full use of both direct and indirect evidence.[14] However, the number of included studies turned out to be very small (2 for each comparison), with a limited number of comparisons (only CCTA vs. SPECT and CCTA vs. usual care). Along with heterogeneity across studies, this made network meta-analysis impossible. Therefore, only standard meta-analysis was conducted and only binary outcomes were eligible. The profile-likelihood random-effects model[15] was used to combine risk differences while incorporating variation among studies. The presence of statistical heterogeneity among the studies was assessed by using the standard Cochran's chi-square test, and the magnitude of heterogeneity was assessed by using the I^2 statistic.[16]

To account for clinical heterogeneity, analyses were stratified by pretest risk. Within each stratum, the number of studies was too small for exploring heterogeneity based on any study-level characteristics. Sensitivity analyses using risk ratios were conducted to check the robustness of results to the choice of effect measure. Conclusions were generally similar and not separately reported. All analyses were performed using Stata®/IC 12.1 (StataCorp, College Station, TX).

Rating the Body of Evidence

The following outcomes were considered to be the most relevant and were the focus of reporting, data pooling, and determination of overall strength of evidence: mortality (all cause), MI, additional noninvasive testing, referral for ICA, and subsequent revascularization (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]). Primary safety outcomes of interest for both the index test and any subsequent downstream testing included harms of testing (e.g., renal failure, allergic reactions, and adverse reactions to contrast or stress agents) and risk and consequences of testing (e.g., radiation exposure, psychological consequences of diagnosis, incidental findings).

The strength of evidence (high, moderate, low, or insufficient) for each primary effectiveness and safety outcome was initially assessed by one researcher.[11,13] To ensure consistency and validity of the evaluation, the strength-of-evidence ratings for all key outcomes were reviewed by multiple investigators, and discrepancies were resolved by consensus. Bodies of evidence consisting of RCTs started as high strength (greatest confidence that the evidence reflects the true effect; further research is unlikely to change our confidence in the effect estimate), while bodies of comparative observational studies began as low-strength evidence (low confidence in the estimate; further research is likely to change the effect estimate and change the confidence in the estimate). The strength of the evidence was then downgraded based on study limitations (i.e., risk of bias, consistency of effect, directness of outcome, precision of effect estimate, and reporting bias).[11] There are also situations in which the observational evidence may be upgraded (e.g., very large size of effect), but we found no instances in which these could be applied in this body of evidence.[11,17] The detailed strength-of-evidence tables and detailed explanations of the various grades can be found in Appendix J of the full report.

Applicability

Applicability of the evidence was considered by examining the characteristics of the patient populations included in studies (e.g., demographic characteristics, presence of relevant cardiac risk factors, and pretest risk for CAD), the sample size of the studies, and the clinical settings in which the studies were performed (e.g., outpatient clinic, ED), as outlined in the AHRQ Methods Guide.[11,18] Variability in the studies may limit the ability to generalize the results to other populations and settings. For example, older studies of established tests may not be as applicable in light of advances in technology, and short-term outcomes based on immediate decisionmaking in the ED may not be generalizable to longer term outcomes and decisionmaking in the outpatient setting.

Peer Review and Public Commentary

Experts in the diagnosis and treatment of CAD, as well as individuals representing other important stakeholder groups, were invited to provide external peer review of this Comparative Effectiveness Review. The AHRQ Task Order Officer and an Evidence-based Practice Center Program Associate Editor also provided comments and editorial review. The draft report was published on the AHRQ Web site for 4 weeks in order to solicit public comments. At the end of this period, the authors considered both the peer and public review comments and generated a final report. A disposition-of-comments report detailing the authors' responses to the peer and public review comments will be made available 3 months after AHRQ posts the final report on the public Web site.

Results

Results of Literature Searches

Database searches identified 17,146 potentially relevant citations. After dual review of abstracts and titles, 310 articles underwent full-text review; of these, 46 studies (in 51 publications) were determined by dual review to meet the inclusion criteria and were included in this report. The evidence base in this report includes data from RCTs as well as observational studies and noncomparative studies. Studies designed to compare one noninvasive test with another, with usual care, or with no testing form the primary basis for our report.

Organization of Results

Given the heterogeneity in how pretest risk was measured and defined across the studies, results could not be reported as delineated by the Key Questions into distinct pretest risk groups (i.e., low risk and intermediate to high risk). Therefore, the results were organized by pretest risk as defined by the study authors, which included populations with low risk, intermediate risk, low to intermediate risk, intermediate to high risk, high risk, and mixed risk (or pretest risk not reported). Studies describing high pretest risk excluded patients with ACS (or if included, those with ACS comprised <20% of the population) and were interpreted as representing the higher risk end of the intermediate pretest risk range. Available data from studies conducted in EDs were primarily for the index ED visit and are noted. Outcomes such as MI at the time of the ED index visit were considered to reflect diagnosis of MI at that time. Where available, data on

longer term followup are presented. An overview of tests compared for the various pretest risk groups is found in Table A.

Evidence for all outcomes in the low and high pretest risk groups was rated as insufficient; this evidence is not summarized here but is presented in the full report. Evidence for other comparators and primary outcomes considered to be insufficient to draw conclusions because of study limitations and/or imprecision in observational studies or lack of evidence are also available in the full report.

Primary results described here and in Tables B–E are organized by tests compared. Additional detailed results are organized by primary outcomes in the full report in Tables 8–15.

Table A. Overview of test comparisons described in the full report and pretest risk groups for which the comparisons were made

Comparator	Pretest Risk Groups With *Usual Care* Comparisons	Pretest Risk Groups With *CCTA* Comparisons	Pretest Risk Groups With *SPECT* Comparisons	Pretest Risk Groups With *Stress ECG* Comparisons	Pretest Risk Groups With *Functional Testing* Comparisons	Pretest Risk Groups With *Stress Echo-cardiography* Comparisons	Pretest Risk Groups With *Nuclear MPI* Comparisons
Usual Care	N/A	• Low • Intermediate • Low to intermediate • Intermediate to high • High (non-ACS) • Mixed population	No comparison	No comparison	No comparison	No comparison	No comparison
CCTA	• Low • Intermediate • Low to intermediate • Intermediate to high • High (non-ACS) • Mixed population	N/A	• Intermediate • Low to intermediate • Intermediate to high • Mixed population	• Low • Intermediate • Low to intermediate • Intermediate to high • Mixed population	• Intermediate	• Mixed population	• Mixed population
SPECT	No comparison	• Intermediate • Low to intermediate • Intermediate to high • Mixed population	N/A	• Intermediate • High (non-ACS) • Mixed population	No comparison	No comparison	No comparison
Stress ECG	No comparison	• Low • Intermediate • Low to intermediate • Intermediate to high • Mixed population	• Intermediate • High (non-ACS) • Mixed population	N/A	No comparison	• Mixed population	• Mixed population

Comparator	Pretest Risk Groups With *Usual Care* Comparisons	Pretest Risk Groups With *CCTA* Comparisons	Pretest Risk Groups With *SPECT* Comparisons	Pretest Risk Groups With *Stress ECG* Comparisons	Pretest Risk Groups With *Functional Testing* Comparisons	Pretest Risk Groups With *Stress Echo-cardiography* Comparisons	Pretest Risk Groups With *Nuclear MPI* Comparisons
Functional Testing	No comparison	• Intermediate	No comparison	No comparison	N/A	No comparison	No comparison
Stress Echocardiography	No comparison	• Mixed population	No comparison	• Mixed population	No comparison	N/A	• Mixed population
Nuclear MPI	No comparison	• Mixed population	No comparison	• Mixed population	No comparison	• Mixed population	N/A

ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; ECG = electrocardiography; MPI = myocardial perfusion imaging; N/A = not applicable; SPECT = single-photon emission computed tomography

Low Pretest Risk of CAD

A total of two RCTs were identified in populations with a low pretest risk of CAD: CCTA versus usual care (1 RCT)[19] and SPECT versus exercise ECG (1 RCT).[20] Evidence was based on subgroup analyses and was insufficient for all outcomes. Details of these studies are found in the full report.

Intermediate Pretest Risk of CAD

A total of seven comparative studies (in 9 publications) were identified in populations with an intermediate pretest risk of CAD: CCTA versus usual care (2 RCTs,[19,21,22] 1 prospective observational study[23,24]), CCTA versus various functional tests (1 RCT),[25] CCTA versus SPECT,[26] and SPECT versus exercise ECG (2 RCTs).[20,27] Table B summarizes the primary findings for this risk category.

CCTA Versus Usual Care

In intermediate-risk patients presenting to the ED, there was low-strength evidence from two fair-quality trials (N = 1,111) that patients in the CCTA and usual-care groups had similar mortality (≤30 days: 0% in both groups); MI (index ED visit: 2.3% vs. 3.6%; 28 days: 0.2% vs. 0.8%); any revascularization (index ED visit: 7.2% vs. 5.6%); PCI (index ED visit: 5% vs. 3%; 28 days: 0.6% in both groups); CABG (index ED visit: 1% in both groups; 28 days: 0% in both groups); and additional testing at the index ED visit and through 28–30 days (28 days: SPECT [1.6% vs. 1.8%], stress echocardiography [0% in both groups], or exercise treadmill testing [2% vs. 3%]). ICA referral was also similar at the index ED visit (13.8% vs. 11.2%; pooled risk difference [RD], 3; 95% confidence interval [CI], 0 to 7 per 100 patients; $I^2 = 0\%$) and after the index visit through 28 days (1.0% vs. 0.8%) (low strength of evidence).

SPECT Versus Exercise ECG

In 824 intermediate-risk women (setting not reported), groups were similar with respect to mortality (1.0% vs. 0.5%), ICA referral (6% in both groups), revascularization (2.0% vs. 1.0%), and hospitalization for chest pain (3.9% vs. 3.1%) through 24 months, based on one fair-quality trial (low strength of evidence). However, moderate-strength evidence from this trial suggests that SPECT is associated with less additional noninvasive testing than exercise ECG (9.4% vs. 18.6%; RD, -9; 95% CI, -14 to -4 per 100 people). Among those randomized to exercise ECG, the frequency of crossover to SPECT (counted as use of an additional test) was 8, 25, and 43 percent for women who had normal, indeterminate, and abnormal ECG results, respectively. Of those randomized to SPECT, this test was repeated in 9, 8, and 15 percent of women with normal, mildly abnormal, and moderately to severely abnormal results, respectively.

A second fair-quality trial reported that in a subgroup of 280 intermediate-risk outpatients, SPECT was associated with fewer referrals to ICA (10.6% vs. 43.1%; RD, -32; 95% CI, -43 to -22 per 100 people) (low strength of evidence) and additional stress testing (0% vs. 38%; RD, -38; 95% CI, -48 to -29 per 100 people) (low strength of evidence) through a mean of 22 months of followup.

Differences in patient characteristics between the two trials may partially explain differences in findings; one trial was comprised of women with a mean age of 63 years who were able to perform ≥5 METs (a measure of energy expenditure) on the Duke Activity Status Index. Findings from the other trial are based on subanalysis of intermediate-risk patients from a

general population composed of more than 50 percent men with mean age of 59 years with any activity ability.

CCTA Versus Functional Testing

In a good-quality trial of 10,003 intermediate-risk outpatients (mean, 53% ± 21% combined Diamond and Forrester and Coronary Artery Surgery Study risk score for likelihood of obstructive CAD), moderate-strength evidence suggested that there was no difference between groups in all-cause mortality (12 months: 0.42% vs. 0.64%; median 25 months: 1.48% vs. 1.50%); nonfatal MI (12 months: 0.36% vs. 0.54%; median 25 months: 0.60% vs. 0.80%); or cardiac hospitalizations (median 25 months: 1.22% vs. 0.92%). There was high strength of evidence that CCTA was associated with more ICA referrals (12.19% vs. 8.11%; RD, 4.08; 95% CI, 2.90 to 5.26 per 100 people) and revascularizations (6.22% vs. 3.16%; RD, 3.07; 95% CI, 2.24 to 3.90 per 100 people), including CABG and PCI evaluated separately, through 90 days. Major procedural complications were rare and similar between groups—procedural stroke (0.02% vs. 0.04%), major bleeding (0.1% in both groups), anaphylaxis or renal failure requiring dialysis (no cases) (moderate strength of evidence).

CCTA Versus SPECT

In a fair-quality trial of 400 intermediate-risk patients admitted to a telemetry ward (mean Diamond and Forrester pretest risk of 37%; mean Thrombolysis in Myocardial Infarction [TIMI] score of 1.3 ± 1.0), low-strength evidence suggested that there was no difference between CCTA and SPECT groups in all-cause mortality through a median of 24.5 months (0.5% vs. 3.0%; RD, -2.5; 95% CI, -5.1 to 0.06 events per 100 people) or in 12-month ICA referral (15.0% vs. 16.0%), additional testing (22.5% in both groups), revascularization (7.5% vs. 6.0%), or PCI (4.0% vs. 5.5%). However, CABG was more common following CCTA than SPECT through 12 months (3.5% vs. 0.5%; RD, 3.0; 95% CI, 0.3 to 5.7 events per 100 people), and cardiac rehospitalization occurred in fewer CCTA than SPECT patients through a median of 40.4 months, although the difference did not achieve statistical significance (25.0% vs. 31.0%; RD, -5.5; 95% CI, -14.3 to 0.03 events per 100 people) (low strength of evidence). No major complications were attributed to the imaging procedure; 30-day death, MI, and stroke were not reported. The composite of periprocedural chest pain, shortness of breath, or palpitations occurred in significantly fewer CCTA than SPECT patients (0.5% vs. 15.9%; RD, -15.4; 95% CI, -20.8 to -10.1 per 100 people), while there were no differences between groups in minor adverse reactions, including headache, nausea, dizziness, or feeling of warmth (24.2% vs. 24.5%) or in rash or pruritus (1.6% vs. 0%). There were no cases of post-test renal dysfunction (low strength of evidence).

Low to Intermediate Pretest Risk of CAD

A total of eight comparative studies (in 9 publications) were identified in populations with low to intermediate pretest risk of CAD: CCTA versus usual care (2 RCTs,[28,29] 1 retrospective observational study[30]), SPECT (2 RCTs,[31,32] 1 retrospective observational study[33]), and exercise ECG (1 RCT,[34] 1 retrospective observational study[35,36]). Table C summarizes the primary findings for this risk category.

CCTA Versus Usual Care

A fair-quality trial of 1,370 low- to intermediate-risk patients presenting to the ED (TIMI risk score, 0 [51%], 1 [36%], and ≥2 [13%]) showed no difference between CCTA and usual-care groups in mortality through 1 month (0% in both groups) or MI diagnosis at the index ED visit (1.0% vs. 0.9%) and through 1 month (1.1% in both groups) (low strength of evidence). Moderate-strength evidence from the same trial suggested that CCTA patients were less likely to be hospitalized at the index visit (50% vs. 77%; RD, -26.8; 95% CI, -31.9 to -21.8 per 100 people), but cardiac-related hospitalizations through 1 month were similar (3% vs. 2%). The CCTA groups were less likely to undergo additional testing at the index visit (13.7% vs. 57.8%; RD, -44.1; 95% CI, -49.2 to -39.1 per 100 people) and through 1 month (23.1% vs. 66.4%; RD, -43.3; 95% CI, -48.4 to -38.1 per 100 people) in the same trial (moderate strength of evidence), and through 3 months (33% vs. 60%; RD, -27; 95% CI, -51 to -2) in one poor-quality trial of 60 patients with risk scores not reported (low strength of evidence). ICA referrals were similar for the groups at the index ED visit (4.1% vs. 3.9%; 1 trial; N = 1,392) and through 1- to 3-month followup in two trials (N = 1,452; pooled estimate, 5.2% vs. 4.7%; RD, 1; 95% CI, -1 to 3 per 100 people). There were slightly more revascularization procedures in the CCTA group at the index visit in the larger trial (2.5% vs. 0.9%; RD, 1.7; 95% CI, 0.3 to 3.0 per 100 people), but revascularization frequency was similar through the followup period across both trials (pooled estimate, 2.7% vs. 1.2%; RD, 1; 95% CI, 0 to 3 per 100 people) (low strength of evidence).

CCTA Versus Exercise ECG

Based on one fair-quality trial of 562 low- to intermediate-risk ED patients, there was low-strength evidence of no differences in mortality through 12 months (0.6% vs. 0.4%) or in diagnosis of MI at the index ED visit (1.9% vs. 1.7%) and through 1 month (no additional cases). The 12-month rates of referral to ICA (9.0% vs. 2.3%; RD, 4.8; 95% CI, 0.8 to 8.9 per 100 patients) and revascularization (4.3% vs. 1.3%; RD, 3.1; 95% CI, 0.5 to 5.7 per 100 patients) were significantly greater following CCTA than exercise ECG (low strength of evidence).

CCTA Versus SPECT

In low- to intermediate-risk patients presenting to the ED (median TIMI score, 1.0), there was low-strength evidence from two trials (N = 952; 1 good and 1 fair quality) of no difference through 6 months in mortality (0% in both groups). There was moderate-strength evidence that there was no difference in MI (diagnosis at index ED visit: 0.3% vs. 1.5%; RD, -1.2%; 95% CI, -2.6% to 0.19%; 6 months: 0% in both groups), as reported by both RCTs, or in cardiac-related hospitalizations (0% in both groups), as reported in one good-quality RCT. Together, the trials of ED patients reported that ICA referrals were similar at both the index ED test (7.6% vs. 5.5%; pooled RD, 4; 95% CI, -4 to 11 per 100 patients; $I^2 = 71.7\%$) and through 6 months (0.7% vs. 1.3%; pooled RD, -1; 95% CI, -5 to 3 per 100 patients; $I^2 = 71.1\%$) (low strength of evidence). Additional noninvasive testing was more common following CCTA at the index visit: the larger good-quality trial reported 10.2% vs. 0.9% for SPECT (RD, 9.4; 95% CI, 6.1 to 12.7 per 100 patients) and the smaller fair-quality trial reported 24% vs. 0% for SPECT (RD, 24 per 100 people; $p < 0.001$) (high strength of evidence from 2 trials). Use of additional noninvasive testing through 6 months was similar (1% vs. 3%) (low strength of evidence from 1 trial). Moderate-strength evidence from both trials of ED patients suggested similar referral for revascularization, including PCI and CABG evaluated separately, at the index visit (3.9% vs. 2.1%) and through 6 months (0.5% vs. 0%).

Intermediate to High Pretest Risk of CAD

A total of two comparative studies (in 3 publications) were identified in populations with intermediate to high pretest risk of CAD: PET versus SPECT (1 prospective observational study)[37,38] and CCTA versus SPECT (1 RCT).[39] Table D summarizes the primary findings for this risk category.

The main comparison for which evidence was found is CCTA versus SPECT. One small poor-quality trial of 180 outpatients with intermediate to high risk (65% intermediate and 29% high risk; mean Framingham risk estimate, 18.7) with a mean of 1.8 months followup found no deaths or MIs (insufficient strength of evidence). Strength of evidence was low that cardiac hospitalizations occurred at a similar rate between groups (12% vs. 11%). CCTA was associated with more revascularizations (8% vs. 1%; RD, 6.6%; 95% CI, 0.7% to 12.5%), as well as slightly more ICA referrals (13% vs. 8%; RD, 5; 95% CI, -4 to 14 per 100 people; p not statistically significant) and slightly but not significantly less noninvasive cardiac imaging testing (3% vs. 10%; RD, -7; 95% CI, -14 to 0.4 per 100 people) through the same followup period (low strength of evidence).

High Pretest Risk of CAD

One study in a population with high pretest risk of CAD compared SPECT and exercise ECG.[20] Evidence was based on subgroup analyses and was insufficient for all outcomes. Results are detailed in the full report.

Mixed Population: Pretest Risk Not Reported or Results Not Stratified by Risk

A total of nine comparative studies were identified in populations with mixed pretest risk of CAD or for which risk was not reported. (One administrative database study reported outcomes for 6 different test comparisons.) The study comparisons were CCTA versus usual care (1 RCT),[19] exercise ECG (1 RCT,[40] 1 administrative database[41]), SPECT (1 prospective registry,[42] 1 administrative database[43]), nuclear MPI (1 prospective observational study,[44] 1 administrative database[41]), and stress echocardiography (1 administrative database);[41] SPECT versus exercise ECG (1 RCT,[20] 1 administrative database[41]); and stress echocardiography versus exercise ECG (1 RCT,[45] 1 prospective observational study,[46] 1 administrative database[41]) and SPECT (1 administrative database).[41] Outcomes with insufficient evidence are not detailed here but are described in the full report. Table E summarizes the primary findings for this risk category.

CCTA Versus Usual Care

In a fair-quality trial of 266 patients presenting to the ED and not stratified by risk (low, 37%; intermediate, 42%; high, 21%), there was low-strength evidence of no difference in 1-month MI (0% vs. 0.8%) or contrast-induced nephropathy (0% in both groups).

SPECT Versus Exercise ECG

In outpatients not stratified by risk (low, 16%; intermediate, 61%; high, 23%), there was low-strength evidence from one fair-quality trial of 457 patients that there was no difference between groups in all-cause mortality (0.8% vs. 0.9%) or MI (0% vs. 0.5%) through a mean of 22 months, while SPECT was associated with fewer revascularizations than exercise ECG (10.8% vs. 17.9%; RD, -7.1; 95% CI, -13.6 to -0.6 per 100 people).

Exercise ECG Versus Nuclear MPI

Low-strength evidence from a large fair-quality administrative database of Medicare outpatients (N = 193,406) suggested that 6-month mortality was similar between groups (0.78% vs. 1.28%; adjusted odds ratio [OR], 0.93; 95% CI, 0.83 to 1.04). Patients who underwent exercise ECG were less likely to undergo ICA through 6 months than those who were tested with MPI (9.04% vs. 12.13%; adjusted OR, 0.72; 95% CI, 0.70 to 0.75); revascularization, including CABG and PCI evaluated separately, was performed with similar frequency between groups (4.31% vs. 4.59%; adjusted OR, 0.90; 95% CI, 0.85 to 0.94) (low strength of evidence for both).

Stress Echocardiography Versus Nuclear MPI

Low-strength evidence from a large fair-quality administrative database of Medicare outpatients (N = 212,947) suggested that 6-month mortality was similar between groups (0.95% vs. 1.28%; adjusted OR, 1.00; 95% CI, 0.90 to 1.10). Through 6 months, ICA referral was statistically less frequent in the stress echocardiography group (9.50% vs. 12.13%; adjusted OR, 0.78; 95% CI, 0.76 to 0.81), while additional noninvasive testing was slightly more common in this group (5.57% vs. 3.22%; adjusted OR, 1.92; 95% CI, 1.83 to 2.0) (low strength of evidence). There were no apparent clinical differences between groups in referral for revascularization (4.22% vs. 4.59%; adjusted OR, 0.93; 95% CI, 0.88 to 0.98), including CABG and PCI evaluated separately (low strength of evidence).

CCTA Versus Exercise ECG

One fair-quality trial of 500 ED patients not stratified by risk (low, 43%; intermediate, 24%; high, 34%) with 12 months of followup found low-strength evidence of no difference between groups in all-cause mortality (0.4% in both groups) or MI (0.41% vs. 0.82%), while there was moderate-strength evidence that cardiac-related hospitalizations were less common in the CCTA group (0.8% vs. 6.9%; RD, -6.1; 95% CI, -9.5 to -2.7 per 100 people). CCTA was associated with more ICAs (27.2% vs. 20.8%; RD, 6.3; 95% CI, -1.2 to 13.9 per 100 people; p = 0.1011) and more revascularizations (15.2% vs. 7.7%; RD, 7.5; 95% CI, 1.9 to 13.0 per 100 people, including PCI [11.9% vs. 4.9%; RD, 7; 95% CI, 2 to 12 per 100 people]), although CABG was used with similar frequency in both groups (3.3% vs. 2.9%) (low strength of evidence).

CCTA Versus Nuclear MPI

One large fair-quality administrative database study of 141,163 mixed-risk Medicare outpatients provided low-strength evidence that all-cause mortality was similar through 6 months (1.05% vs. 1.28%). CCTA patients were more likely to undergo ICA (22.94% vs. 12.13%; adjusted OR, 2.19; 95% CI, 2.08 to 2.32), additional noninvasive testing (4.98% vs. 3.22%; adjusted OR, 1.52; 95% CI, 1.37 to 1.69), and revascularization (11.41% vs. 4.59%; adjusted OR, 2.76; 95% CI, 2.56 to 2.98), including PCI and CABG evaluated separately, through 6 months (low strength of evidence).

One fair-quality registry study of 1,856 patients provided low-strength evidence that revascularization was more common following CCTA through a median of 1.42 years (% not reported; adjusted OR, 1.62; 95% CI, 1.20 to 2.18); the setting was not reported.

Table B. Summary of findings and strength of evidence: intermediate pretest risk

Comparison	Number of Studies (N)	Findings*	Strength of Evidence
CCTA vs. usual care†	2 RCTs (N = 1,098), 1 observational study (N = 200)	No statistically significant differences between tests were found for all-cause mortality (28–30 days in 2 trials), myocardial infarction (index visit in 1 trial, 28–30 days in 2 trials, and 3 months in 1 observational study), ICA referral (index visit in 1 trial and 28–30 days in 2 trials), any revascularization (index visit in 2 trials), PCI (index visit and 28 days in 1 trial, and 3 months in 1 observational study), CABG (28 days in 1 trial and 3 months in 1 observational study), additional noninvasive testing (index visit and 28 days in 1 RCT), and cardiac hospitalizations (ED index visit in 2 trials, 3 months in 1 observational study).	Low
SPECT vs. exercise ECG	1 RCT (N = 824 women)	SPECT was associated with significantly less additional noninvasive testing (including stress testing with or without imaging) through 24 months (**9.4% vs. 18.6%; RD, -9; 95% CI, -14 to -4 per 100 people**).	Moderate
	2 RCTs (N = 824 women only, N = 280 in intermediate-risk subgroup of a trial of men and women)	No statistically significant differences were found between tests through 24 months for all-cause mortality, revascularization, ICA referral, hospitalization for chest pain (trial of women only), and additional noninvasive testing (trial of the general population). SPECT was associated with a significantly lower referral rate for ICA through 22 months in 1 trial of the general population (**10.6% vs. 43.1%; RD, -32; 95% CI, -43 to -22 per 100 people**).	Low
CCTA vs. functional testing	1 RCT (N = 10,003)	CCTA was associated with a significantly higher referral rate through 3 months for ICA (**12.19% vs. 8.11%; RD, 4.08; 95% CI, 2.90 to 5.26 per 100**), any revascularization (**6.22% vs. 3.16%; RD, 3.07; 95% CI, 2.24 to 3.90 per 100 people**), PCI (**4.8% vs. 2.4%; RD, 2.4; 95% CI, 1.7 to 3.1 per 100 people**), and CABG (**1.44% vs. 0.76%; RD, 0.68; 95% CI, 0.27 to 1.09 per 100 people**).	High
	1 RCT (N = 10,003)	Statistically significant differences between tests were not found for all-cause mortality (12 months and 25 months), nonfatal MI (12 months and 25 months), cardiac hospitalization (25 months), and major procedural complications (stroke, major bleeding). CCTA was associated with a significantly increased risk of hospitalization for unstable angina **(1.22% vs. 0.82%; RD, 0.40; 95% CI, 0.01 to 0.80 per 100 people)** and minor side effects from testing such as stress-induced symptoms and mild contrast reactions (0.74% vs. 0.42%**; RR, 1.77; 95% CI, 1.05 to 3.01),** although it is unclear if the differences are clinically meaningful.	Moderate
CCTA vs. SPECT	1 RCT (N = 400)	No statistically significant differences between tests were found for all-cause mortality (median, 24.5 months); cardiac hospitalization (median, 40.4 months); ICA referral, any revascularization, PCI, and additional noninvasive testing, including myocardial perfusion imaging, stress echocardiography, and CCTA (through 12 months); and minor adverse reactions (including headache, nausea, dizziness, or feeling of warmth), rash or pruritus, and post-test renal dysfunction. CCTA was associated with a significantly higher risk of CABG through 12 months (**3.5% vs. 0.5%; RD, 3.0; 95% CI, 0.3 to 5.7 per 100 people**) and a significantly lower incidence of the composite of periprocedural chest pain, shortness of breath, or palpitations (**0.5% vs. 15.9%; RD, -15.4; 95% CI, -20.8 to -10.1 per 100 people**).	Low

CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ED = emergency department; ICA = invasive coronary angiography; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SPECT = single-photon emission computed tomography

*Statistically significant differences are indicated in bold font.

†Usual care consisted of a conventional diagnostic strategy using serial ECG and cardiac biomarkers.

Table C. Summary of findings and strength of evidence: low to intermediate pretest risk

Comparison	Number of Studies (N)	Findings*	Strength of Evidence
CCTA vs. usual care†	1 RCT (N = 1,392)	No statistically significant differences between tests were found for cardiac hospitalization after the index visit through 1 month. CCTA was associated with significantly less additional noninvasive testing at the index visit in 1 trial (**13.7% vs. 57.8%; RD, -44.1; 95% CI, -49.2 to -39.1 per 100 people**), as well as through 1 month in 1 trial (**23.1% vs. 66.4%; RD, -43.3; 95% CI, -48.4 to -38.1 per 100 people**). CCTA was also associated with a decreased risk of cardiac hospitalization at the ED index visit in 1 trial (**50% vs. 77%; RD, -26.8; 95% CI, -31.9 to -21.8 per 100 people**).	Moderate
	2 RCTs (N = 1,452), 1 observational study (N = 1,788)	No statistically significant differences between tests were found for all-cause mortality (at 1 month in 1 trial and in the observational study), myocardial infarction (at index visit and 1 month in 1 trial and up to 1 month in the observational study), ICA referral (at index visit in 1 trial and at 1–3 months in 2 trials), any revascularization (at 1–3 months in 2 trials and through 1 month in the observational study), PCI and CABG (both at 3 months in 1 trial), and bradyarrhythmia (1 trial). CCTA was associated with more revascularization procedures at the index visit in 1 trial (**2.5% vs. 0.9%; RD, 1.7; 95% CI, 0.3 to 3.0 per 100 people**), and with less additional stress testing at the index visit in 1 trial (**13.7% vs. 57.8%; RD, -44.1; 95% CI, -49.2 to -39.1 per 100 people**) and through 3 months in the other (**33% vs. 60%; RD, -27; 95% CI, -51 to -2 per 100 people**), as well as through 3 months in 1 observational study (**4% vs. 21%; p <0.001**). ICA referral was less common with CCTA (1% vs. 3%) in the retrospective observational study; although authors reported statistical significance (p <0.001), clinical significance is unclear.	Low
CCTA vs. exercise ECG	1 RCT (N = 562), 1 observational study (N = 498)	No statistically significant differences were found between tests in all-cause mortality (at 30 days in 1 trial and at 12 months in both studies) and myocardial infarction (at index visit and 30 days in 1 trial, and at 12 months in the observational study). CCTA was associated with a significantly higher referral rate for ICA (**9.0% vs. 2.3%; RD, 4.8; 95% CI, 0.8 to 8.9 per 100 people**) and revascularization (**4.3% vs. 1.3%; RD, 3.1; 95% CI, 0.5 to 5.7 per 100 people**) through 12 months in 1 trial.	Low
CCTA vs. SPECT	2 RCTs (N = 952)	CCTA was associated with higher rates of additional noninvasive testing at the index visit: 10.2% vs. 0.9% in the larger trial (**RD, 9.4; 95% CI, 6.1 to 12.7 per 100 patients**) and 24% vs. 0% in the smaller trial (**RD, 24 per 100 people; p <0.001**).	High
	2 RCTs (N = 952)	No statistically significant differences between tests were found for revascularization, PCI, and CABG at the index visit and through 6 months (2 trials), and for cardiac hospitalization through 6 months (1 trial) and 30 months (1 observational study).	Moderate
	2 RCTs (N = 952), 1 observational study (N = 252)	No statistically significant differences between tests were found for all-cause mortality at 6 months (2 trials) and at 30 months (1 observational study), myocardial infarction and ICA referral at index visit and through 6 months (2 trials), and additional testing through 6 months (1 trial).	Low

CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ED = emergency department; ICA = invasive coronary angiography; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RD = risk difference; SPECT = single-photon emission computed tomography
*Statistically significant differences are indicated in bold font.
†Usual care consisted of a conventional diagnostic strategy using serial ECG and cardiac biomarkers.

Table D. Summary of findings and strength of evidence: intermediate to high pretest risk

Comparison	Number of Studies (N)	Findings*	Strength of Evidence
CCTA vs. SPECT	1 RCT (N =180)	No statistically significant differences were found between tests through a mean 1.8 months for ICA referral, additional noninvasive testing, and coronary artery disease–related hospitalization. CCTA was associated with more revascularizations through a mean of 1.8 months (**8% vs. 1%; RD, 6.6; 95% CI, 0.7 to 12.5**).	Low

CCTA = coronary computed tomography angiography; CI = confidence interval; ICA = invasive coronary angiography; RCT = randomized controlled trial; RD = risk difference; SPECT = single-photon emission computed tomography
*Statistically significant differences are indicated in bold font.

Table E. Summary of findings and strength of evidence: mixed pretest risk

Comparison	Number of Studies (N)	Findings*	Strength of Evidence
CCTA vs. usual care†	1 RCT (N = 266)	No statistically significant differences were found between tests through 30 days for myocardial infarction and contrast-inducted nephropathy.	Low
SPECT vs. exercise ECG	1 RCT (N = 457)	No statistically significant differences were found between tests at 22 months for all-cause mortality and myocardial infarction. SPECT was associated with significantly fewer revascularizations through 22 months (**10.8% vs. 17.9%; RD, -7.1; 95% CI, -13.6 to -0.6 per 100 people**).	Low
Exercise ECG vs. nuclear MPI	1 observational study (N = 193,406 Medicare)	No statistically significant differences between tests were found for all-cause mortality at 6 months. Exercise ECG was associated with significantly fewer referrals for ICA (**9.04% vs. 12.13%; adjusted OR, 0.72; 95% CI, 0.70 to 0.75**), any revascularization (**4.31% vs. 4.59%; adjusted OR, 0.90; 95% CI, 0.85 to 0.94**), and PCI (**2.57% vs. 3.37%; adjusted OR, 0.72; 95% CI, 0.68 to 0.77**), and significantly higher rates of CABG (**1.82% vs. 1.29%; adjusted OR, 1.37; 95% CI, 1.26 to 1.49**) and additional noninvasive testing (**19.34% vs. 3.22%; adjusted OR, 7.46; 95% CI, 7.16 to 7.77**) through 6 months, although it is unclear if the differences for any revascularization, PCI, and CABG are clinically meaningful.	Low
Stress echocardio-graphy vs. nuclear MPI	1 observational study (N = 212,947 Medicare)	No statistically significant differences between tests were found for all-cause mortality at 6 months. Stress echocardiography was associated with significantly fewer referrals for ICA (**9.50% vs. 12.13%; adjusted OR, 0.78; 95% CI, 0.76 to 0.81**), any revascularization (**4.22% vs. 4.59%; adjusted OR, 0.93; 95% CI, 0.88 to 0.98**), and PCI (**2.61% vs. 3.37%; adjusted OR, 0.76; 95% CI, 0.72 to 0.81**), and significantly higher rates of CABG (**1.69% vs. 1.29%; adjusted OR, 1.40; 95% CI, 1.29 to 1.52**) and additional noninvasive testing (**5.57% vs. 3.22%; adjusted OR, 1.92; 95% CI, 1.83 to 2.0**) through 6 months, although it is unclear if the differences for any revascularization, PCI, and CABG are clinically meaningful.	Low

Comparison	Number of Studies (N)	Findings*	Strength of Evidence
CCTA vs. exercise ECG	1 RCT (N = 500)	CCTA resulted in significantly less additional noninvasive testing (**2.4% vs. 31.3%; RD, -29; 95% CI, -37 to -23 per 100 people**), as well as fewer cardiac rehospitalizations (**0.8% vs. 6.9%; RD, -6.1; 95% CI, -9.5 to -2.7 per 100 people**), through 12 months.	Moderate
	1 RCT (N = 500)	No statistically significant differences between tests were found for all-cause mortality, myocardial infarction, referral for ICA, and CABG through 12 months. CCTA was associated with a significantly increased risk of any revascularization (**15.2% vs. 7.7%; RD, 7.5; 95% CI, 1.9 to 13.0 per 100 people**) and PCI (**11.9% vs. 4.9%; RD, 7; 95% CI, 2 to 12 per 100 people**) through 12 months.	Low
CCTA vs. nuclear MPI	2 observational studies (N = 141,163 Medicare, N = 1,856 general population)	No statistically significant differences between tests were found for all-cause mortality at 6 months in the Medicare population. CCTA was associated with significantly higher referral rates for ICA (**22.94% vs. 12.13%; adjusted OR, 2.19; 95% CI, 2.08 to 2.32**), PCI (**7.85% vs. 3.37%; adjusted OR, 2.49; 95% CI, 2.28 to 2.72**), CABG (**3.71% vs. 1.29%; adjusted OR, 3.00; 95% CI, 2.63 to 3.42**), and additional testing (**4.98% vs. 3.22%; adjusted OR, 1.52; 95% CI, 1.37 to 1.69)** through 6 months in the Medicare population**;** for any revascularization through 6 months in the Medicare population (**11.41% vs. 4.59%; adjusted OR, 2.76; 95% CI, 2.56 to 2.98**), and for any revascularization through a median 1.42 years in the general population **(% not reported; adjusted OR, 1.62; 95% CI, 1.20 to 2.18**).	Low

CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ICA = invasive coronary angiography; MPI = myocardial perfusion imaging; OR = odds ratio; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RD = risk difference; SPECT = single-photon emission computed tomography
*Statistically significant differences are indicated in bold font.
†Usual care consisted of a conventional diagnostic strategy using serial ECG and cardiac biomarkers.

Discussion

Key Findings and Strength of Evidence

Evidence to determine the comparative effectiveness and safety of different noninvasive testing strategies for CAD is limited. While there is a robust body of literature on the diagnostic performance of these tests based on traditional measures of test accuracy (e.g., sensitivity, specificity), only a small number of studies were identified that evaluated the impact of noninvasive testing on clinical outcomes measures in the population of interest for this report. The key findings and strength of evidence for the outcomes identified as being most clinically important are summarized in Tables B–E in the Results section; factors used to determine the overall strength of evidence are summarized in Appendix J of the full report.

A total of 24 comparative studies that evaluated the impact of noninvasive testing on clinical outcomes and/or clinical management outcomes in the population of interest for this report form the basis of this review: 14 RCTs (2 good quality, 9 fair quality, and 3 poor quality)[19-21,25-29,31,32,34,39,40,45] and 10 comparative observational studies (7 fair quality and 3 poor quality).[23,24,30,33,35-38,41-44,46] Common methodological shortcomings in the RCTs include unclear description of randomization sequence and/or test allocation and lack of blinded outcomes assessment. In the observational studies, lack of controlling for confounding and/or blinding of outcomes assessment were common methodological shortcomings. The comparative studies

served as the basis of the report and were stratified based on pretest risk, test type (anatomic or functional), and setting. For most outcomes reported in trials, the strength of evidence was rated as low (meaning that our confidence in the estimates of effect is low) based on concerns related to precision and study limitations. However, for some outcomes reported by trials, the strength of evidence was found to be moderate or high. For the majority of outcomes reported by comparative observational studies, the strength of evidence was found to be insufficient because of study limitations, although some outcomes were graded as low strength of evidence when the estimates were considered to be at low risk for imprecision and confounding was controlled. Eight RCTs and one observational study were conducted in ED settings or specialized chest pain clinics[40] and compared CCTA with functional testing[31,32,34,40] or usual care.[19,21,23,24,28,29] In these studies, most of the available data were reported for the index ED visit, and with the exception of two trials reporting 12-month followup, the maximum followup in ED studies was 6 months. The remaining 5 trials[20,25,27,39,45] and 13 comparative observational studies were conducted in outpatient, various, or unspecified settings; in general, these studies had longer followup periods, which ranged from a mean of 55 days to 30 months. Pretest risk could not be standardized across studies, and was variably determined and defined across studies. Thus, categories of pretest risk used here are based on how the study authors defined risk.

Clinical Outcomes

There was no clear difference in MI or in all-cause mortality between different testing strategies across settings and pretest risk groups that included patients with intermediate pretest risk, based on low- to moderate-strength evidence from eight trials. The definition of intermediate pretest risk was broad. The frequency of all-cause mortality was low across studies in all settings. In trials enrolling outpatients, the frequency of all-cause mortality ranged from 0 to 1.5 percent for a variety of noninvasive testing strategies, and the frequency in trials in the ED setting past the initial index visit ranged from 0 to 1.08 percent across a variety of noninvasive testing or usual-care strategies, with no statistical difference between any groups. Similarly the frequency of MI was low, ranging from 0 to 0.8 percent (up to a median of 25 months) in outpatient settings and 0 to 3 percent (up to 12 months) in ED settings, with no statistical differences between groups. The strongest evidence came from three trials: one that compared CCTA with functional testing in an outpatient setting[25] and two that compared CCTA with SPECT in an ED setting.[31,32] For the trial of CCTA versus functional testing, which was also the largest trial (N = 10,003), there were no differences in all-cause mortality between groups through 12 months (0.42% vs. 0.64%) or at a median of 25 months followup (1.48% vs. 1.50%) or in nonfatal MI at 12 months (0.36% vs. 0.54%; RD, -0.18; 95% CI, -0.44 to 0.08 per 100 people) or at a median of 25 months followup (0.60% vs. 0.80%; RD, -0.20; 95% CI, -0.53 to 0.13 per 100 people);[25] strength of evidence was moderate for both outcomes. Across the two trials comparing CCTA with SPECT in an ED setting, there was low-strength evidence that there was no difference between tests for mortality or MI; no deaths or MIs were reported through a mean of 6 months past the initial ED visit.[31,32] Across the remaining trials, no difference was found between tests because of lack of precision and study limitations (low strength of evidence). Higher quality observational studies (i.e., those that controlled for confounding) supported these findings. No conclusions can be drawn regarding the impact of testing on clinical outcomes for patients at low risk or high risk (without ECG changes, troponin elevation, or other characteristics of ACS), as only subanalyses of fewer than 100 patients were available.

Several factors may have contributed to finding no statistical differences between tests on clinical outcomes. Given the low incidence of mortality and MI in the studies previously noted, sample sizes in even the largest trials may have been too small to detect differences between tests. The low incidence of mortality and MI suggests that study populations may generally have been at the lower end of the intermediate pretest risk range. Improvements in medical therapy in the past few decades, including use of statins, may contribute to the low incidence of these outcomes. An additional consideration is the possibility that differences between tests in true sensitivity to detect treatable CAD or ability to identify high-risk disease are not large. Small differences in sensitivity may have little impact on the probability of disease when the pretest probability is low. Even if two tests do not have the same sensitivity, the lack of difference in the occurrence of outcome events in most studies between people who were assigned to receive different tests could result from either the lack of efficacy of treatments administered to test-positive people or the lack of difference in the receipt of effective treatments between test-positive and test-negative people. Given that studies do not present data on treatments administered to individual study participants (or how testing directed those decisions), we cannot distinguish between these alternatives. Furthermore, information on post-test risk stratification or treatment based on such stratification was not reported in most studies. Information on clinical decisions and outcomes based on whether tests were positive, negative, or indeterminate was not given in most comparative studies. It is possible that over- or undertreatment may have contributed to similarity in clinical findings. Length of followup may have also impact the findings of no difference in clinical outcomes. Two larger trials in outpatient settings (SPECT vs. stress ECG[27] and CCTA vs. functional testing[25]) followed patients for 2 or more years. There was insufficient evidence to draw conclusions regarding longer term clinical outcomes from studies in the ED setting because most did not provide data beyond 6 months after the ED visit.

Referral for Invasive Coronary Angiography

There was some variability in conclusions regarding ICA referral following noninvasive testing. In most studies, ICA was more common following CCTA than following various functional tests. The strongest evidence came from one good-quality trial that compared CCTA with functional testing in outpatients; it found that ICA was significantly more common in the CCTA group than the functional testing group by 90 days (12.19% vs. 8.11%; RD, 4.08; 95% CI, 2.90 to 5.26 per 100 people) (high strength of evidence). Interestingly, fewer catheterizations in the CCTA group showed no obstructive CAD (3.4% vs. 4.3%),[25] perhaps because of a lower false-positive rate with CCTA. The strength of the quality of evidence regarding ICA referral was low across the remaining trials. Two fair-quality trials comparing CCTA with exercise ECG suggest that ICA referral is more common following CCTA up to 12 months following an initial ED visit, with RD of 4.8 (95% CI, 0.8 to 8.9 per 100 people) in one trial of patients with low to intermediate risk and RD of 6.3 (95% CI, -1.2 to 13.9 per 100 people) in the trial of mixed-risk patients; statistical significance was not reached and strength of evidence was low because of study limitations and lack of precision.

A large administrative data study in Medicare patients found that ICA was significantly more common following CCTA than following MPI (22.94% vs. 12.13%; adjusted OR, 2.19; 95% CI, 2.08 to 2.32) (low strength of evidence).[41] In contrast, across studies comparing CCTA with usual care, there were no statistical differences between testing strategies in any of the trials regardless of pretest risk or setting. However, in the small high-risk group from one trial, fewer CCTA patients had ICA at the index visit (RD, -18; 95% CI, -37 to 0.8; $p = 0.0714$) (low

strength of evidence). Evidence from observational studies for comparisons of CCTA with other tests was considered insufficient because of study limitations and lack of precision. Regarding comparisons of functional tests, two RCTs[20,27] and one large administrative database study[41] provided low-strength evidence on ICA referral in outpatient settings. One trial comparing SPECT with exercise ECG in intermediate-risk women reported a 6-percent referral for ICA in each test group by 24 months. However, the other trial making this comparison reported a significantly lower frequency of ICA referral by 22 months following SPECT in a subgroup of patients with intermediate pretest risk (RD, -32; 95% CI, -43 to -22 per 100 people), as well as in a subgroup of high-risk patients (RD, -41; 95% CI, -58 to -24 per 100 people)[20] This same trial used Bayesian methods to model post-test risk and reported that 86 percent of those with low pretest risk finished with low post-test risk. Patients in either arm whose tests were normal or indicated low risk did not receive ICA; 3 percent and 38 percent in the intermediate and high post-test risk groups had ICA following SPECT, compared with 13 percent and 85 percent in the intermediate and high post-test risk groups following exercise ECG. This type of modeling is not a standard approach to post-test risk assessment, so the generalizability of these results is not clear. The administrative database study of Medicare patients reported that, compared with nuclear MPI, ICA referral was lower following exercise ECG (OR, 0.72; 95% CI, 0.70 to 0.75) and stress echocardiography (OR, 0.78; 95% CI, 0 .76 to 0.81)[41] (low strength of evidence). Evidence from the remaining observational studies was considered insufficient.

None of the studies provided analysis or explicit information regarding unnecessary treatment or testing.

Revascularization

Findings were inconsistent across diagnostic strategies with regard to revascularization referral. There was high-strength evidence from one large trial that any revascularization within 90 days was more common following CCTA compared with functional testing (RD, 3.07; 95% CI, 2.24 to 3.90 per 100 patients); the same was true for PCI specifically (RD, 2.4; 95% CI, 1.7 to 3.1 per 100 patients)[25] (high strength of evidence). Revascularization was also more common 6 to 12 months following CCTA compared with exercise ECG across two studies (1 RCT, 1 observational study)[40,41] of mixed-risk ED patients (low strength of evidence), as well as across two observational studies comparing CCTA with nuclear MPI[41,44] in outpatient settings up to 1.4 years (low strength of evidence). In contrast, the frequency of revascularization was similar for CCTA and SPECT (pooled RD, 2 per 100 patients; 95% CI, 0 to 4 per 100 patients) at the index ED visit and at 6 months (pooled RD, 0; 95% CI, 0 to 1 per 100 patients) across two trials (moderate strength of evidence).[31,32] PCI and CABG frequencies in these trials were also similar between tests; strength of evidence was moderate. Further, there was low-strength evidence of no statistical differences in revascularization frequency between CCTA and usual care at the index visit or at 1 to 3 months followup based on data from four trials.[19,21,28,29] Evidence comparing functional tests was inconsistent, with one small trial reporting fewer revascularizations following SPECT than exercise ECG (RD, -7.1; 95% CI, -13.6 to -0.6 per 100 people)[20] (low strength of evidence) and one large Medicare administrative database study reporting a similar frequency of revascularization, including PCI and CABG, for exercise ECG (4.31% vs. 4.59%) and stress echocardiography (4.22% vs. 4.59) as for nuclear MPI (low strength of evidence). For the latter study, although the differences between groups were statistically significant for both comparators, they may not be clinically significant. Studies did not describe post-test reclassification of risk or decisionmaking for treatment.

Additional Noninvasive Testing

Additional noninvasive testing, which impacts the cost and efficiency of care, was common in most studies. In the ED setting, there was high-strength evidence from two trials of patients with low to intermediate risk that additional noninvasive testing was significantly more common following CCTA than SPECT at the index visit (RD for largest trial, 9.4; 95% CI, 6.1 to 12.7 per 100 patients).[31,32] In the same setting, there was moderately strong evidence that CCTA was associated with less frequent noninvasive testing compared with usual care at the index visit in one trial[28] and compared with exercise ECG through 12 months past the index ED visit[40] in another trial. In intermediate-risk patients, the frequency of additional testing following CCTA was similar to the frequency following usual care up to 1 month past the ED visit in one trial (low strength of evidence), possibly because many in the usual-care group also received noninvasive imaging.[21] In outpatient settings, the strength of evidence was moderate that SPECT was associated with significantly less additional noninvasive testing compared with exercise ECG through 22 months, based on one large trial of intermediate-risk women (RD, -9; 95% CI, -14 to -4 per 100 people),[27] as well as a from a subgroup of intermediate-risk patients in another trial (RD, -38; 95% CI, -48 to -29 per 100 people).[20] These results likely indicate greater clinician confidence when stress testing is paired with imaging, based on general understanding from accuracy studies that positive and negative predictive values are better for SPECT than for stress testing. In the Medicare administrative database study, both CCTA and stress echocardiography were associated with a significantly higher frequency of additional noninvasive testing compared with nuclear MPI (OR, 1.52; 95% CI, 1.37 to 1.69 and OR, 1.92; 95% CI, 1.83 to 2.0, respectively), but strength of evidence is low. Studies generally did not describe post-test reclassification of risk or decisionmaking for related further testing.

Hospitalization

Cardiovascular-related hospitalizations varied somewhat among pretest risk groups across studies. There was moderate-strength evidence from one large trial of ED patients with low to intermediate risk that the CCTA group was significantly less likely than the usual-care group to be hospitalized or admitted for observation at the index visit (RD, -26.8; 95% CI, -31.9 to -21.8 per 100 people), but that after this visit through 1 month, there was no difference (3% for CCTA vs. 2% for usual care).[28] Low-strength evidence from a large trial of intermediate-risk ED patients suggested that there were fewer hospitalizations following CCTA compared with usual care at the index visit (RD, -33; 95% CI, -39 to -28 per 100 patients).[21] These data imply clinician confidence in the negative predictive value of the anatomic test, yet there is a predisposition of patients to return with unexplained symptoms that can be from a variety of other causes of chest pain, including vasospasm and microvascular dysfunction. In contrast, no statistical differences between CCTA and usual care were identified for ACS hospitalization at the index visit based on subgroups of low- or high-risk patients in one trial,[19] but strength of evidence was low. There was moderate-strength evidence that there was no difference in cardiovascular hospitalizations between CCTA and functional testing groups in low- to intermediate-risk ED patients within 6 months (0% in both groups) based on one trial[31] and through 30 months based on one observational study[33] that compared CCTA with SPECT. In another trial of mixed pretest risk patients presenting to specialized chest pain clinics,[40] moderate-strength evidence suggested that hospitalization for cardiac causes occurred less frequently in the CCTA group compared with the exercise ECG group (RD, -6.1; 95% CI, -9.5 to -2.7 per 100 people) through 12 months. Two trials conducted in outpatient settings reported no

differences in cardiac-related hospitalizations between groups. The strongest evidence came from the large trial comparing CCTA with functional testing, which reported no differences at a median of 25 months (RD, -0.30; 95% CI, -0.10 to 0.71 per 100 people)[25] (moderate strength of evidence). The trial of SPECT versus exercise ECG in women also found no difference between groups (low strength of evidence).[27]

Special Populations

With regard to evaluation of special populations, one good-quality trial comparing CCTA with functional testing reported that none of the prespecified subgroups modified the primary composite outcome (all-cause death; nonfatal MI; hospitalization for unstable angina; or a major procedural complication, such as stroke, major bleeding, anaphylaxis, or renal failure requiring dialysis). Results across subgroups were consistent with those for the entire study population. Subgroups examined included age sex, race, pretest risk assessment, CAD equivalence, and pretest probability of CAD.[25] None of the other studies identified evaluated differential effectiveness or safety for the primary outcomes. As noted earlier, one fair-quality trial of exercise SPECT compared with exercise ECG in women found no differences between tests for mortality, ICA referral, revascularization, or hospitalization, but that trial reported a significantly lower use of additional noninvasive testing following SPECT.[27] The strength of evidence was moderate for additional testing and low for other outcomes. An additional small poor-quality RCT in women compared stress echocardiography with exercise ECG; this trial reported similar frequency of a composite outcome that included cardiac death, MI, unstable angina, or coronary angiography demonstrating 50-percent or more luminal narrowing (7.7% vs. 7.4%).[45] However, the strength of evidence was insufficient because of high risk of bias, lack of precision, and unknown consistency. Also as noted earlier, a large fair-quality administrative data study in the Medicare population was identified.[41] Consistent with findings in other studies, this study found no differences in adjusted effect estimates for all-cause mortality for the comparisons of nuclear MPI with stress echocardiography, exercise ECG, or CCTA. CCTA was significantly associated with increased referral for ICA and revascularization (particularly PCI) and use of additional noninvasive testing compared with nuclear MPI (strength of evidence was low for these outcomes and comparisons).

Harms and Consequences of Testing

Harms of testing were rarely reported and details on comparisons of harms for tests were sparse, with many studies stating only that no harms were observed and not providing further detail; 16 of the 27 comparative studies made no mention of evaluation of harms. There were no compelling safety outcomes data that can be used to recommend one approach versus another (low or insufficient strength of evidence). No differences in major procedural complications were identified in the trial comparing CCTA with functional imaging, although mild contrast reactions were significantly more common in the CCTA group than in the functional testing group (moderate strength of evidence).[25] No differences were reported between CCTA and usual care in bradyarrhythmia in one trial[28] or periprocedural complications in another[21] (low strength of evidence for both). A third trial reported that there was no clinical or laboratory evidence of contrast-induced nephropathy in either the CCTA or the usual-care group.[19] One observational study reported incidental findings requiring further investigation in 7.1 percent of those receiving CCTA (insufficient evidence).[33] Evidence from observational studies regarding test-related harms and impact of incidental findings following CCTA was insufficient to draw conclusions.

An important patient safety concern related to noninvasive testing is exposure to low to moderate levels of ionizing radiation, which add to cumulative lifetime radiation exposure. To the extent that noninvasive tests for CAD reduce the need for conventional angiography, cumulative exposure might be reduced. To the extent that they result in the need for additional testing, it may be increased. The true attributable risk from radiation-based diagnostic tests cannot be determined. Some experts consider the potential for harm from radiation exposure (based on either deterministic or stochastic modeling) to be clinically significant, particularly since patients may be likely to have additional tests using radiation over many years. Estimates of radiation exposure from included studies are provided in Appendix G of the full report (Table G4); the Introduction section of the full report provides contextual information on radiation exposure ranges for testing. Radiation exposure from included studies for initial testing strategies ranged from 3.8 to 17 mSv for CCTA and 10.5 to 38 for SPECT. One study reported a mean of 4.0 mSv for PET,[38] and another study[21] reported a mean of 4.7 mSv for usual care. Consideration of cumulative radiation exposure related to downstream testing and intervention is important when discussing with patients the benefits and consequences of the different noninvasive tests and their contribution to lifetime radiation exposure. Higher mean cumulative radiation accounted for by additional testing was seen in single trials following CCTA compared with usual care (14.3 ± 10.9 vs. 5.3 ± 9.6 mSv)[21] and functional testing (12.0 ± 8.5 vs. 10.1 ± 9.0 mSv).[25] One study reported higher cumulative exposure following CCTA than following SPECT in patients referred for ICA (median, 15.2 mSv; interquartile range, 12.7 to 17.1 vs. median, 10.8 mSv; interquartile range, 10.2 to 11.7).[42] In contrast, another trial reported lower cumulative exposure for additional testing following CCTA versus SPECT (median, 7.3 mSv; interquartile range, 5.1 to 13.7 vs. median, 13.3 mSv; interquartile range, 13.1 to 38.0).[39] One observational study of CCTA and exercise ECG reported greater cumulative radiation exposure as a result of index plus downstream testing for CCTA in patients whose tests were negative, positive, or inconclusive. However, among those who tested positive and had revascularization, mean cumulative exposure was slightly higher in the ECG group (28 vs. 32 mSv).[35] Consideration of patient preferences with regard to the impact of radiation exposure should be part of shared decisionmaking around noninvasive testing.

Findings in Relationship to What Is Already Known

Few prior reviews have evaluated the impact of noninvasive testing on clinical and management outcomes. Systematic reviews and studies on noninvasive testing for CAD identified from our search focused on traditional measures of test performance (e.g., sensitivity, specificity) compared with ICA and generally did not directly compare the effectiveness and safety of different modalities with regard to impact on clinical outcomes specifically in the population of interest in this report. Consistent with this review, prior systematic reviews[47,48] have reported few or no comparative studies evaluating the impact of noninvasive tests on clinical outcomes, decisionmaking, or use of additional testing, and they note that harms are rarely reported. Relevant studies from these reports were included in this systematic review. The recent AHRQ report on noninvasive testing for CAD in women reported that there was insufficient evidence from three studies that treatment decisionmaking and clinical outcomes were impacted by noninvasive testing;[49] consistent with our report, there were no differences in clinical events or hospitalization in studies comparing noninvasive tests. The authors also concluded that studies were underpowered to detect clinical outcomes.

Applicability

A number of factors that impact the applicability of this report's findings are discussed in this section.

Patients

Eight of the 13 trials identified were in patients presenting to the ED with CAD symptoms; however, the largest trial was in an outpatient setting. Patients presenting to the ED represent a broad spectrum of pretest risk probabilities, including those at low or intermediate risk as well as those at high risk for CAD. The severity, newness, and duration of symptoms may differ from those seen in outpatient settings, where patients generally present with more mild to moderate symptoms. Definitions of pretest risk varied across included studies, and some did not report or stratify by pretest risk, making it difficult to fully evaluate results based on pretest risk across settings. It is likely that the patients enrolled in the included studies are representative of those in the broad range of clinical practice regardless of setting.

Interventions and Comparators

The evidence may be skewed toward newer testing modalities, and studies of established tests may not reflect current technology and diagnostic performance. CCTA was the noninvasive test most often assessed, accounting for 48 percent of included studies. The high proportion of studies dealing with CCTA may be because it is a newer modality and thus is compared with established tests, such as stress echocardiography and MPI. Few studies comparing different types of functional testing, particularly established functional tests, such as stress echocardiography, exercise ECG, and nuclear stress testing, were identified. A recent systematic review suggests that over the past 2 decades, there has been a substantial decline in investigations related to echocardiography and nuclear cardiology, compared with a marked increase in cardiac CT imaging studies.[50] Input from clinical team members and the Technical Expert Panel suggests that there is substantial variation in clinical practice with regard to which test may be ordered as an initial test based on patient presentation, testing availability, and clinical perspective. The applicability of this report may be impacted by lack of clarity on the extent to which CCTA may or may not be the initial noninvasive test for firstline evaluation of symptomatic patients without known CAD after a resting ECG. None of the included studies included a "no testing" arm. To the extent that clinical decisionmaking is based on clinical evaluation and judgment without testing, findings in this report may be less applicable to settings where testing is not routinely done.

Outcomes

Findings related to rare outcomes of death, MI, or hospitalization may not be fully applicable to broader clinical populations, in part because of small study sizes and inability to fully characterize such outcomes, particularly over the longer term. Moreover, the impact of a negative test or the treatment downstream from a positive test may extend beyond traditional major adverse coronary events to quality of life, reduction in symptoms, and level of activity. These outcomes were not examined in the majority of included studies. The majority of trials reported outcome at the time of an index ED visit, and the clinical management objectives are somewhat different in an ED setting than in an outpatient setting.

Settings

Most RCTs were conducted in the ED, where test data help determine immediate disposition for discharge or the need for additional evaluation and/or hospitalization. The initial goal is to make a diagnosis for the cause of chest pain in order to inform appropriate treatment and next steps at the index visit. Thus, MI reported at the index visit may reflect a test's ability to make the diagnosis for immediate decisionmaking but not the test's ability to impact future clinical outcomes. Testing is able to affect events only after the index visit, and long-term followup from ED studies was limited. Thus the applicability of findings from ED studies to general outpatient settings over the long term is likely limited. Six RCTs evaluating CCTA were multicenter studies; five were in single-center sites. It is possible that results from single-center trials may be different and less generalizable than results from multicenter trials. Assessing discernible patterns between the multicenter and single-center site studies in this report is a challenge given the heterogeneity across studies with regard to pretest risk and how comparators such as usual care are defined.

Implications for Clinical and Policy Decisionmaking

The 2012 ACCF/AHA Guideline states that diagnostic testing is most valuable when the pretest probability of ischemic heart diseases is intermediate (10%–90%) and provides a range of options for which test may be used in a given scenario.[9] However, the effectiveness of different modalities with regard to impact on clinical outcomes is not compared. Currently, a variety of tests as the initial (and additional) diagnostic tests for patients at intermediate pretest risk of CAD are employed, and there is uncertainty regarding which tests, if any, may be most suitable and beneficial in patients who present with symptoms suggestive of CAD but have no prior history of it. Although several ACCF/AHA Appropriate Use Criteria are available, including the 2013 multimodality imaging Appropriate Use Criteria,[51] they do not explicitly compare multiple noninvasive testing modalities, nor do they make specific recommendations for the timing and sequencing of tests or for repeat testing based on pretest risk group.

Low- to moderate-strength evidence from nine trials suggested that there is no clear difference in MI or in all-cause mortality between different testing strategies across settings and pretest risk groupings that included those at intermediate risk. Possible contributors to this finding, including lack of power to detect a difference, were previously described. Information from two studies that provided data on groups with low and high pretest risk (without ACS) do not provide insight into the best testing strategies in those groups; the strength of evidence was insufficient for the few outcomes reported and no conclusions can be drawn. Across studies that enrolled intermediate-risk groups, no clear benefits of one testing strategy versus another were seen, and no clear picture of harms for various tests was available from included studies. One apparent trend uncovered by the review is that tests that evaluate coronary anatomy, such as CT, result in a greater likelihood of referral for ICA and subsequent intervention than functional tests do; however, the strength of evidence varied from high to low depending on the comparator, and the impact on clinical outcomes is not known, as most studies did not present data on treatments administered to individual study participants. Thus, it is not clear if the increased referrals were helpful or not with regard to influencing clinical outcomes. In addition, potential harm from use of invasive treatments (which carry specific risks) if clinical benefit is not clear was not described. Only two studies provided limited information on the overall impact of testing and resulting treatment strategies on patient symptoms and quality of life. No studies that compared

testing with an arm that received no testing were identified, so the impact of any of the noninvasive testing pathways on clinical evaluation is not known.

As defined in the ACCF/AHA Guideline, the intermediate pretest group is broad and heterogeneous (10%–90%), and in the absence of information on post-test risk, the value of the various tests for influencing important management decisions at each end of the spectrum is not clear. The ACCF/AHA Guideline and various Appropriate Use Criteria[52-55] provide general recommendations for testing and treatment.

In general, next steps following a positive result from an initial noninvasive test are in part based on the post-test annual predicted rate of cardiac mortality as described in the 2012 ACCF/AHA Guideline: low risk (<1% per year), intermediate risk (1%–3% per year), or high risk for cardiac mortality (>3% per year).[9] Clinical presentation and test results are both considered in this determination. In general, for people who would be categorized as being at low risk (negative test result) or intermediate risk and who do not exhibit characteristics of ACS, medical management may be appropriate. In most instances, patients in these categories can be managed without invasive assessment. In patients who are considered to be at high risk based on noninvasive testing and presentation, ICA for further risk stratification and assessment of appropriateness for revascularization may be the next logical steps. In general, indications for revascularization are based on the clinical presentation (ACS or stable angina); the severity of the angina (based on Canadian Cardiovascular Society Classification); the extent of ischemia on noninvasive testing; and the presence or absence of other prognostic factors, including congestive heart failure, depressed left ventricular function, and diabetes; the extent of medical therapy; and the extent of anatomic disease.[56,57]

Thus, post-test disease probability is an important factor in determining next steps for testing and treatment. From the included studies, however, it is not clear how post-test risk was assessed, which clinical pathways were followed after the initial test, which test(s) may lead to the most appropriate treatment given the post-test risk, or whether the treatments impacted outcomes. While the ACCF/AHA Guideline and various Appropriate Use Criteria provide a range of options for which test may be used in a given scenario and which treatment initiated, the effectiveness of different testing modalities leading to appropriate treatment are not compared with regard to impact on clinical outcomes.

In the absence of high-strength evidence regarding testing options, including the possibility of not testing, decisions must necessarily be made on the basis of other factors related to the initial test and potential followup. The ability of a test to accurately diagnose treatable CAD is important; so too are the costs and consequences beyond the initial test, such as followup of false-negative results (e.g., tests with high false-positive rates in a population with low pretest risk), and the costs and consequences of missing significant disease (e.g., dismissal from the ED of patients with CAD needing treatment). The costs and consequences depend to some extent on the role a test plays in the diagnostic workup pathway, as well as the availability and convenience of a test. Patient pretest probability of disease and consideration of the likelihood ratios with regard to goals of ruling in or ruling out CAD should be a part of the decisionmaking process. Consequences of testing that need to be considered include those related to patient anxiety and patient quality of life and those related to radiation exposure of the index test, as well as potential downstream exposure from additional testing resulting from the initial test and future testing and/or treatment. Consideration of patients' preferences based on their understanding the range of consequences of initial and downstream testing is an important part of shared decisionmaking for initiating noninvasive testing.

Limitations of the Systematic Review Process

This review has some potential limitations. Stratifying by pretest risk, which was in keeping with the intent of the Key Questions, may have resulted in fewer studies to pool and left single studies for most comparisons. This, combined with substantial heterogeneity in how pretest risk was defined, the timeframes over which outcomes were evaluated, and clinical heterogeneity between the tests evaluated, resulted in too few studies for head-to-head meta-analysis for most outcomes, and network meta-analysis was not feasible.

Variable reporting on patient symptoms and characteristics related to CAD risk precluded application of a standardized method for calculating or assigning pretest risk across studies. In light of this, test comparisons were evaluated according to pretest risk as specified by authors to discern patterns within and across pretest risk levels and settings, and qualitatively synthesize outcomes when pooling was not possible. This approach resulted in limited ability to truly examine the evidence by pretest risk.

Inclusion was restricted to studies published in English; however, this is not likely to have impacted the evidence base, as few potential non–English-language studies were seen in the searches. Given the paucity of RCTs, comparative observational studies were included. Despite a focus on outcomes in studies that controlled for confounding, there is a possibility that residual confounding influenced reported results, lowering confidence in effect estimates. The comparative studies included may not adequately capture harms safety issues in the population of interest. The focused criteria on inclusion of studies comparing an established firstline test (beyond a resting ECG) narrowed the review scope substantially, but this focus was intended to provide a clearer approach to addressing the areas of uncertainty. It is possible that older historical studies outside of our population of interest could provide more detailed information about the safety of various tests, particularly more established tests.

There were too few studies of any given comparison to meaningfully evaluate reporting and publication bias. Where available, protocols of trials were reviewed to consider the extent to which outcomes were reported selectively, and information from Scientific Information Packets requested from stakeholders was evaluated; while overt publication bias was not detected, there is always the possibility it may be present. This review provides a snapshot of currently available evidence on the questions posed. Included studies may not reflect technological advances that have been made in the various testing modalities.

Limitations of the Evidence Base

Important limitations of the evidence base include the paucity of studies that compared the impact of different noninvasive tests on hard clinical outcomes, such as mortality and myocardial infarction; few RCTs were available, in particular for comparisons of established functional tests in the population of interest. No trials that included a no-testing arm were identified. Methods for assessing pretest risk, defining cardiovascular outcomes, and defining usual care were poorly reported and not standardized. The variable methods for determination and classification of pretest risk across studies and inability to implement a standardized method for assessing pretest risk across studies precluded detailed evaluation of testing strategies by pretest risk level to determine the comparative values of tests for a given pretest risk. The intermediate risk range is broad (10%–90%). Studies did not provide information on the impact of test results on post-test risk stratification or clinical decisionmaking for treatment or further testing, precluding evaluation of the impact of testing in this group. Some studies reported composite cardiovascular

outcomes, which can be misleading, depending on the effects on the individual components.[58] Studies did not evaluate aspects of unnecessary testing. Reporting of harms was suboptimal; 16 of the 27 comparative studies made no mention of evaluation of harms and another 3 merely stated that there were no adverse events. With the exception of one study, authors reported few details about harms. As mentioned previously, study sample sizes and short-term followup may preclude evaluation of rare events. Studies did not describe the impact of testing on treatment choices. Few studies on PET, CACS, and established tests such as stress echocardiography were identified.

Research Gaps and Recommendations

The gaps in the available evidence are many. Two primary issues relate to the need to improve reporting and standardization of pretest CAD risk and to enhance the evidence linking testing strategies and clinical pathways with clinical outcomes. Use of standardized risk models that refine and narrow the currently broad "intermediate–risk" group is needed. For example, because of health care trends to streamline and reduce the cost of care, newer risk models such as the Duke Clinical Score have narrowed the intermediate range and tend to reclassify many of those classified as "intermediate risk" in the Diamond and Forrester model to "low risk."[59] Documentation of post-test risk stratification and its impact on clinical management (treatment and referral for additional testing) is needed to determine optimal testing strategies and roles of tests in different pretest risk groups. This may facilitate comparison of tests to effectively parse out patients at the highest risk end and those at the lower risk end, as well as evaluation of the impact of management decisions in these groups, as they likely will differ. Documentation of management of those who test positive compared with those who test negative and followup of these groups for sufficient time to evaluate clinical outcomes are needed. Prospective cohort studies that address selection bias and confounding by indication have the potential to enhance the evidence base and may be more feasible than RCTs for some settings. Studies comparing testing versus clinical evaluation without testing would provide valuable information for assessing the need for testing, possible overuse of testing, and the impact of testing in general. Comparative studies (RCTs, pragmatic trials, or prospective cohorts) of functional tests that reflect technological advances as applied to symptomatic patients without known CAD would update the evidence base. Meta-analysis of patient-level data from existing trials may allow for more specific stratification by pretest probability or specific risk factors. Important insights into the overall impact of testing on long-term outcomes could come from studies that (1) document how test results specifically influence decisionmaking regarding further testing and treatment strategies, and (2) follow patients to evaluate the impact of the testing pathway. Future research also needs to incorporate evaluation of patient-centered outcomes, such as quality of life, symptom status, and the impact of testing.

Primary gaps and considerations for future research are summarized in Table F.

Table F. Overview of research gaps and recommendations

Research Components	Evidence Gap	Future Research Recommendations
Study design methods and reporting	Gaps include lack of a standardized approach to determining and reporting pretest risk across studies; variable definitions of pretest risk, which precluded effective stratification by pretest risk; the large range of pretest likelihoods for "intermediate" risk patients (10%–90%), which precluded detailed evaluation of the impact of testing for patients at the lowest and highest ends of the range.	A standardized approach for determination of pretest risk that can be applied across study designs is needed. Future research should use risk models that further refine the range of pretest probability for those at intermediate risk (e.g., the Duke Clinical Score) to delineate the impact of testing on clinical decisionmaking at the lower and higher ends of the range. Tools that refine the range may also be clinically useful.
	Studies describing outcomes at the index ED visit do not allow conclusions regarding the impact of testing on clinical outcomes over the longer term.	Longer followup (>12 months) and documentation of the impact of testing on treatment decisions and hard clinical outcomes are needed. RCTs, pragmatic trials, or prospective cohort studies that address selection bias and confounding by indication could be employed.
	None of the included studies evaluated issues of unnecessary testing or treatment in patients without known CAD.	As a first step, a priori definitions for necessary vs. unnecessary testing or treatment are needed, and they should be evidence based. Given the variability of clinical practice and medicolegal concerns, this may be challenging. Evaluation of Appropriate Use Criteria and examination of evidence on the clinical outcomes based on application of such criteria may help further define necessary vs. unnecessary.
Patient populations	There is a paucity of studies on patients with low or very low pretest probability of CAD, and the value of testing is not clear for this population.	Studies (RCTs, pragmatic trials, or methodologically rigorous comparative cohort studies) that compare a testing strategy (and related clinical management) with a strategy of no testing (and related clinical management) are needed. Sufficient sample size may be a challenge, given the low prevalence of CAD that is likely in this group.
	Few active trials listed in ClinicalTrials.gov pertain to symptomatic patients without known CAD, yet this group of patients commonly presents for evaluation and testing, particularly in outpatient settings. (See Appendix K in the full report.)	Future studies focused on those without known/prior CAD history or studies that analyze outcomes for this group of patients separately from those with known CAD are needed.
	There is a paucity of high-quality studies comparing various testing strategies in outpatient clinic populations.	Studies of patients who typically present in outpatient settings are needed. Greater integration of cardiologists into hospital settings may facilitate the conduct of studies of outpatients and enhance opportunities for followup of patients initially presenting to the ED.
	Studies do not generally report the extent to which clinical decisionmaking and clinical outcomes may be modified by patient characteristics, sociodemographic factors (e.g., age, sex, race, ethnicity, education, socioeconomic status), or provider characteristics.	RCTs or pragmatic trials with sufficient sample size to compare differential effectiveness and safety of testing strategies based on prespecified analyses are needed.

Research Components	Evidence Gap	Future Research Recommendations
Interventions and comparators	There is a lack of studies comparing outcomes following testing and resulting treatment strategies vs. a strategy of clinical evaluation without testing and resultant treatment strategies.	Studies (RCTs, pragmatic trials, or methodologically rigorous comparative cohort studies) that compare a testing strategy (and related clinical management) with a strategy of no testing (and related clinical management) are needed.
	Older studies of established tests (particularly functional tests) may not be as applicable in light of advances in technology. There was a paucity of studies comparing functional tests with each other.	Studies (RCTs, pragmatic trials, or methodologically rigorous comparative cohort studies) that compare functional tests using more state-of-the art technology and methods with each other and with anatomic tests are needed. New studies should focus on the impact each test makes on clinical decisionmaking and hard clinical outcomes.
Outcome measures	Studies comparing of the impact of noninvasive testing on hard clinical outcomes in those without known CAD are few compared with studies of test accuracy.	Additional sufficiently powered studies examining the impact of testing on hard clinical outcomes (death, MI) at longer term followup (>12 months) are needed.
	There is limited high-quality comparative evidence linking established tests with clinical decisionmaking and subsequent outcomes in the population of interest by pretest risk, particularly in nonemergent settings and over the longer term. Further, there is limited evidence on the impact of tests on post-test risk stratification and the best testing strategy(ies) for post-test risk stratification to identify patients who may be at highest risk and may benefit most from various treatment strategies. It is not clear whether the individuals who would most benefit from given treatment strategies were referred to those strategies and whether the strategies were effective.	Studies that document and compare tests with regard to their impact on prespecified clinical decisionmaking components (e.g., referral for additional testing, initiation or change in medication), particularly in outpatient settings, are needed. Such documentation should also include post-test risk stratification and factors that influenced its determination, what decisions were made based on the test results (positive, negative, or inconclusive results), and impact on hard clinical outcomes (death, MI) over time.
	There is limited evidence on the impact of testing strategies (including consequences of downstream testing and treatment) on patient-related outcomes, such as quality of life and symptom status.	Future studies should incorporate standardized validated measures for patient-reported outcomes and document the impact of testing, including downstream testing, on patient psychological status (particularly with false-positive results), health status, and resource use.
	Adverse events and consequences of testing are poorly reported.	Future study protocols should delineate, a priori, possible adverse events and consequences (including those related to psychological aspects of testing, radiation exposure, resource use) and report their occurrence per the protocol.
Analysis	The lack of a standardized approach to determining and reporting pretest risk across studies and variable definitions of pretest risk used in included studies precluded the ability to effectively stratify by pretest risk or pool data.	Individual patient data meta-analysis of RCTs may provide opportunities to use a standardized approach for pretest risk stratification and may facilitate evaluation of modification by patient characteristics and other factors.
	A number of studies did not provide details for pretest risk or report results stratified by pretest risk.	Studies should stratify by pretest risk of CAD using a standard method and report outcomes based on pretest risk strata.

CAD = coronary artery disease; ED = emergency department; MI = myocardial infarction; RCT = randomized controlled trial

Conclusion

A review of current studies found no clear differences between testing strategies across settings with regard to clinical or management outcomes that would allow recommendation of one strategy over another for any given pretest risk group that included patients with intermediate pretest risk. No conclusions regarding low-risk patients or those without ACS at high risk are possible. Limited evidence from RCTs found no clear differences between CCTA versus other strategies in clinical outcomes across risk groups, although anatomic testing may result in a higher frequency of referral for ICA and revascularization. The frequency of all-cause mortality and MI was low across studies in all settings. The absence of information on post-test risk stratification and subsequent decisionmaking precluded evaluation of the impact of testing on patient management or outcomes of management. Testing strategies vary in radiation exposure; there is inadequate comparative evidence to make judgments regarding exposure for the initial test or downstream testing. Assessment of harms was limited. Future research using more refined evidence-based definitions of pretest risk, coupled with information on post-test risk stratification, its impact on clinical management (treatment and referral for additional testing), and longer term followup to assess clinical outcomes, is needed to determine optimal testing strategies and roles of tests in different pretest risk groups.

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Introduction

Background

Nature and Burden of Coronary Artery Disease

The public health and economic burdens of coronary artery disease (CAD) are substantial. CAD causes one in six deaths in the United States and is the leading cause of death globally.[1] Annually, approximately 635,000 Americans experience a new coronary event, 280,000 have a recurrent ischemic event, and an additional 150,000 have a silent first myocardial infarction (MI).[2] A large proportion of ambulatory health care visits are for evaluation of patients with suspected CAD, with an estimated 1.5 percent of the population presenting to health care providers with chest pain every year.[3] An estimated $108.9 billion are spent annually on CAD treatment.[4] Optimizing the process for assessing these patients presents an opportunity to improve patient outcomes and target health resources to where they can have the most impact.

The most common underlying cause of CAD is atherosclerosis, a disease process in which plaque (which has a complex and varied composition that includes lipids, inflammatory cells, smooth muscle cells, and connective tissue) builds up on artery walls. Plaque formation can lead to the partial or complete blockage of coronary arteries and as a result prevent the heart from receiving blood, oxygen, and vital nutrients. Plaque causes blockage by two mechanisms: (1) progressive narrowing of the artery because plaque compromises the vessel lumen and (2) thrombotic occlusion of the artery, which occurs when the hard surface of a plaque tears or breaks off, exposing the inner fatty pro-thrombotic, platelet-attracting components to the site, resulting in enlargement of the blockage. The resulting reduction in blood flow can be either acute or chronic and leads to an inadequate blood supply to the myocardium.[5,6] Areas of atherosclerosis can also cause vascular dysfunction, which is an imbalance between relaxation and constriction in either large conduit arteries or the microcirculation. This process can occur in areas of plaque development or can occur in the absence of significant plaque but in the presence of certain predisposing diseases or atherosclerotic risk factors (e.g., lipid disorders, diabetes, smoking, and sedentary lifestyle).

The most common symptom of obstructive CAD is chest pain (angina), which is the first presenting symptom in at least 50 percent of patients with CAD.[7] Other common symptoms include the angina equivalents dyspnea, early fatigue with exertion, indigestion, palpitations, tightness in the throat, and neck or arm pain. However, because these symptoms are also seen in many common noncardiac conditions, such as gastroesophageal reflux, esophageal spasm, and cervical disc disease, they are much less reliable predictors of CAD. Women and people with diabetes are less likely to experience classic angina, adding to the challenges of early CAD diagnosis in these populations. Although the onset of symptoms and clinical impact of CAD depend in part on the number and distribution of atheromatous plaques, the degree and length of coronary narrowing, microvascular function, and cardiac blood flow demand (determined by factors such as degree of usual daily activity, blood pressure, and heart rate), lesion severity is poorly correlated with symptoms and CAD may remain asymptomatic for many years.

Patient Assessment and Pretest Risk of CAD

The 2012 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline categorizes the pretest probability of CAD as low (<10%), intermediate

(10%–90%), or high (>90%).[8] Estimation of pretest probability starts with evaluation of patient history and presentation, including type of chest pain, age, and sex. Pretest risk of CAD can be based on a number of factors, including the presence of risk factors such as diabetes mellitus, hypertension, dyslipidemia, personal smoking history, and family history of premature atherosclerotic cardiovascular disease; however, pretest risk is often ascertained based on age, sex, and type of chest pain (i.e., typical or atypical).[9] Chest pain has classically been subdivided into typical (or definite) angina, atypical (or probable) angina, and nonanginal chest pain. Typical cardiac angina is characterized by (1) a substernal discomfort which is precipitated by physical exertion or emotional stress, (2) is relieved by rest or nitroglycerine in less than 10 minutes, and (3) may be accompanied by radiation of the discomfort to either the shoulder, the jaw, or the inner aspect of the arm. Atypical angina is that which meets only two of the three characteristics of typical angina, while nonanginal chest pain only meets only one of the three characteristics of typical angina. The type of chest pain together with age and sex allow for a rough estimation of pretest probability of CAD using validated clinical risk scores such as the Diamond and Forrester Chest Pain Prediction Rule.[10,11] Using this algorithm, a 55-year-old man presenting with typical chest pain would be estimated to have approximately 80 percent probability of having obstructive CAD; but this pretest likelihood would be 50 percent if the pain were atypical and 33 percent if it was nonanginal in nature. There are a number of other clinical risk prediction tools for bedside prediction of pretest probability in patients with suspected CAD, including the Morise Score, Thrombolysis in Myocardial Infarction (TIMI) risk score, and the Goldman Reilley criteria (Goldstein).[12,13,14-16] However, these are rarely documented in clinical practice and baseline level of risk often revolves around the clinician's overall assessment of sociodemographic characteristics, the description of the chest pain, and the findings on resting electrocardiography (ECG).[17]

Diagnosis of CAD: Overview

The first step in diagnosing CAD is a thorough clinical work-up which consists of a physical examination, patient history, obtaining some combination of a resting ECG, chest x-ray, and/or serum biomarkers such as cardiac troponins. If the cardiac troponins are consistent with myocardial injury or the ECG is suggestive of myocardial ischemia then patients should be treated according to the appropriate guidelines for an acute coronary syndrome (ACS).[18]

If the presentation is not acute, the ECG is nonspecific, and cardiac troponins are normal, then the stable patient may discharged. Alternatively, the patient may receive further testing to help determine the etiology of chest pain and the appropriate management, in which case the risk of CAD must be assessed based on patient history and presentation. A patient's pretest CAD risk can inform which test or procedure is most appropriate as a first step towards diagnosing CAD.

A diagnosis of CAD can be made by looking for evidence of the pathophysiologic processes of disease, including anatomic changes of the arterial wall, impaired myocardial perfusion, or consequences of impaired perfusion such as myocardial contractile dysfunction. Historically, invasive coronary angiography (ICA) has been considered the standard reference diagnostic test for anatomic CAD, defined here as any obstructive lesion that is consistent with symptoms or that may carry an increased risk of ACS, although its invasive nature makes it less ideal in many patients because of its associated risks and costs. Noninvasive tests are another option, and provide diagnostic and prognostic information that can improve risk stratification, thus guiding subsequent testing and interventions. Noninvasive diagnostic tests can be broadly divided into two categories: functional tests and anatomic tests. Functional tests provide information not

provided by standard ICA, such as whether symptoms are correlated with areas of ischemia. Functional tests include exercise ECG, exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single-photon emission computed tomography (SPECT) or positron emission tomography (PET), pharmacologic stress magnetic resonance imaging (MRI), computed tomography (CT), and Doppler ultrasound-derived flow reserve measurements. Noninvasive anatomic tests include coronary CT angiography (CCTA) and coronary artery calcium scoring (CACS). ACCF/AHA Appropriate Use Criteria suggest that, as a general rule, functional testing is more informative than noninvasive anatomic evaluation and exercise testing is more informative than pharmacologic testing.[19] Each of these tests is described in more detail in the following sections.

Impact of Pretest Risk on Choice of Diagnostic Test

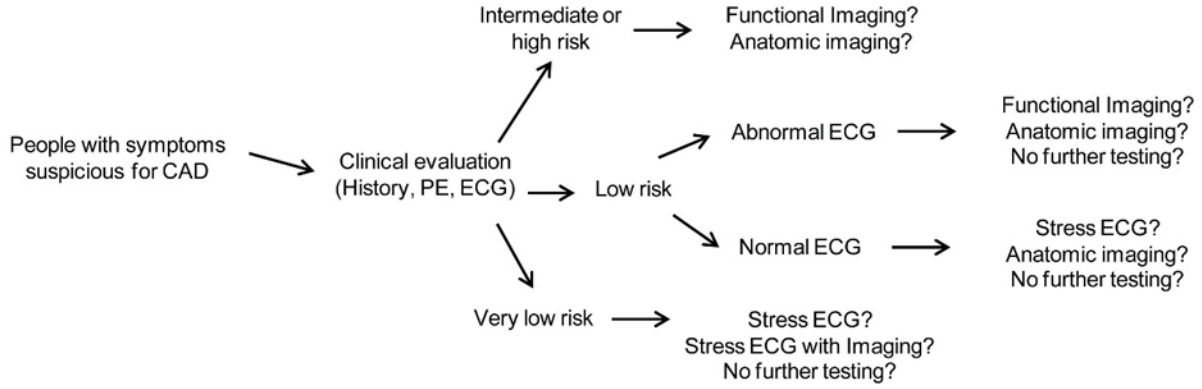
Further diagnostic testing beyond the resting ECG may be considered appropriate in patients who are symptomatic based on whether they are considered as low (less than 10% pretest probability of CAD), intermediate (10%–90% pretest probability of CAD), or high (greater than 90% pretest probability of CAD). The 2012 ACCF/AHA Guideline states that diagnostic testing is most valuable when the pretest probability of ischemic heart diseases is intermediate (10%–90%)[8] and provides a range of options for which test may be used in a given scenario. However, the effectiveness of different modalities with regard to impact on clinical outcomes is not compared.[8] Currently, clinical practice utilizes a variety of tests as the initial (and additional) diagnostic tests for patients at intermediate pretest risk of CAD.

Three primary areas of uncertainty exist regarding which tests, if any, may be most suitable and most beneficial for specific patient scenarios in patients who present with symptoms suggestive of CAD but do not have prior history of it, and these areas helped to frame to Key Questions of this systematic review. Namely:

- In patients with low pretest probability of CAD (<10%), are clinical outcomes improved by use of nonimaging stress testing, imaging stress testing, or no further testing? It is not clear whether imaging may be necessary in this group of patients or if there are specific subgroups of low-risk patients who might benefit more from one type of testing than another or who should have no further testing.
- How do tests compare with regard to improvement in clinical outcomes (e.g., MI, premature mortality, and congestive heart failure) in patients whose risk is very low (<5%) or in patients with intermediate to high risk? How do tests differ in their ability to reclassify patient risk after the test and to influence appropriate patient management?
- Are there differences in clinical outcomes following anatomic versus functional testing in either the low-risk group or the group with intermediate to high risk?

The overarching conceptual flow for initiating noninvasive testing based on pretest risk assessment is shown in Figure 1.

Figure 1. Overarching conceptual flow for initiating noninvasive testing based on risk assessment following initial clinical evaluation



CAD = coronary artery disease; ECG = electrocardiogram; PE = physical exam

Patients at low pretest risk may undergo noninvasive testing to further delineate their risk and to provide a basis for clinical decisionmaking, although in some cases, an alternate explanation for the symptoms (such as heart burn, costochondritis, or pulmonary disease) may be evaluated first. Patients at intermediate risk commonly undergo noninvasive testing followed by appropriate treatment for comorbidities and risk factors. The ACCF/AHA intermediate range is intentionally broad, reflecting the availability of noninvasive tests that have been viewed as both safe and effective, to further stratify risk in the "intermediate pretest risk" category. In other words, the low end of the intermediate range is extended irrespective of cost because of the important health consequences of missing disease, but also results in a situation in which testing is performed in a very large number of individuals who do not have disease.[9] The high end is extended because of the combination of the somewhat high cost and risk of ICA and reasonably high sensitivity of testing to detect high-risk obstructive disease. Patients at high risk may undergo noninvasive testing, although at times clinicians may appropriately decide to bypass noninvasive stress testing and proceed directly to ICA.[19] This is more frequently done in patients who present to the emergency department (ED) with typical symptoms. In patients for whom clinical judgment remains equivocal, an additional test to further identify risk may be pursued.

Noninvasive Diagnostic Tests

Noninvasive Functional Tests

Functional tests of interest include exercise ECG, exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with SPECT or PET, and pharmacologic stress MRI. Additional details for each test are available in Table 1.

Exercise ECG is often the recommended initial test. Exercise testing is more physiologic and allows for documentation of the workload at which a patient develops symptoms or ischemia (defined as >1 mm ST depression in 2 contiguous ECG leads). Exertional capacity (measured in metabolic equivalents) and hemodynamic response (abnormal heart rate or blood pressure response) to exercise also provides important prognostic information.[20] The Duke treadmill score incorporates the exercise time, development of symptoms, and ST segment deviation on a treadmill test and has been correlated with outcomes.[21] Exercise testing is widely available, does not require intravenous access or radiation exposure, is relatively inexpensive, and is widely

validated. Despite these advantages, there are limitations including the fact that some patients are unable to exercise, some may have certain baseline ECG abnormalities that make the ECG uninterpretable during stress (left bundle branch block, left ventricular hypertrophy with repolarization abnormalities, ST segment depression of greater than or equal to 1 mm, and ventricular pre-excitation), and certain medications can cause false positive ST changes (notably digoxin).[20]

Stress echocardiography may be performed with exercise or through pharmacologic means (typically dobutamine). Stress echocardiography boasts improved sensitivity and specificity compared with ECG with improved localization of the at risk territory in a similar examination time frame and without radiation. It is limited by a poor image quality (often because of body habitus or pulmonary disease) and is operator dependent.

SPECT and PET are two forms of radionuclide imaging. Of the two, SPECT is more readily available and more commonly used. PET testing is much less frequently used because of limited availability and a relatively high cost. SPECT can be performed with exercise or pharmacologic agents and offers improved sensitivity and specificity compared with ECG testing and comparable diagnostic characteristics compared with echocardiography.[22,23] In the case of patients with poor echocardiographic quality, this is the preferred test. SPECT can also be limited by artifacts from breast tissue, motion, and liver/gallbladder uptake of the imaging agents. While SPECT relies on relative blood flow and can miss balanced ischemia, PET provides absolute quantification of blood flow and offers improved visual certainty, which translates into improved sensitivity and specificity.[24] Radionuclide imaging requires exposure to radiation which ECG testing and echocardiography do not.

Cardiac magnetic resonance imaging is an imaging modality which offers the ability to evaluate rest and stress perfusion for ischemia, cine imaging for cardiac function, and late gadolinium enhancement for evaluation of prior infarction. The operational diagnostic characteristics are superior to echocardiography and SPECT imaging.[25,26] Despite its improved sensitivity and specificity, this modality is not readily available, in part because of high cost of equipment and limited availability. In addition, exploration is needed regarding information on the impact of such advances in imaging on patient well-being, downstream testing, use of procedures, and unintended findings.[27] Because of technological limitations it is also, practically, limited to pharmacologic stress agents.

Noninvasive Anatomic Tests

Noninvasive anatomic tests include CCTA and CACS, although CACS is rarely considered appropriate in symptomatic patients. Additional details for each test are available in Table 2.

CCTA is a relatively accessible test that has a rapid scanning time. The necessary hardware is available in most hospitals, and state-of-the-art machines have a 64-slice scanner and the ability to inject contrast. Software packages available for most modern CT scanners assist in the acquisition and processing of images. However, there are many patient-related factors which can interfere with diagnostic quality, including irregular heart rate (such as atrial fibrillation), heart rates that are too fast (>70 bpm), inability to sustain a breath hold for 5 seconds, severe calcification of the coronary arteries, and small coronary artery vessel diameter (<1.5 mm). There are additional risks incurred by the injection of iodinated contrast agents for patients who have a history of allergy or those with reduced renal function and there is some radiation exposure. Overall, adoption of CCTA has been variable across institutions and states in clinical

practice. CCTA may be favored for patients considered at low risk for CAD because of its perceived high negative predictive value. It is often perceived as a “rule-out” test for CAD.[28-31]

CACS is obtained through performance of a noncontrast CT scan followed by a post-processing algorithm to determine an Agatson score, a volume score, or the presence of a calcium mass. The most widely used and best established measure of coronary artery calcium is the Agatson score. CACS is readily obtained and highly reproducible, and is most frequently used in asymptomatic patients for cardiovascular risk assessment. CACS is rarely appropriate for symptomatic patients, as the inability to detect calcium in the coronary arteries does not eliminate the possibility of significant stenoses.[19,32]

Table 1. Overview of included functional noninvasive tests

Test	General Use	Advantages	Disadvantages	Diagnostic Threshold and Post-Test Risk
Exercise Electrocardiography, Exercise Treadmill Testing	• Preferred initial test if there are no contraindications • Not appropriate if there are baseline abnormalities in the ECG • Not appropriate for patients who cannot exercise (leg claudication, deconditioning, arthritis, pulmonary disease) • Typically avoided in premenopausal women because of poor sensitivity and specificity • Typically performed on a treadmill using various protocols (commonly Bruce protocol)	• Low cost; quick • Functional capacity assessed • High sensitivity for severe CAD such as multivessel disease or left main occlusive CAD	• Suboptimal sensitivity • Low detection rate for single vessel disease • Nondiagnostic with abnormal ECG • Patient needs to achieve maximum heart rate • Wide variability in sensitivity and specificity for exercise ETT has been reported across studies • There are specific ECG criteria which determine positive and high risk for a treadmill test	Abnormal: • >1 mm ST depression in 2 contiguous leads • Arrhythmia • Below average exercise capacity High risk: • Stress Score less than or equal to -11 • Abnormal hemodynamic response
Stress Echocardiography (exercise or pharmacologic)	• Assessment of ventricular size and function • Assessment of wall motion abnormalities • Visual assessment of myocardial response to stress agent. • Exercise can be upright or supine bicycle or treadmill • Dobutamine can be used for patients unable to exercise • Preferred in those who are unable to exercise • Can be used in patients with abnormal ECGs (except LBBB)	• Improved sensitivity and specificity vs. ECG • Short exam time; simple and convenient to perform • No radiation • Evaluate cardiac function and structural abnormalities at the same time • Allows localization of ischemia • Exercise and dobutamine stress have similar value	• Decreased sensitivity for detection of single vessel disease or mild stenosis with post-exercise imaging • Infarct zone ischemia can be difficult to detect • Operator dependent; no quantitative analysis • Limited by poor image quality (body habitus, pulmonary disease) and interpretation is more difficult if resting wall motion abnormalities	Abnormal: • New WMAs with stress • Abnormal LVEF with stress High Risk: • LVEF <35% at rest or during exercise • WMA involving at least 2 of 16 segments developing with exercise or low dose dobutamine (10 mcg/kg/min) on a stress echocardiography • WMA (>2 segments) developing at a low heart rate (<120 bpm) • Evidence of extensive ischemia on stress testing

Test	General Use	Advantages	Disadvantages	Diagnostic Threshold and Post-Test Risk
Single Photon Emission Computed Tomography*, aka myocardial scintigraphy, aka nuclear stress testing (this may be combined with scintigraphy or planar imaging)*	• Assessment of ventricular size and function (computer generated) • Assessment of wall motion abnormalities (visual assessment; quite limited) • Assessment of viability • Preferred for patients with LBBB • Appropriate for those with poor echocardiography windows • Stress agents include: regadenoson, adenosine, dipyridamole, and dobutamine • Imaging agents include: 99mTc-MIBI (sestamibi), thallium, technetium, and tetrofosmin	• Evaluate perfusion (both viability and ischemia) and function • Improved sensitivity and specificity vs. ECG • Exercise and pharmacologic stress have similar value • Can be quantitative	• Limited by soft tissue attenuation (body habitus, breast artifact, and liver artifact) and motion artifact • Involves radiation exposure (~12 mSv to 37 mSv if dual isotope protocol used) • Relative flow not absolute (can miss 3 vessel disease because of "balanced ischemia")	Abnormal: • Any perfusion defect • WMAs High Risk: • Perfusion defect representing ≥10% of myocardium (particularly if anterior) • Multiple moderate perfusion defects • Large fixed defect with transient ischemic LV dilation or increase in Lung to Heart Ratio • Stress induced moderate defect with transient ischemic LV dilation or increase in Lung to Heart Ratio
Stress Positron Emission Testing	• Less clinically available • Preferred in women and obese patients • Assessment of ventricular size and function (visual with computer aid) • Assessment of ischemia and viability	• Accurate quantification of blood flow (absolute) because of trace kinetic modeling and attenuation correction • PET has higher interpretive certainty than SPECT because of improved image quality (in particular for women and obese patients) • Measures absolute myocardial blood flow	• Restricted to pharmacologic stress • High cost • Low availability • Radiation exposure (10–14 mSv)	Abnormal: • Any perfusion defect High Risk: • Perfusion defect representing ≥10% of myocardium (particularly if anterior)

Test	General Use	Advantages	Disadvantages	Diagnostic Threshold and Post-Test Risk
Stress Cardiac Magnetic Resonance Imaging	• Less clinically available • Typically receive assessment of structure and function at the same time and can assess some cardiac indices (stroke volume) • Typically pharmacological – generally vasodilator perfusion stress is more commonly performed than dobutamine functional stress	• High spatial resolution • Visualization of subendocardial perfusion • Assessment of viability (delayed gadolinium enhancement, does not require stress agents) • No radiation • Can provide anatomical evaluation as well	• More costly than many other noninvasive tests • Not readily available • Complex exam requiring specialized training	Abnormal: • Vasodilator: any perfusion abnormality and/or infarct on late gadolinium enhancement • Dobutamine: any or worsening new wall motion abnormality High Risk: • >3 of 32 stress perfusion defects • >2 dobutamine-induced dysfunctional segments (out of 17 segments)

CAD = coronary artery disease; ECG = electrocardiography; ETT = exercise treadmill test; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; mSv = milliSeivert; PET = positron emission tomography; SPECT = single photon emission computed tomography; WMA = wall motion abnormality

Table 2. Overview of included anatomic noninvasive tests

Test	Use	Advantages	Disadvantages	Diagnostic Threshold and Post-Test Risk
Coronary Computed Tomography Angiography *(≥64 slice)*	• Used as a rule-out test for low likelihood patients with chest pain • Identify or exclude coronary luminal diameter stenoses exceeding 50% • Clinically used in patients (assuming no diagnosis of CAD) with atypical symptoms or nondiagnostic results of a stress test or those at high risk for catheterization • In practice it is most common to use 64-slice or more • Can be retrospective or prospective (ECG-gated) • In EBCT or MDCT the X-ray source point is stationary, but electron beam is swept electronically • This will almost always include a coronary artery calcium score • Contrast agents used include: iopamidol (Isovue), iohexol (Omnipaque), ioversol (Optiray), ioxilan (Oxilan), ioxaglate (Hexabrix), and iodixanol (Visipaque)	• Noninvasive angiogram to rule out significant stenosis • Unlike cardiac CT-quantified calcium scoring, angiography detects obstructive CAD • Rapid • Good negative predictive value • Other causes of chest pain (aortic aneurysm) • High sensitivity	• Ischemia not confirmed • Quality depends on slow heart rate • Specificity 60%-80% • Distal vessels difficult • Cardiac motion artifact • Poor quality if heart rate not well controlled (requires beta blockers) • Heavy calcification causes “bloom artifact” limiting assessment of lumen • Fractional flow reserve is limited to proprietary software with limited validation (excluded from this analysis) • Required reconstruction of images and is time intensive • Radiation exposure (modern is ~3 mSv) • Limited by fast or irregular heart rate and/or motion	Abnormal: • Any luminal irregularities (important for establishing need for secondary prevention strategies for preventing disease advancement) High Risk: • Left main ≥50% narrowing • Proximal LAD ≥70% narrowing • 3 vessel disease • Left main equivalent (i.e. proximal LAD and proximal circumflex artery)

Test	Use	Advantages	Disadvantages	Diagnostic Threshold and Post-Test Risk
Coronary Artery Calcium Score	• Typically used as a screening test for asymptomatic patients • Uses the amount of calcium present in an artery to calculate a score (typically using Agatson method) • Can be performed using most CT modality and does not require contrast agent	• Screening test for asymptomatic patients to detect coronary artery calcium	• Does not detect ischemia or degree of vessel narrowing • Radiation exposure	Various thresholds exist. The presence of any calcium in a young population is abnormal (i.e. score >0) and any calcium is associated with a higher risk. There are age/sex matched norms. >100 is associated with a 10 fold higher risk than zero. >400 is considered an indication for statin in the current guidelines regardless of other risk factors.

CAD = coronary artery disease; CT = computed tomography, ECG = electrocardiography; EBCT = electron beam computed tomography; MDCT = multidetector computed tomography; LAD = left anterior descending artery

Invasive Coronary Angiography

Historically, ICA has been considered the standard reference diagnostic test for anatomic CAD and provides information on coronary artery anatomy and lumen obstruction through introduction of a radiopaque contrast dye while obtaining concurrent fluoroscopic cine images. ICA allows visualization of the size, position, and possible stenotic areas in vessels. Various thresholds for occlusion have been used (e.g., ≥50% or ≥70% occlusion) for diagnosis of CAD. Access to the arterial system is most commonly obtained through placement of a sheath in the femoral or the radial artery and requires instrumentation in the ascending thoracic aorta proximal to the head vessels. Complications and death are rare in ICA procedures with a majority of the literature reporting ICA harms being case studies. Adverse reactions to the contrast dye may occur, including allergic response; renal dysfunction; vascular injury including arterial dissection or perforation; and embolism (i.e., strokes, transient ischemic attacks, or limb ischemia). In addition, the procedure exposes patients to ionizing radiation.

ICA may overestimate or underestimate disease depending on a variety of technical factors as well as the complexity of coronary anatomy and plaque configuration. Many lesions are eccentric, so the apparent degree of stenosis can vary depending on the angle of visualization, and reproducibility on measurement of stenosis is considered only moderate.[8,33-35] ICA depicts coronary anatomy in a planar two-dimensional silhouette of the arterial lumen and interpretation can be confounded by vessel tortuosity, overlap of radiodense structures, and irregularities in plaque shape or flow of the contrast dye.[34] There are aspects of the coronary anatomy which portend a high risk for future events including arterial remodeling, and many high-risk features of a plaque (e.g., a vulnerable plaque) are not evident with ICA. ICA serves best as reference standard for anatomic tests and to date, there is not a comparable reference standard for tests evaluating functional changes secondary to ischemic heart disease. These limitations have led some to question the true value of ICA as the best reference standard for determining test accuracy, particularly for functional tests. Efforts to improve the diagnostic accuracy of coronary angiography have led to intravascular ultrasound (IVUS) and fractional flow reserve (FFR) though both techniques are reliant on having obtained earlier angiographic views.

Accuracy of Noninvasive Tests Compared With ICA

Increasingly, experts in cardiovascular health indicate that evidence on the value of noninvasive diagnostic cardiovascular testing needs to expand beyond traditional measures of test performance, such as sensitivity and specificity compared with a given reference standard and focus on evaluating the impact of such testing on hard cardiovascular outcomes.[36] Thus, while diagnostic accuracy measures provide important information on test performance, the primary focus of this report is to determine whether noninvasive tests improve clinical health outcomes and impact patient management. In keeping with this focus, information on the traditional test parameters of diagnostic accuracy are described here in order to provide a foundation for the report and were not examined via the formal systematic review process.

To provide a general overview of the diagnostic accuracy of the included noninvasive tests in the target population of symptomatic patients without known CAD, a targeted search of the literature was done to identify one or two moderate- to high-quality systematic reviews (based on the AMSTAR checklist[37]) that compared noninvasive tests included in this report (see Tables 1 and 2) with the historic gold standard of ICA in terms of traditional diagnostic test performance

measures (i.e., sensitivity, specificity, positive/negative predictive value, and positive/negative likelihood ratio).

The diagnostic test characteristics of all the included tests compared with the test results from ICA are summarized in Table 3, with more specific details available in Appendix H. The values of the various diagnostic test characteristics in these tables were taken from or calculated from the values reported in the included systematic reviews. Measures of diagnostic accuracy among patients with suspected CAD varied among the various tests: sensitivity ranged from 62 to 100 percent; specificity ranged from 68 to 89 percent; positive predictive value ranged from 57 to 94 percent; and negative predictive value ranged from 72 to 99 percent. Exercise ECG had the lowest overall diagnostic accuracy and CCTA had the highest diagnostic accuracy relative to ICA, which is perhaps consistent with CCTA as the test most similar to ICA in what it measures. The two tests classified as anatomic tests (CACS and CCTA) had the highest negative predictive values, which indicate a lower percentage of patients with significant coronary artery stenosis by ICA that would be missed by these two tests. Otherwise, there is no clear pattern to the characteristics of the different tests. For individual tests or across various tests, there is also no clear pattern in the differences between test characteristics among patients suspected of CAD only compared with all patients (i.e., suspected CAD and known CAD combined). The fact that the functional tests had lower negative predictive values does not imply that these tests would necessarily perform worse than ICA for purposes of predicting clinical outcomes such as worsening angina, incident MI, or CAD death, which is the focus of the current systematic review.

Table 3. Summary of diagnostic accuracy of noninvasive tests compared with invasive coronary angiography

Test	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	Prevalence
Exercise Electrocardiography	Overall*	67%	46%	41%	72%	NR	NR	NR
	Suspected CAD	62%	68%	57%	72%	1.94	0.56	41%
Stress Echocardiography	Overall†	84–87%	72–77%	85–89%	69–73%	3.08–3.65	0.18–0.21	66–68%
	Suspected CAD	88%	89%	93%	80%	8.35	0.13	64%
Single Photon Emission Computed Tomography	Overall	83–85%	77–85%	79–85%	79–85%	3.56–5.13	0.18–0.22	50%
	Suspected CAD	83–84%	79–85%	72–85%	84%	3.88–5.01	0.19–0.21	41%‡
Positron Emission Tomography	Overall	82–90%	86–88%	93–96%	53–84%	5.57–5.88	0.11–0.21	63–80%
	Suspected CAD	90–91%	82–91%	94%	75–84%	4.97–8.89	0.11	75%‡
Stress Magnetic Resonance Imaging	Overall	83%	86%	94%	68%	5.93	0.20	71%
	Suspected CAD	81%	87%	93%	70%	6.39	0.21	67%
Coronary Artery Calcium Scoring	Suspected CAD	98–99%	35–40%	65–68%	93–95%	1.51	0.04	55–56%
Coronary Computed Tomography Angiography (Low radiation dose)§	Suspected CAD	100%	89%	93%	99%	9.2	0.00	58%
Coronary Computed Tomography Angiography (Radiation dose not specified)	Suspected CAD	98.2%	81.6%	90.5%	99.0%	NR	NR	59.9% (28–85%)

CAD = coronary artery disease; LR + = positive likelihood ratio; LR - = negative likelihood ratio; angiography; NPV = negative predictive value; NR = not reported; PPV = positive predictive value

*Values for diagnostic test measures are taken from or derived from systematic reviews cited in Appendix H.

†Values reported are for combined groups of patients with known CAD and patients with suspected (but not confirmed) CAD.

‡Mean prevalence only available or calculable for one of the two included reviews.

§All included studies used prospective electrocardiography gating for CT; uses much lower radiation doses than other techniques.

Radiation Exposure in Noninvasive Cardiac Testing

Medical imaging is the largest controllable source of radiation exposure to the American public[38] and scrutiny of cardiac imaging procedures has increased based on concerns related to greater utilization and lack of adherence to quality control procedures.[39] In clinical decisionmaking, the levels of exposure for a given test need to be put in the context of other radiation-utilizing tests that may be part of the clinical pathway, as the possible cumulative effects of repeated radiation exposure are of concern. Potential benefits and risks, including any related to not performing the test, should be carefully considered before ordering tests that will expose patients to ionizing radiation. Final determination of net benefit for a given clinical scenario reflects the values and judgments of the individuals making the decisions.

Current guidance from regulatory bodies is that no threshold exits and that exposure should be kept as low as reasonably achievable (ALARA). ALARA takes into consideration the importance of assessing the "benefit to risk ratio" to balance the importance of information needed from a procedure with the potential risks related to radiation exposure.

ACCF/AHA Guidelines recommend following ALARA in all patient populations and provide recommendations for specific cardiac testing modalities that involve ionizing radiation and note that care should be taken when exposing low-risk patients, particularly young patients, to ionizing radiation.[8] They further note that all noninvasive stress testing carries some risk, even if ionizing radiation is not involved. The American College of Radiology reports that ICA is not usually appropriate for diagnosing CAD in patients with low probability.[40] SPECT, CCTA, echocardiography, and MRI are all considered more appropriate than ICA for low CAD probability. Of these modalities, the ACR considers CCTA with various contrast and dose techniques to be the most appropriate – receiving the rating of "usually appropriate".

To date, no large-scale epidemiologic studies evaluating cancer risk associated with cardiac imaging procedures involving ionizing radiation have been published, and there is uncertainty and controversy with regard to the actual risk of low-dose radiation from cardiac testing. For context, estimates of typical effective dose for environmental and medical sources of radiation are outlined in Table 4. Some radiation exposure occurs naturally and during activities of daily living. As seen in Table 4, estimated radiation dose for various noninvasive tests for CAD vary by test. The effective doses for imaging techniques from studies included in this report range from <1 mSv to 16 mSv. The CT radiation dose is influenced by a number of factors including prospective versus retrospective gating, use of multidectors rows, type of processing, and patient body morphometrics. Use of prospective gating significantly reduces the effective dose while obtaining a higher quality of image compared with retrospective gating.[41] Further, using prospective gating with a tube potential of <100 kVp requires a lower effective dose than prospective gating used with a tube potential ≥100 kVp.[42] Other imaging parameters such as contrast media used and slice number affect the effective dose of CCTA, which is why effective dose ranges widely for this imaging technique. The values in the following table are based on literature estimates and are subject to change dependent on the imaging parameters utilized.

Table 4. Overview of radiation exposure ranges*

Radiation Exposure Type			Total Effective Dose (mSv)
Environmental Exposures	Round-trip flight, New York – Seattle		0.06
	Naturally occurring		3/year
	July 1971 lunar landing		5
	Nuclear worker		20
Diagnostic and Procedural Exposures	Echocardiography		0
	CMRI		0
	ECG		0
	Dental CT		0.2
	Mammogram		0.4
	CACS	Range found in studies in this report	0.69–0.8
		Range reported in Einstein 2014	1–5
	ICA	Range reported by Einstein 2014	2–20
		Range reported by ACR	1–10 (with or without ventriculography)
	CCTA	Range found in studies in this report	3.8–15.1
		Range reported in Einstein 2007 and 2014	<0.5–30
		Range reported by ACR	1–30 (using various contrast and dose techniques)
		Range reported by Cerqueira 2010	5–10
	Fluoroscopy for PCI	Range reported by Einstein 2014	5–57
	PET	Range found in studies in this report	6.0
		Range reported in Einstein 2014	2 (^{13}N ammonia); 4 (^{82}Rb); 7 (^{18}F FDG – not currently FDA approved)
	SPECT	Range found in studies in this report	10.5–14
		Ranges reported in Einstein 2014	2.3–14 (^{99m}Tc Tetrofosmin); 2.7–18 (^{99m}Tc Sestamibi); 15 (^{201}Tl); 22 (^{201}Tl/^{99m}Tc Tetrofosmin dual-isotope); 23 (^{201}Tl/^{99m}Tc Sestamibi dual-isotope)
		Range reported by ACR	10–30
		Reported by Halliburton 2011	11 (^{99m}Tc)
	Coronary radiofrequency ablation		15
	Pelvic vein embolization		60

CACS = coronary artery calcium scoring; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; ECG = electrocardiogram; ECHO = echocardiography; ICA = invasive coronary angiography; mSv = milliSeiverts; PCI = percutaneous coronary intervention; PET = positron emission tomography; SPECT = single-photon emission tomography

*The overview was compiled using data from several publications.[38-40,43-46]

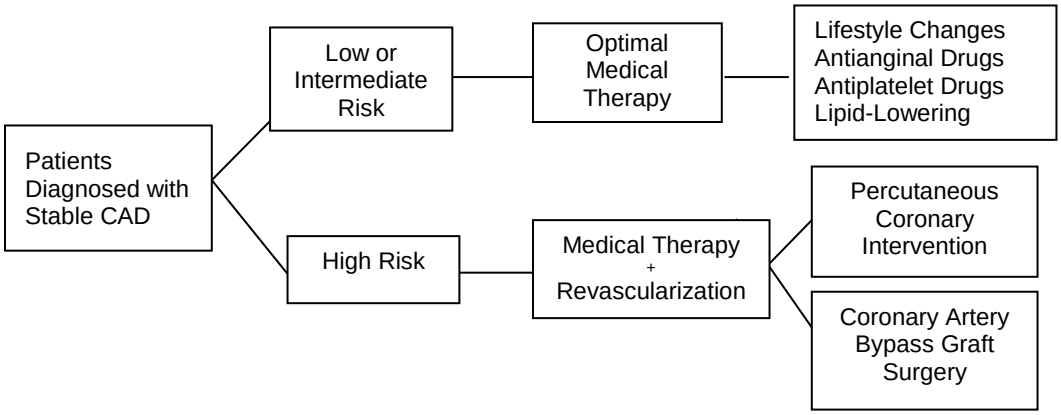
Treatment of Stable Coronary Artery Disease

The goal of testing is to identify people who would benefit from treatment. Where efficacious treatment is available and test costs and adverse events are comparable, test

sensitivity may be most important to consider. In situations in which there is little difference in treatment outcomes, avoiding false positives is important and thus specificity may be more important. The focus of this report is on stable, symptomatic patients without prior CAD presenting for an initial test to determine the presence of CAD. There are a number of treatment options for this population. The extent to which a test leads to the appropriate treatment is reflected in the impact on clinical outcomes. Because one of the outcomes of interest for this report is whether noninvasive tests differ in terms of referral for treatment (e.g., revascularization), a brief background on treatment options is provided here.

Treatment of stable CAD is initially guided by the patient's post-test risk stratification, symptoms, and non-CAD comorbidities.[8,47,48] Based on the predicted annual cardiac mortality rate, recent clinical guidelines provide thresholds of low risk (≤1% per year), intermediate risk (1%–3% per year), and high risk (≥3% per year).[8] As shown in Figure 2, patients considered to be at low or intermediate risk of cardiac mortality should generally be treated with medical therapy alone, while those found to be at high risk should receive both medical therapy and revascularization.

Figure 2. Initial treatment pathways for patients diagnosed with CAD



CAD = coronary artery disease

Medical Therapy

Optimal (or guideline-directed) medical therapy is optimized on a per-patient basis depending on patient characteristics and guideline recommendations. Medical therapy includes lifestyle modifications (physical activity, smoking cessations, weight management, and dietary changes), treatment of secondary conditions such as diabetes and hypertension, risk modification with antiplatelet drugs, management of lipid levels, and treatment of angina symptoms if present.

Lifestyle interventions including primary risk reduction strategies such as exercise and increased physical activity, smoking cessation, and weight management are associated with lower rates of cardiovascular outcomes and can improve outcome following a nonfatal event. Both antiplatelet drugs (primarily aspirin) and lipid-lowering drugs (e.g., statins) are used to reduce the risk of thrombotic coronary events through stabilization of the coronary plaque to prevent rupture and thrombosis. Angina is treated with a variety of drugs that reduce myocardial oxygen demand and therefore reduce anginal events including beta-blockers, calcium channel blockers, nitrates, and ranolazine. Beta-blockers are typically recommended as first-line treatment because of evidence that they reduce the risk of mortality post-MI and in those with

hypertension. In low- to intermediate-risk patients treated only with medical therapy, the benefits of initial treatments identified in Figure 2 are outlined in Table 5.

Table 5. Effects of medical therapy for stable coronary artery disease

Intervention	Purpose of Treatment	Coronary Event Benefits	Potential Harms
Antiplatelet; Aspirin	Reduce risk of clot development	33% reduction in serious vascular event such as nonfatal MI, nonfatal stroke, or vascular death.[49]	Risk of a major extracranial bleed with aspirin (<75 to 325 mg): odds ratios 1.4 to 1.7; absolute event rates 1.8 to 2.5%.[49]
Lipid-lowering; Statins	Reduce risk of cholesterol-related effects	18% reduction in coronary death rate, 24% reduction in the composite of nonfatal MI or coronary death, nonfatal or fatal stroke and coronary or noncoronary revascularization.[50] 22% reduction in risk of CAD death, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke with high dose vs. standard dose statin (i.e. atorvastatin 10 mg vs. 80 mg).[51]	Potential myalgias, rhabdomyolysis, elevated liver enzymes.
Beta-blockers	Reduce angina symptoms	At least 50% reduction in the frequency of angina attacks.[52] No impact on cardiovascular outcomes except when used post-MI.	Potential reduced heart rate with exercise, low blood pressure, lethargy.
Calcium Channel Blockers	Reduce angina symptoms	Both dihydropyridines and nondihydropyridine calcium channel blockers reduce the frequency of angina attacks by at least 50%.[53] Benefit on cardiovascular outcomes has not been shown.	Peripheral edema, flushing, headaches Verapamil: constipation short-acting nifedipine: reflex tachycardia. Verapamil and diltiazem: reduce cardiac contractility and slow cardiac conduction.
Nitrates	Reduce angina symptoms	Immediate release preparations used for treatment of acute angina. Longer-acting forms improve exercise tolerance and reduce degree of ST segment depression during exercise, but tolerance develops quickly. Intermittent dosing may help. No benefit in the frequency of angina attacks has been found.[54]	Flushing, headache hypotension. Development of tolerance. Multiple contraindications exist.
Ranolazine	Reduce angina symptoms	22% reduction in recurrent ischemia, 33% reduction in worsening angina, results in greater exercise duration (514 vs. 482 seconds).[55]	Dose-dependent increase in the QT interval; multiple contraindications and drug interactions exist.

CAD = coronary artery disease; MI = myocardial infarction

Revascularization

Revascularization methods include coronary artery bypass graft (CABG) surgery and percutaneous coronary interventions (PCI). The determination of which revascularization

approach is used depends in part on patient presentation and characteristics, primarily severity of CAD (e.g., number of vessels involved, degree of stenosis, and SYNTAX [Synergy Between PCI With Taxus and Cardiac Surgery] score), but other factors such as age, diagnosis of diabetes, peripheral vascular disease or heart failure, and smoking status also play a role. The SYNTAX score is an assessment of overall coronary lesion complexity, with higher scores representing more complex coronary disease (low scores is defined as ≤22, an intermediate score as 23–32, and a high score ≤33).

PCI is an X-ray guided procedure that involves threading a catheter through a major artery to the site of the damaged vessel and inflating an attached balloon (or other device) to open the affected vessel. A stent may be placed at the damaged site to keep the vessel open. PCI methods have progressed with time, beginning with balloon angioplasty, then bare metal stent placement, and more recently drug eluting stent placement. The drugs in the drug eluting stents (e.g., sirolimus, paclitaxel, zotaralimus, everolimus, and biolimus) inhibit vascular smooth muscle cell proliferation and reduce stent thrombosis and restenosis. To date, relative to medical therapy alone, PCI has not been shown to significantly improve all-cause death, cardiac death or MI, or nonfatal MI in any individual trial, or in meta-analyses of trials when limited to those that exclude patients with recent ACS,[56-58] and may increase the risk of MI in the short term.[59-62] In a recent meta-analysis of eight trials (7229 patients) comparing medical therapy alone with coronary stent placement plus medical therapy in patients with stable CAD (including post-MI), rates of death, nonfatal MI, unplanned revascularization and persistent angina were not found statistically different through a mean of 4.3 years followup.[63] However, PCI has been shown to reduce symptoms and incidence of angina. In a study with 10-year followup, 59 percent of patients who underwent PCI were free of angina compared with 43 percent of those treated with medical therapy.[64]

CABG, or heart bypass surgery, involves grafting of arteries (internal mammary) and/or veins (e.g., saphenous vein) in order to allow blood flow to bypass the damaged vessel(s). This procedure has been shown to improve outcomes in patients with left main coronary artery disease when compared with medical therapy alone. In the most recent trial, 10-year survival rates were similar for CABG versus medical therapy, but rates of MI, repeat revascularization, and a composite endpoint (overall mortality, Q-wave MI, or refractory angina that required revascularization) were significantly worse with medical therapy.[64]

CABG versus PCI. A recent systematic review that included results from 13 RCTs and 5 meta-analyses evaluated the relative effects of the revascularization options in patients with unprotected left main disease (ULMD), multivessel CAD, diabetes mellitus, and left ventricular dysfunction (LVD).[65] The review concluded that in patients with more complex CAD, CABG results in a lower risk of mortality and a composite outcome (all-cause mortality, MI, stroke, or repeat revascularization) versus PCI with drug eluting stents. Further, PCI resulted in higher rates of revascularization. However, the risk of stroke is higher after CABG than after PCI. Consistent with other reports, patients with diabetes have a lower risk of the composite endpoint following CABG versus PCI. Another meta-analysis of individual patient-level data from 10 CAD trials compared CAGB PCI (with balloon angioplasty or bare-metal stents) or CABG and found that the 5-year mortality rate was slightly lower in patients with stable symptoms as well as in those with no history of MI.[66]

Scope and Key Questions

The objective of this review is to assess the effectiveness of noninvasive technologies for the diagnosis of CAD or dysfunction that results in symptoms attributable to myocardial ischemia in patients who present with signs or symptoms suggestive of CAD, whose condition is considered to be stable, and who have no known history of CAD. The intended focus is on clinical outcomes and clinical pathways following the first diagnostic test performed as result of initial risk assessment, which includes clinical presentation and physical exam, family history of CAD, and findings on resting ECG. Further, this report focuses on established tests for diagnosing CAD. Harms related to both the initial test and subsequent testing are evaluated. Information on traditional measures of accuracy (e.g., sensitivity and specificity) of noninvasive tests versus the historically accepted gold standard of ICA is presented for context. The report focuses on patients with stable symptoms of suspected CAD; patients with definite ACS were excluded or did not comprise greater than 20 percent of study populations.

Key Questions

In stable, symptomatic patients with suspected CAD who do not have previously diagnosed CAD and who have had a resting ECG:

1. For patients considered to be at ***very low or low risk*** for CAD, what is the comparative effectiveness of **anatomic tests (compared with each other, usual care, or no testing):**
    a. For improving primary clinical health outcomes (e.g., quality of life, avoidingMI)? In the absence of comparative studies linking testing with outcomes, do the tests predict future clinical events (predictive accuracy)?
    b. What are the adverse effects, consequences, or harms of testing?
    c. How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
    d. What harms are associated with additional testing following anatomic tests?
    e. Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities) or the patient's ability to exercise?

2. For patients considered to be at ***very low or low risk*** for CAD, what is the comparative effectiveness of **functional tests (compared with each other, usual care, or no testing):**
    a. For improving primary clinical health outcomes (e.g., quality of life, avoidingMI)? In the absence of comparative studies linking testing with outcomes, do the tests predict future clinical events (predictive accuracy)?
    b. What are the adverse effects, consequences, or harms of testing?
    c. How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
    d. What harms are associated with additional testing following anatomic tests?
    e. Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities) or the patient's ability to exercise?

3. For patients considered to be at ***intermediate to high risk*** for CAD, what is the comparative effectiveness of **anatomic tests (compared with each other usual care, or no testing):**
    a. For improving primary clinical health outcomes (e.g., quality of life, avoidingMI)? In the absence of comparative studies linking testing with outcomes, do the tests predict future clinical events (predictive accuracy)?
    b. What are the adverse effects, consequences, or harms of testing?
    c. How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
    d. What harms are associated with additional testing following anatomic tests?
    e. Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities) or the patient's ability to exercise?

4. For patients considered to be at ***intermediate to high risk*** for CAD, what is the comparative effectiveness of **functional tests (compared with each other, usual care, or no testing):**
    a. For improving primary clinical health outcomes (e.g., quality of life, avoiding MI)? In the absence of comparative studies linking testing with outcomes, do the tests predict future clinical events (predictive accuracy)?
    b. What are the adverse effects, consequences, or harms of testing?
    c. How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
    d. What harms are associated with additional testing following anatomic tests?
    e. Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities) or the patient's ability to exercise?

5. What is the comparative effectiveness of **anatomic tests versus functional tests** in those who are at ***very low or low risk*** for CAD?
    a. For improving primary clinical health outcomes (e.g., quality of life, avoiding MI)?
    b. What are the adverse effects, consequences, or harms of testing?
    c. How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
    d. What harms are associated with additional testing following anatomic tests?
    e. Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities) or the patient's ability to exercise?

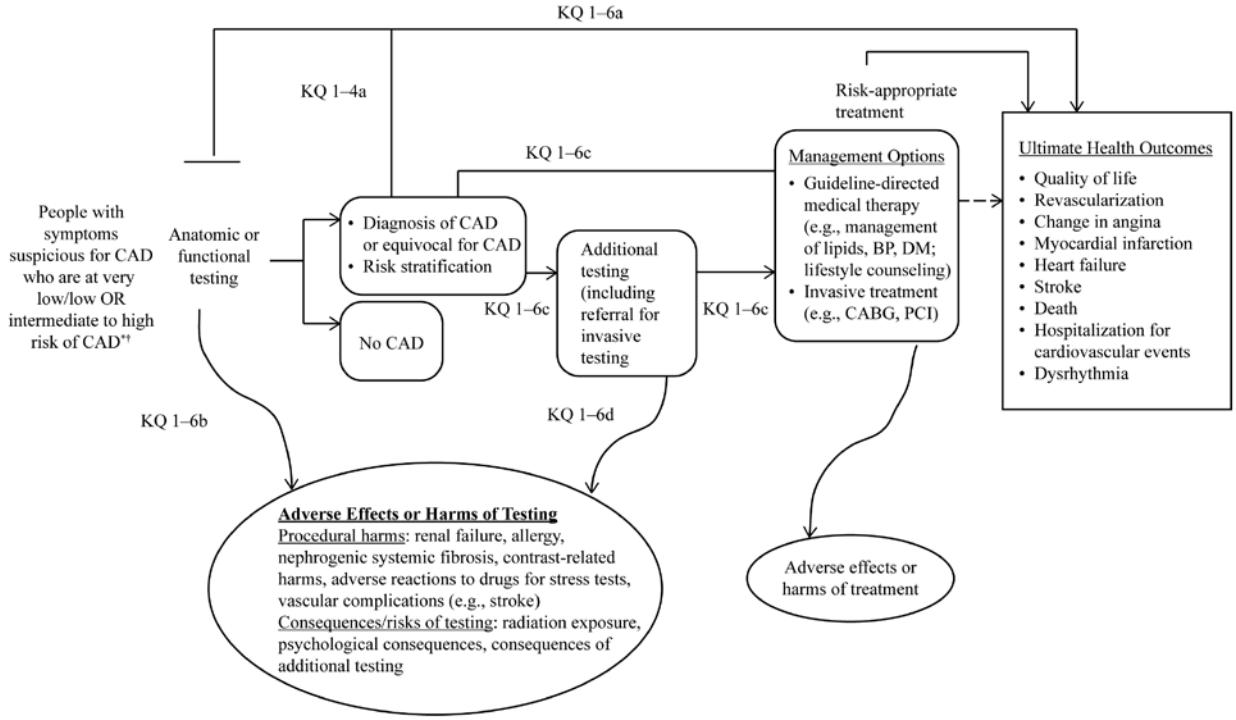
6. What is the comparative effectiveness of **anatomic tests versus functional tests** in those who are at ***intermediate to high risk*** for CAD?
    a. For improving primary clinical health outcomes (e.g., quality of life, avoiding MI)?
    b. What are the adverse effects, consequences, or harms of testing?
    c. How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
    d. What harms are associated with additional testing following anatomic tests?

e. Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities) or the patient's ability to exercise?

Analytic Framework

The analytical framework for the systematic review is presented in Figure 3.

Figure 3. Analytic framework for noninvasive testing for coronary artery disease



BP = blood pressure; CABG = coronary artery bypass graft; CAD = coronary artery disease; DM = diabetes mellitus; KQ = Key Question; PCI = percutaneous coronary intervention

*People at very low or low risk are evaluated separately from those at intermediate to high risk when possible.

†KQ 1–6e: Potential modifiers related to differential efficacy and/or safety include patient factors (e.g., age, sex), comorbidities, and ability to exercise.

Methods

The methods for this Comparative Effectiveness Review follow the guidance in the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (Methods Guide).[67]

Topic Refinement and Review Protocol

The topic for this Comparative Effectiveness Review was ranked as a priority topic by a panel of stakeholders convened through the Duke Evidence-based Practice Center's Cardiovascular Topic Identification project. The preliminary Key Questions and scope were developed with input from Key Informants, representing practicing clinicians, patients, payers, and others with experience in making health care decisions. The Key Questions were posted on AHRQ's Web site for public comment for 4 weeks. Public comments and input from the Technical Expert Panel (TEP) were used to develop the final Key Questions and protocol. The TEP, convened to provide high-level content and methodological guidance to the review process, consisted of experts in cardiology and cardiac diagnostic testing, radiology, internal medicine, and health services research, as well as professional organizations and policymakers. TEP members disclosed all financial or other conflicts of interest prior to participation. The AHRQ Task Order Officer and the investigators reviewed the disclosures and determined that the TEP members had no conflicts of interest that precluded participation.

Both the final topic refinement document and the systematic review protocol, developed prior to initiation of the review, can be found on the AHRQ Web site at www://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/. The protocol is also registered with the PROSPERO international database of prospectively registered systematic reviews (CRD42015022081).

Literature Search Strategy

Search Strategy

A research librarian conducted searches for primary studies in the following databases through July 2015: Ovid MEDLINE®, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Evidence-Based Medicine Reviews–Health Technology Assessment. A search strategy was developed based on an analysis of the medical subject heading (MeSH) terms and text words of key articles identified a priori. The full search strategy is available in Appendix A. Search start dates were not restricted. The reference lists of included articles and relevant review articles were also reviewed. All citations were downloaded and imported into an electronic database (EndNote® X7 Thomson Reuters, Philadelphia, PA). A list of relevant drugs and manufacturers was provided to the Scientific Resource Center, which requested Scientific Information Packets, and relevant published and unpublished studies were assessed for inclusion in the final report.

Because of the large number of citations retrieved by our database searches, two experienced team members created a list of search terms using the exclusion criteria in the PICOTS (populations, interventions, comparators, outcomes, timing, and setting) table and applied a systematic search in EndNote in order to further exclude studies with a high likelihood of not being relevant. The full list of terms and methods used is available in Appendix A. Citations without abstracts, those not available in English, and certain publication types (case report,

narrative review) were excluded. For the remaining citations, titles were searched for terms related to unequivocally excluded populations (e.g., stent, cardiomyopathy), interventions (e.g., ultrasound, Doppler, screening), and outcomes. The title was chosen as the search field because it should contain only terms most relevant to the purpose of the study. Out of a total of 17,146 citations, 8,186 were excluded using this method.

Literature searches were updated during the public comment and peer review period in order to ensure that any new publications that meet our inclusion criteria were incorporated into the final report.

Inclusion and Exclusion Criteria

Criteria for inclusion and exclusion of studies were based on the Key Questions and the PICOTS (populations, interventions, comparators, outcomes, timing, and setting) approach, as described in Table 6. Studies of stable symptomatic adult patients undergoing their first noninvasive diagnostic test for suspected coronary artery disease (CAD) were sought. Studies of patients with known CAD, prior myocardial infarction (MI), or prior revascularization were excluded. In keeping with the review protocol, studies of patients with definite acute coronary syndrome (ACS), non-ST-elevation acute coronary syndromes (NSTE-ACS), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) were excluded (or were included only if these patients did not comprise >20% of the study population), as were studies of patients with unstable angina and elevated serum cardiac biomarkers or electrocardiogram (ECG) changes. For all Key Questions, the focus was on evidence from comparative studies with the least potential for bias. Noncomparative studies of predictive accuracy were considered if there was a lack of comparative data for a specific diagnostic modality. Interventions of interest included functional tests (i.e., stress ECG, stress echocardiography, stress nuclear imaging [single photon emission computed tomography (SPECT) and positron emission tomography (PET)], and stress magnetic resonance imaging [MRI]) and anatomic imaging (i.e., coronary computed tomography angiography [CCTA], coronary calcium scoring via electron beam, or multidetector computed tomography [CT]). Comparators included other noninvasive tests included in the interventions, usual care (as defined by the authors), or no testing. Studies that included technologies that are not widely available, are no longer used, or have not been established for the diagnosis of CAD were excluded.

The primary outcomes listed in the PICOTS table (Table 6) were considered to be the most clinically important and were the focus of reporting, decisions for data pooling, and determination of overall strength of evidence. Additional outcomes are reported in the detailed evidence synthesis sections of Results, organized by the Key Questions with a focus on outcomes common across studies. Where applicable and where data were available, results from the index emergency department (ED) visit and the followup period were reported separately. For studies of predictive accuracy, only hard clinical outcomes (i.e., MI, death, composite cardiac outcome, or heart failure) were evaluated. For both the initial test and any subsequent downstream testing, the primary safety outcomes were related to harms of testing (e.g., adverse reaction or allergy to contrast or stress agents) and risks and consequences of testing (e.g., radiation exposure). Studies focused on “per-vessel” or “per-segment” analysis without per-patient findings were excluded, and treatments and outcomes of treatments were beyond the scope of this report.

Studies published only as conference abstracts, non-English-language articles, and studies of nonhuman subjects were excluded. Studies had to report original data to be included.

Table 6. Summary of inclusion and exclusion criteria

PICOTS	Inclusion Criteria	Exclusion Criteria
Patients	Adult patients (≥18 years of age) with suspected CAD who present with stable (nonemergent) typical or atypical symptoms suspicious for CAD (e.g., chest pain, chest tightness, chest burning, shoulder pain, palpitations, jaw pain, or nonchest pain symptoms, such as dyspnea or worsening effort tolerance) and who are considered to be at very low, low, or intermediate to high risk of CAD based on initial clinical assessment (including resting ECG) prior to first noninvasive test. Special populations and circumstances of interest include: • Patients with renal insufficiency, diabetes, LBBB, HIV, or other comorbidities • Women • Those who are/are not able to exercise • Those with atypical symptoms/atypical presentation • Socioeconomic factors • Clinical setting (e.g., emergency department, outpatient clinic)	• Asymptomatic patients • Patients with known CAD • Patients who have had previous revascularization (CABG, PTCA, stenting) • Studies in populations with >20% asymptomatic or with known CAD unless data are stratified by symptom status/CAD status • Patients being evaluated for other cardiac diseases (e.g., valvular disease, etiology of cardiomyopathy) • Patients with unstable angina who have elevated serum cardiac biomarkers, ECG changes, etc.; those with NSTE-ACS, NSTEMI, STEMI, or definite acute coronary syndrome
Interventions	**Functional tests** (including use of exercise, vasodilator and/or dobutamine as stressor when appropriate) • Exercise electrocardiogram without imaging • Exercise/pharmacologic echocardiography (with or without myocardial contrast) • Exercise/pharmacologic radionuclide imaging with SPECT or PET • Pharmacologic stress magnetic resonance imaging **Anatomic imaging** • Coronary calcium scoring via EBCT or MDCT • CCTA	• Invasive coronary angiography • Screening applications of tests (application of tests to asymptomatic people, those who are being evaluated for noncardiac surgery) • CT (other than CT for calcium scoring): studies not using 64–slice or higher resolution • Testing for conditions other than evaluation of CAD (e.g., arrhythmia, valvular disease) • Technologies that are not widely available or have not been established for the diagnosis of CAD or those being assessed for feasibility (e.g., gene expression testing, Corus CAD by CardioDx, myocardial contrast echocardiography, myocardial strain imaging (post-ischemic shortening as a marker for ischemic memory), coronary FDG PET, BMIPP ischemic memory imaging, transthoracic Doppler FFR, CT-based FFR, MRA, TEE, CT perfusion) • Technologies that are no longer available or no longer widely used (e.g., MUGA, planar nuclear imaging) • Drugs or devices used in testing that are not available in the United States

PICOTS	Inclusion Criteria	Exclusion Criteria
Comparators	Other noninvasive tests included in the interventions, usual care, or no testing	• Invasive coronary angiography • Studies which do not specify components of "usual care" if that is the comparator
Outcomes	**Clinical outcomes (primary focus)** • Quality of life • Change in angina (e.g., worsening) • MI • Heart failure • Stroke • Death • Cardiovascular hospitalization for acute coronary syndrome, heart failure, arrhythmias • Dysrhythmia (For studies of predictive accuracy that do not compare tests, only hard clinical outcomes will be evaluated: These are MI, death, heart failure) **Intermediate outcomes** (to be evaluated based on comparative studies only) • Need for additional testing (including referral for invasive testing) • Clinical decisionmaking and management based on revised risk stratification such as use of guideline-directed medical therapy, including management of lipids, blood pressure and diabetes; counseling related to diet, physical activity, smoking cessation, alcohol use, and management of psychological factors; use of additional therapies to reduce risk of MI and death (e.g., antiplatelet therapy) • Any need for subsequent revascularization (PCI or CABG) **Harms, risks and consequences of testing (both initial and subsequent testing)** • Harms of testing (renal failure, allergy, nephrogenic systemic fibrosis, contrast-related harms, adverse reaction to medications used for stress testing), vascular complications • Risks and consequences (radiation exposure, psychological consequences of diagnosis, need for additional testing)	• Studies focused on "per-vessel" or "per-segment" analysis without per patient findings • Treatments and outcomes of treatments will not be evaluated

PICOTS	Inclusion Criteria	Exclusion Criteria
Timing	At time of first noninvasive test for evaluation (other than initial resting ECG)	
Settings	Non-emergent inpatient settings, or ambulatory/ outpatient settings, including emergency department	
Study Design	• High-quality systematic reviews with or without meta-analysis • Prospective studies (RCT or observational) directly comparing interventions with comparators based on established diagnostic criteria will be sought. Retrospective studies will be considered if there are insufficient prospective studies and they are at low risk of bias. • Studies of prognosis and decisionmaking will be included if testing results are reported in relation to clinical outcomes and if there is control for confounding as appropriate; studies of predictive accuracy will be considered if they provide clinical outcomes in untreated people.	• Studies of technique or feasibility or reporting only on the technical aspects of testing • Studies exploring prediction models for diagnostic criteria or prognosis • Studies comparing pharmacological agents for stress testing with each other • Studies of serial assessment of one test • Studies with ≤20 patients • Non-systematic reviews • Narrative reviews • Abstracts, editorials, letters, conference proceedings • White papers • Articles identified as preliminary reports when results are published in later versions • Case series, case reports
Publication Type	• Studies published in English in scholarly journals, published health technology assessments, or publicly available FDA reports • Gray literature (e.g., ongoing or unpublished clinical trial data)	• Single site reports from multicenter trials • Duplicate publications of the same study that do not report on unique outcomes or time points

BMIPP = beta-methyl iodophenyl pentadecanoic acid; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CT = computed tomography; EBCT = electron beam computed tomography; ECG = electrocardiography; FDA = U.S. Food and Drug Administration; FDG-PET = Fludeoxyglucose (18F) positron emission tomography; FFR = fractional flow reserve; HIV = human immunodeficiency virus; LBBB = left bundle branch block; MDCT = multidetector computed tomography; MI = myocardial infarction; MRA = magnetic resonance angiography; MUGA = multigated acquisition scan; NSTE-ACS = non-ST elevation acute coronary syndromes; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PET = positron emission tomography; PICOTS = patients, interventions, comparators, outcomes, timing, settings, study designs; PTCA = percutaneous transluminal coronary angioplasty; RCT = randomized controlled trial; SPECT = single photon emission computed tomography; STEMI = ST-segment elevation myocardial infarction; TEE = transesophageal echocardiography

Study Selection

Abstracts for all citations from the literature searches were independently reviewed by two team members and results were recorded in EndNote. All citations that either reviewer found to be potentially appropriate for inclusion underwent full-text review. Two investigators independently evaluated each full-text article for final inclusion. For inclusion, both reviewers had to agree that inclusion criteria were met. Differences between reviewers were resolved through consensus and discussion. A record of studies excluded at the full-text level with reasons for exclusion is included in Appendix C.

Data Extraction

The investigative team created a form in Microsoft® Excel for abstracting the data elements for the Key Questions. The data abstraction forms were piloted by two members of the team and

refinements made as needed. Two staff members were responsible for abstracting demographic information for each study and five experienced team members entered data for the outcomes of interest. After data extraction, at least one other staff member and one investigator each verified the accuracy and completeness of abstraction for each study included. Discrepancies were resolved by discussion and consensus.

Reviewers extracted information on general study characteristics (e.g., study design, study period, followup, study setting, funding, and authors' conflicts of interest), study patients (patients approached/eligible/enrolled, age, sex, comorbidities, cardiac risk factors, pretest risk for CAD as defined by the authors), intervention arm details (tests evaluated, patients treated, patients with followup, type of stressor used, type of contrast used, definition of a positive test), test results, clinical health and management outcome measures, adverse events, and information related to study quality. Outcome measures and adverse events were prespecified during the creation of the extraction form to maintain consistency in data reporting. However, unique results were added during the abstraction process as needed. Outcomes that occurred during the index ED visit were reported separately from those that occurred during the followup period; however, for some studies it was unclear if the followup period included the index visit. Limited data were extracted from studies of predictive accuracy with a focus on hard clinical outcomes (i.e., MI, death, composite cardiac outcome, and heart failure). An outline of the specific information included in the data extraction forms is available in Appendix D.

Quality (Risk-of-Bias) Assessment of Individual Studies

Predefined criteria were used to assess the quality (risk of bias) of included randomized controlled trials (RCTs) and observational studies by using clearly defined templates and criteria as appropriate and following guidance from the AHRQ Methods Guide.[67] Assessment of RCTs followed appropriate criteria and methods established in *the Cochrane Handbook for Systematic Reviews of Interventions*.[68] Comparative observational studies were assessed for study design features and sources of potential bias. The quality of each comparative study was rated based on the following: methods used for randomization (RCTs only, requirement of computer-generated random numbers, random numbers tables, coin toss, or opaque sequentially numbered envelopes), allocation concealment (RCTs only, requirement of sealed opaque envelopes, centralized randomization, on-site computer based system with a randomization sequence that is not readable until allocation, or blocked randomization), intention to treat analysis (RCTs only), independent or blind outcome assessment, patients comparable at baseline on key CAD risk factors, prespecified threshold or definition for a positive test, acceptable attrition (≤20%), comparable attrition between treatment groups (≤10% difference between groups), controlling for possible confounding, and full reporting on prespecified outcomes. These criteria and methods were used in concordance with the AHRQ schema, wherein each study was rated as being "good," "fair," or "poor" quality.[69] Two investigators independently assessed the quality of each study and any discrepancies were resolved through discussion and consensus.

Studies rated "good" are considered to have the least risk of bias, and their results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated "fair" are susceptible to some bias, although not enough to invalidate the results. These studies may not meet all the criteria for a rating of good quality, but no flaw is

likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid.

Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies are least as likely to reflect flaws in the study design as the true difference between the compared interventions. Studies rated as being poor in quality a priori were not excluded, but considered to be less reliable than higher-quality studies when synthesizing the evidence, particularly if discrepancies between studies were present.

Each study evaluated was independently reviewed for quality by two team members. Any disagreements were resolved by consensus. The final quality assessments are described in detail in Appendix I.

Data Synthesis

When adequate data were reported in at least two studies, meta-analysis was conducted in order to provide more precise estimates for outcomes. To determine the appropriateness of conducting meta-analysis, clinical and methodological diversity and assessed statistical heterogeneity were considered. Given the multiple interventions included in this report, a network meta-analysis was planned to estimate the relative effects of interventions that were not directly compared, and to make full use of both direct and indirect evidence.[70] However, the number of included studies turned out to be very small (2 for each comparison) with a limited number of comparisons (only CCTA vs. SPECT and CCTA vs. usual care). Along with heterogeneity across studies, this made network meta-analysis impossible. Therefore, only standard meta-analysis was conducted and only binary outcomes were eligible. The profile-likelihood random-effects model[71] was used to combine risk differences while incorporating variation among studies. The presence of statistical heterogeneity among the studies was assessed by using the standard Cochran's chi-square test, and the magnitude of heterogeneity was assessed by using the I^2 statistic, which describes the percentage of variability in effect estimates because of heterogeneity versus chance (sampling error).[72] Risk differences were used to describe absolute effect sizes for RCT data. The absolute approach is helpful for decisionmaking from the perspective of knowing which test has more cases per 100 (or 1000) of a clinical outcome (e.g., MI) than the other (after patients have gone through the decision/treatment pathway). The risk difference helps provide information on the difference in the number of people with a given outcome identified with each test.

To account for clinical heterogeneity, we stratified analyses by pretest risk. Within each strata, the number of studies was too small for exploring heterogeneity based on any study level characteristics. Sensitivity analyses using risk ratios were conducted to check the robustness of results to the choice of effect measure. Conclusions were generally similar and not separately reported. All analyses were performed using Stata®/IC 12.1 (StataCorp, College Station, TX).

Strength of the Body of Evidence

The strength of evidence for each primary efficacy/effectiveness and safety outcome described previously was initially assessed by one researcher using the approach described in the AHRQ Methods Guide, also available from the AHRQ Web site.[67,69]

In determining the strength of a body of evidence regarding a given outcome, the following domains are considered:

- Study limitations: the extent to which studies reporting on a particular outcome are likely to be protected from bias; graded as low, medium, or high level of study limitations
- Consistency: the extent to which studies report the same direction of effect for a particular outcome; graded as consistent, inconsistent, or unknown (in the case of a single study)
- Directness: reflects whether the outcome is directly or indirectly related to health outcomes of interest
- Precision: describes the level of certainty of the estimate of effect for a particular outcome and includes consideration of the sample size and number of events; graded as precise or imprecise
- Reporting bias: suspected if there was evidence of selective reporting, otherwise considered to be undetected.

A final strength of evidence grade was assigned by evaluating and weighing the combined results of the previously-described domains; final grades are presented in the Discussion, and tables detailing how final grades were determined are available in Appendix J. To ensure consistency and validity of the evaluation, the strength of evidence ratings for all key outcomes were reviewed by the entire team of investigators, and discrepancies were resolved by consensus.

Bodies of evidence consisting of RCTs started as high-strength while bodies of comparative observational studies began as low-strength evidence. The strength of the evidence was then downgraded based on the limitations described previously. There are also situations in which the observational evidence may be upgraded (e.g. very large size of effect), but we found no instances in which these could be applied in this body of evidence. (See the AHRQ Methods Guide for details on upgrading; see also the AHRQ *Methods Guide for Medical Test Reviews*[73]). The overall grades and their definitions are as follows:

- High—We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate—We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low—We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient—We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Applicability

Applicability of the evidence was considered by examining the characteristics of the patient populations included in studies (e.g., demographic characteristics, presence of relevant cardiac risk factors, and pretest risk for CAD); the sample size of the studies; and clinical settings in which the studies are performed (e.g., outpatient clinic, ED) as outlined in the AHRQ Methods

Guide.[67,74] Variability in the studies may limit the ability to generalize the results to other populations and settings. For example, older studies of established tests may not be as applicable in light of advances in technology, and short-term outcomes based on immediate decisionmaking in the ED may not be generalizable to longer-term outcomes and decisionmaking in the outpatient setting.

Peer Review and Public Commentary

Experts in the diagnosis and treatment of CAD, as well as individuals representing other important stakeholder groups, were invited to provide external peer review of this Comparative Effectiveness Review. The AHRQ Task Order Officer and an Evidence-based Practice Center Program Associate Editor also provided comments and editorial review. The draft report was published on the AHRQ Web site for 4 weeks in order to solicit public comments. At the end of this period, the authors considered both the peer and public review comments and generated a final report. A disposition-of-comments report detailing the authors' responses to the peer and public review comments will be made available 3 months after AHRQ posts the final report on the public Web site.

Results

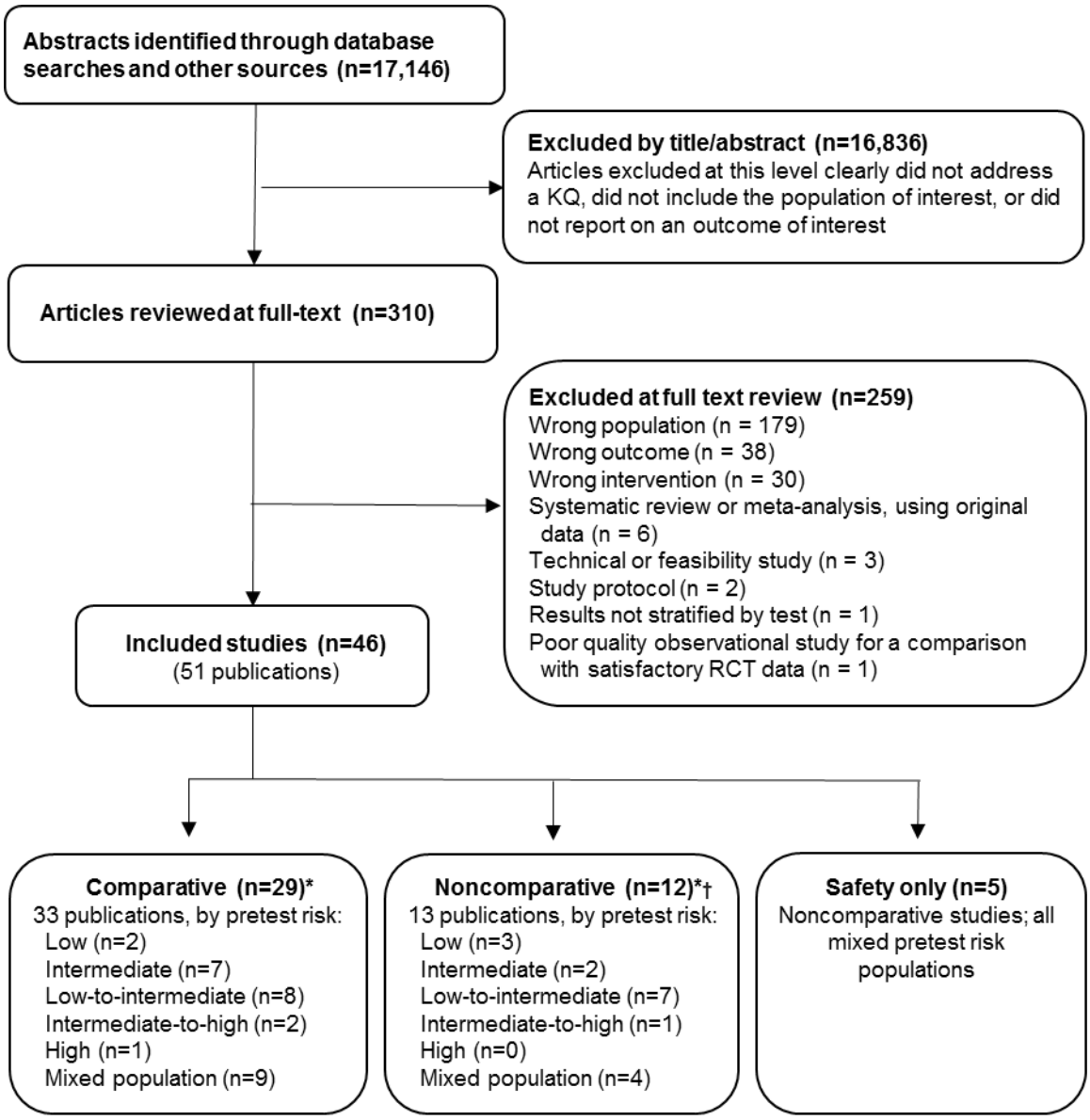
Results of Literature Searches

The results of the literature search and study selection are summarized in the flow chart (Figure 4). A total of 17,146 potentially relevant citations were identified. After dual review of abstracts and titles, 16,836 articles were excluded. The remaining 310 articles underwent dual review at the full-text level and 46 studies (in 51 publications) met the inclusion criteria and were included in this report: 14 randomized controlled trials (RCTs),[75-89] 15 comparative observational studies,[90-107] and 17 noncomparative studies.[108-125] Of those, 24 studies were designed to compare one noninvasive test to another in separate patient groups and reported our primary outcomes of interest; these studies form the primary basis for our report.

A total of 15 studies compared coronary computed tomography angiography (CCTA) with either usual care (4 RCTs,[75,80,81,83,89] 1 prospective observational,[92,94] 1 retrospective observational[107]); various functional testing (1 RCT);[76] single photon emission computed tomography (SPECT) (3 RCTs,[77,78,84] 1 retrospective observational[90]); or with exercise electrocardiography (ECG) (2 RCTs,[79,82] 1 retrospective observational,[100,106] 1 administrative database[102]). Three studies compared SPECT with exercise ECG (2 RCTs,[85,87] 1 administrative database[102]). A total of four studies compared stress echocardiography with either exercise ECG (1 RCT,[86] 1 prospective observational,[96] 1 administrative database[102]) or SPECT (1 administrative database).[102] Only one prospective registry was identified that investigated positron emission tomography (PET) scanning which was compared with SPECT.[93,95] No comparative studies of magnetic resonance imaging (MRI) or calcium scoring that met our inclusion criteria were found. CCTA was only anatomic test for which we found comparative data. No other relevant test comparisons were identified. A list of included studies can be found in Appendix B.

A total of 259 articles that did not meet one or more of the inclusion criteria were excluded after full-text review. Appendix C provides a list of these articles with reasons for exclusion (also see Figure 4. The primary reason for exclusion (70% of citations) was that studies did not include the population of interest (i.e., no known history of coronary artery disease [CAD]).

Figure 4. Flow chart showing results of literature search



KQ = Key Question; RCT = randomized controlled trial
*Some studies were included in more one than one risk strata or reported outcomes for more than one comparison or test of interest.
†Noncomparative studies reporting predictive accuracy.

Organization of Results

Given the heterogeneity in how pretest risk was measured and defined across the studies (see Appendix Tables E44-45 for details), results could not be reported as delineated by the Key Questions into distinct pretest risk groups (i.e., low-risk and intermediate-to-high risk). Therefore, the results were organized by pretest risk as defined by the study authors, which included populations with low risk, intermediate risk, low to intermediate risk, intermediate to high risk, high risk, and mixed risk (or pretest risk not reported). Studies describing high pretest risk excluded patients with acute coronary syndrome (ACS) and were interpreted as representing the higher risk end of the intermediate pretest risk range. Available data from studies conducted in emergency departments (EDs) were primarily for the index ED visit and are noted. Outcomes such as myocardial infarction (MI) at the time of the ED index visit were considered to reflect diagnosis of MI at that time. Where available, data on longer-term followup are presented. An overview of tests compared for the various pretest risk groups is found in Table 7.

For each section, within the specified pretest risk categories, key points were presented followed by detailed information from evidence synthesis for the following test comparisons, presented in this order: anatomic testing (CCTA or calcium scoring via CT) versus usual care; functional testing versus functional testing (any combination of the following: stress echocardiography, stress ECG, stress echocardiography, SPECT, PET, or MRI); and anatomic testing versus functional testing (any comparison of tests from the previously described categories). Following a brief description of the study populations, detailed results are reported in terms of clinical outcomes, clinical management outcomes, harms of index and additional testing, and differential effectiveness or safety in subgroups. Limited evidence from noncomparative studies reporting on predictive accuracy is included at the end of each risk category only for tests for which no or little comparative data were available.

Table 7. Overview of test comparisons and pretest risk groups for which the comparisons were made

Comparator	Pretest Risk Groups With *Usual Care* Comparisons	Pretest Risk Groups With *CCTA* Comparisons	Pretest Risk Groups With *SPECT* Comparisons	Pretest Risk Groups With *Stress ECG* Comparisons	Pretest Risk Groups With *Functional Testing* Comparisons	Pretest Risk Groups With *Stress Echo-cardiography* Comparisons	Pretest Risk Groups With *Nuclear MPI* Comparisons
Usual care	N/A	• Low • Intermediate • Low to intermediate • Intermediate to high • High (non-ACS) • Mixed population	No comparison	No comparison	No comparison	No comparison	No comparison
CCTA	• Low • Intermediate • Low to intermediate • Intermediate to high • High (non-ACS) • Mixed population	N/A	• Intermediate • Low to intermediate • Intermediate to high • Mixed population	• Low • Intermediate • Low to intermediate • Intermediate to high • Mixed population	• Intermediate	• Mixed population	• Mixed population
SPECT	No comparison	• Intermediate • Low to intermediate • Intermediate to high • Mixed population	N/A	Intermediate High (non-ACS) Mixed population	No comparison	No comparison	No comparison
Stress ECG	No comparison	• Low • Intermediate • Low to intermediate • Intermediate to high • Mixed population	• Intermediate • High (non-ACS) • Mixed population	N/A	No comparison	• Mixed population	• Mixed population
Functional Testing	No comparison	• Intermediate	No comparison	No comparison	N/A	No comparison	No comparison
Stress Echocardiography	No comparison	• Mixed population	No comparison	• Mixed population	No comparison	N/A	• Mixed population
Nuclear MPI	No comparison	• Mixed population	No comparison	• Mixed population	No comparison	• Mixed population	N/A

ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; ECG = electrocardiography; MPI = myocardial perfusion imaging; N/A = not applicable; SPECT = single-photon emission computed tomography

Low Pretest Risk of Coronary Artery Disease

Key Points

Given the focus of the report on evaluation of testing based on pretest risk, results for the low pretest risk groups are presented here even though evidence from these groups was rated as insufficient.

CCTA Versus Usual Care

- In a small subgroup of low-risk patients presenting to the ED, there was insufficient evidence from one fair-quality trial to draw conclusions regarding differences between CCTA and usual care in all-cause mortality or hospitalization for acute coronary syndrome through 30 days. At the index ED visit, frequency of ICA referral and revascularization was similar (insufficient evidence).

SPECT Versus Exercise ECG

- In a small subgroup of low-risk outpatients, there was insufficient evidence from one fair-quality trial that SPECT patients had less additional noninvasive stress testing than exercise ECG patients through a mean of 22 months. SPECT patients were slightly more likely to have ICA referral through the same followup period (insufficient evidence), although the difference was not statistically significant.

Detailed Synthesis

A total of five studies were identified in populations with a low pretest risk of CAD and two included the following comparisons: CCTA versus usual care (1 RCT)[75] and SPECT versus exercise ECG (1 RCT)[85] (Table 8); three additional noncomparative studies (4 publications) reported on the predictive accuracy of stress echocardiography.[108,113,118,119]

Anatomic Tests Versus Usual Care

CCTA Versus Usual Care

One fair-quality trial compared CCTA with usual care in low-risk patients (see Appendix E and G for details); no other studies compared anatomical testing with usual care in this population. The trial enrolled 266 patients presenting with chest pain to a single ED in South Korea.[75] Study funding was not reported. Results were stratified based on pretest risk, with 99 of the 266 patients at low pretest risk. CCTA was performed with 64-slice scanning in 50 low-risk patients; usual care consisted of a conventional diagnostic strategy (e.g., serial ECGs, and cardiac biomarkers) and was used in 49 low-risk patients. Subsequent diagnostic tests were done at the discretion of the treating physician. Overall, groups were similar in age (mean 57.5 years), sex (38.7% female), and cardiac risk factors, however these characteristics were not compared for low-risk patients only. Methodological shortcomings included unclear randomization method, allocation concealment, and blinding of outcomes assessment.

Clinical Outcomes

No deaths occurred in either group through 1 month of followup; MI occurred at a similar rate between groups at the index visit (4% in both groups).[75] The frequency of hospital

admissions at the index visit was similar between groups in terms of those for acute coronary syndrome (6% in both groups) and total admissions (14% for CCTA vs. 16% for usual care). Patients in the CCTA group were less likely to have an unnecessary hospital admission at the time of the index visit (0% vs. 6%), though this result did not achieve statistical significance (risk difference [RD] -6, 95% confidence interval [CI] -13 to 0.6 per 100 people). Clinical outcomes based on test results were not reported.

Clinical Management

ICA referral at the index visit was similar following CCTA versus usual care (6% vs. 10%, RD -4, 95% CI -15 to 7 per 100 people), as was revascularization (6% vs. 2%, RD 4, 95% CI -4 to 12 per 100 people).[75] Noninvasive stress testing was done in 80 percent of usual care patients but data on noninvasive stress testing were not reported for the CCTA group. Revascularization at the index visit was similar between CCTA and usual care groups (6% vs. 2%, RD 4, 95% CI -4 to 12 per 100 people).

Harms of Index Test and Consequences of Index and Additional Testing; Differential Effectiveness or Safety in Subgroups

Not reported for low-risk patients.

Functional Tests Versus Functional Tests

SPECT Versus Exercise ECG

One fair-quality trial compared SPECT with exercise ECG in low-risk patients (see Appendix E and G for details); no other studies compared different types of functional testing in this population.[85] The trial included 457 patients referred for stable chest pain to a single outpatient center in the United Kingdom; funding grants were received from Bristol-Myers Squibb and Northwick Park Cardiac Research, as well as from an individual. Results were stratified based on pretest risk; 71 patients had low pretest likelihood of CAD. Patients underwent either SPECT (n=27) or exercise ECG (n=44). Treadmill exercise was employed in both groups; pharmacological stress was employed in some patients receiving SPECT. Groups were similar overall in age (mean age 59 years), sex (43.5% female), and cardiac risk factors, but these characteristics were not compared within the low-risk group. Patients were followed for a mean of 22 months; loss-to-followup was not reported. Methodological shortcomings included unclear randomization method, allocation concealment, and blinding of outcomes assessment.

Clinical Outcomes

Not reported for low-risk patients.

Clinical Management

SPECT recipients had a slightly higher frequency of ICA referral compared with exercise ECG over a mean of 22 months followup in low-risk patients (7% vs. 0%), although the difference did not achieve statistical significance (RD 7 per 100 people, p=0.07). This trial used Bayesian methods to model post-test risk and reported that 86 percent of those with low pretest risk finished with low post-test risk (SPECT 78% vs. ECG 91%) and that those with a normal or low-risk test in either arm did not receive ICA. SPECT was associated with less additional imaging than was exercise ECG (0 vs. 13.6%, RD -14 per 100 people, 95% CI -24 to -4).

Medication therapy based on the initial test was statistically similar between SPECT and exercise ECG patients (92.6% vs. 86.3%, RD 6, 95% CI -8 to 20 per 100 people).

Harms of Index Test and Consequences of Index and Additional Testing; Differential Effectiveness or Safety in Subgroups

Not reported for low-risk patients.

Noncomparative Studies: Functional

No noncomparative studies of anatomical testing in patients at low risk met the inclusion criteria that reported outcomes of interest. For functional testing in this population, only studies of stress echocardiography were identified.

Stress Echocardiography

Three noncomparative studies of stress echocardiography in low pretest risk patients reported on predictive accuracy, two of which were conducted in an ED setting. Stressors included exercise or dobutamine in one trial[118,119] and two used exercise only.[108,113] Study sizes ranged from 149 to 1618 patients. In terms of test-positive patients, cardiac events occurred in no patients through 6 months in one ED study, and in 3 to 5 percent of patients through a median of 36 months (outpatient setting) or a mean of 54 months (ED setting) followup, respectively. The frequency of any cardiac event in those who tested negative was 1 per 100 people in all studies (see Appendix F for details).

Table 8. Summary of findings and strength of evidence: Low pretest risk

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	CCTA vs. usual care†	1 RCT (n=99 in low-risk subgroup)	ED	No deaths through 1 month in either group. Definitive conclusions are not possible.‡	Insufficient
Invasive Coronary Angiography Referral	CCTA vs. usual care†	1 RCT (n=99 in low-risk subgroup)	ED	Similar frequency of referral (CCTA 6% vs. usual care 10%) at index visit (RD -4, 95% CI -15 to 7 per 100 people, p=NS). Definitive conclusions are not possible.‡	Insufficient
	SPECT vs. exercise ECG	1 RCT (n=68 in low-risk subgroup)	Outpatient	Somewhat more common following SPECT (7%) vs. exercise ECG (0%) through a mean of 22 months (RD 7 per 100 people, p=0.0690). Definitive conclusions are not possible.‡	Insufficient
Revascularization	CCTA vs. usual care†	1 RCT (n=99 in low-risk subgroup)	ED	Revascularization at the index visit was similar between CCTA (6%) and usual care (2%) (RD 4, 95% CI -4 to 12 per 100 people, p=NS). Definitive conclusions are not possible.‡	Insufficient
Additional Testing	SPECT vs. exercise ECG	1 RCT (n=68 in low-risk subgroup)	Outpatient	SPECT was associated with less subsequent stress testing with imaging than exercise ECG through a mean of 22 months (0% vs. 14%, respectively) (RD -14, 95% CI -24 to -4 per 100 people). Definitive conclusions are not possible.‡	Insufficient
Hospitalization (Cardiac related)	CCTA vs. usual care†	1 RCT (n=99 in low-risk subgroup)	ED	Hospitalization for ACS was similar for CCTA and usual care groups (4% vs. 2%). Definitive conclusions are not possible.‡	Insufficient

ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ED = emergency department; NS = not statistically significant; RCT = randomized controlled trial; RD = risk difference; SPECT = single-photon emission computed tomography

*Primary outcomes not listed in this table had no evidence, and thus insufficient strength of evidence.

†Usual care consisted of a conventional diagnostic strategy using serial ECGs and cardiac biomarkers.

‡Definitive conclusions are not possible because of lack of data from subgroup analyses in RCTs.

Intermediate Pretest Risk of Coronary Artery Disease

Key Points

Evidence for all primary outcomes and comparators not listed was insufficient to draw conclusions because of study limitations and/or imprecision in the observational study or because of lack of evidence.

CCTA Versus Usual Care

- In intermediate-risk patients presenting to the ED, there was low-strength evidence from two fair-quality trials that patients in the CCTA and usual care groups had similar mortality, MI, any revascularization, PCI, CABG, or additional testing at the index ED visit and through 28 to 30 days. ICA referral was also similar at the index visit and after the index visit through 28 days (low strength of evidence).

SPECT Versus Exercise ECG

- In intermediate-risk women (setting not reported) groups were similar with respect to mortality, ICA referral, revascularization, and hospitalization through 24 months based on one fair-quality trial (low strength of evidence). However, moderate-strength evidence from this trial suggested that SPECT is associated with less additional noninvasive testing than exercise ECG.
- A second fair-quality trial on the general population reported that in a subgroup of intermediate-risk outpatients, SPECT was associated with fewer referrals to ICA (low strength of evidence) and additional stress testing (low strength of evidence) through a mean of 22 months of followup.
- Differences in patient characteristics between the two trials may partially explain differences in findings; one trial was comprised of women with a mean age of 63 years who were able to perform ≥5 METS on the Duke Activity Status Index. Findings from the other trial were based on subanalysis of intermediate-risk patients from a general population of >50 percent men with mean age of 59 years old with any activity ability.

CCTA Versus Functional Testing

- In intermediate-risk outpatients, moderate-strength evidence suggested that all-cause mortality, nonfatal MI, and cardiac hospitalizations were similar between groups through 12 months and a median of 25 months based on one good-quality trial. There was high-strength evidence that CCTA was associated with more ICA referrals and revascularizations (including CABG and PCI evaluated separately) through 90 days. Major procedural complications were similar between groups (moderate strength of evidence).

CCTA Versus SPECT

- In a fair-quality trial of 400 intermediate-risk patients admitted to a telemetry ward, low strength evidence suggested that there is no difference between CCTA and SPECT groups in all-cause mortality through a median of 24.5 months or in 12-month ICA referral, additional testing, revascularization, or PCI. However, CABG was more

common following CCTA versus SPECT through 12 months and cardiac rehospitalization occurred in fewer CCTA versus SPECT patients through a median of 40.4 months, although the difference did not achieve statistical significance (low strength of evidence). No major complications were attributed to the imaging procedure; 30-day death, MI, and stroke were not reported. The composite of periprocedural chest pain, shortness of breath, or palpitations occurred in significantly fewer CCTA versus SPECT patients, while there were no differences between groups in minor adverse reactions (including headache, nausea, dizziness, or feeling of warmth) or in rash or pruritus. There were no cases of post-test renal dysfunction (low strength of evidence).

Detailed Synthesis

A total of nine studies were identified in populations with an intermediate pretest risk of CAD and seven (9 publications) included the following comparisons: CCTA versus usual care (2 RCTs,[75,80,89] 1 prospective observational study[92,94]), CCTA versus various functional testing (1 RCT),[76] CCTA versus SPECT (1 RCT),[88] and SPECT versus exercise ECG (2 RCTs)[85,87] (Table 9); two additional noncomparative studies reported on the predictive accuracy of coronary artery calcium scoring (CACS).[123,125]

Anatomic Tests Versus Usual Care

CCTA Versus Usual Care

Two fair-quality trials compared CCTA with usual care in patients with intermediate pretest risk (see Appendix E and G for details);[75,80] an additional publication from one of these trials evaluated possible modification by sex.[89] One large trial (ROMICAT-II) enrolled 1,000 intermediate-risk patients with chest pain across nine EDs in the United States.[80] The trial was funded by grants from the National Institutes of Health and from the National Heart, Lung, and Blood Institute. Patients underwent testing with 64-slice (or higher) CCTA (n=501) or usual care (n=499) which employed the standard evaluation strategy used at each ED. One trial of chest pain patients presenting to a single ED in South Korea stratified results according to pretest risk; 111 (of 266 total) patients were categorized as having intermediate pretest probability of ACS.[75] Study funding was not reported. Patients were tested with 64-slice CCTA (n=55) or usual care (n=56) which consisted of a conventional diagnostic strategy using serial ECGs and cardiac biomarkers. Subsequent diagnostic tests were done at the discretion of the treating physician. Within each trial, the CCTA and usual care groups were similar in age, sex, and cardiac risk factors. However, the two trials differed somewhat in overall patient characteristics. The study by Chang et al. 2008 included slightly older patients (mean age 58 vs. 54 years), more males (61% vs. 53%), and fewer people with hypertension (44% vs. 54%) or dyslipidemia (27% vs. 45%) compared with the Hoffman et al. 2012 study. Neither study provided a baseline risk score for their population. Methodological shortcomings included unclear randomization method and allocation concealment (Chang et al. 2008), lack of a prespecified definition of a positive test (Hoffmann 2012, et al.), and unclear blinding of outcomes assessment (both trials).

One poor-quality prospective observational study compared CCTA with usual care in 200 patients at intermediate pretest risk (according to the Thrombolysis in Myocardial Infarction [TIMI] risk score; scores/mean not reported), with relevant results published in two separate papers.[92,94] The study was conducted in a single ED in Germany; funding was not reported. Patients received CCTA testing (n=100) or usual care (n=100) to include repeated biomarker

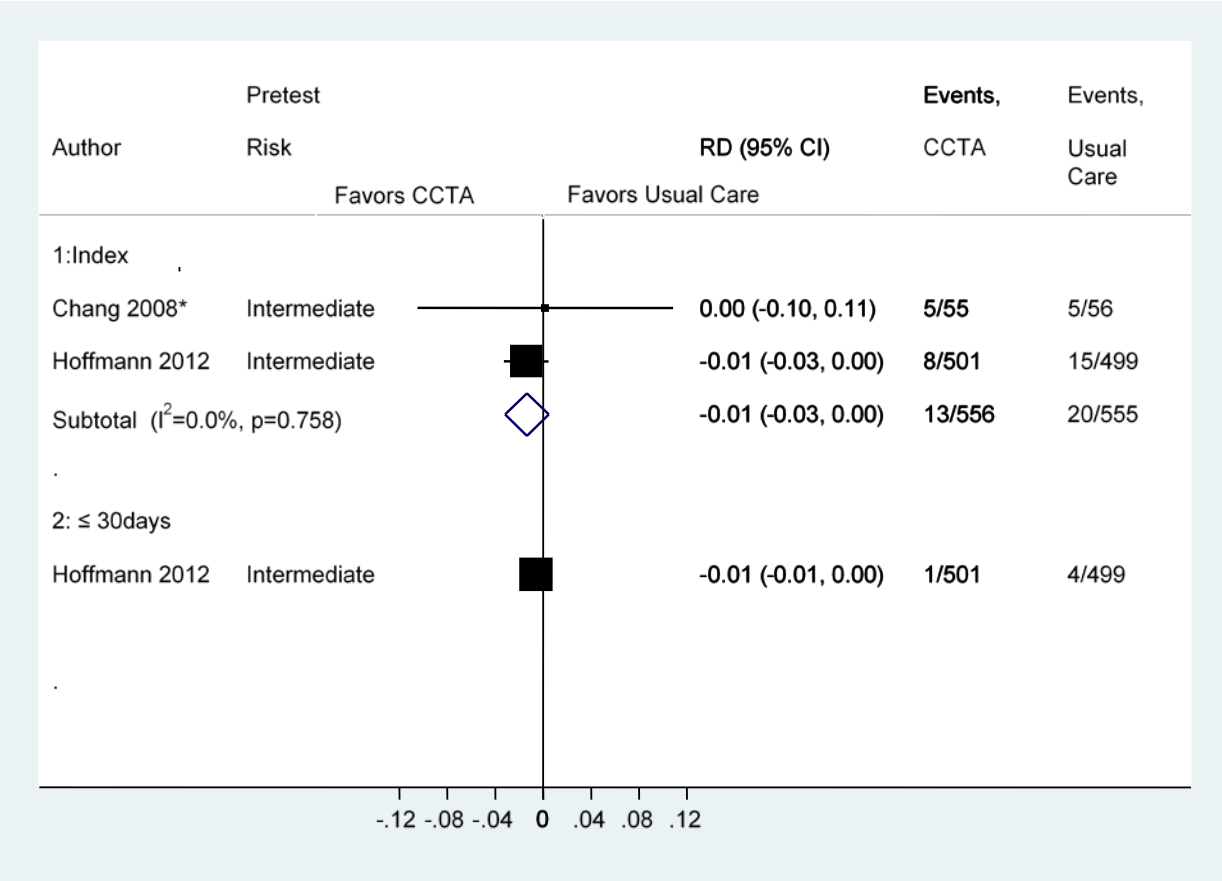
measurements, stress testing (e.g., exercise ECG, stress echocardiography, SPECT), and clinical observation. Patients in the CCTA group were younger (mean age 58 vs. 66 years) and more likely to be female (48% vs. 39%) than those in the usual care group; cardiac risk factors were similar between groups. Methodological shortcomings included unclear blinding of outcomes assessment and lack of controlling for baseline differences between groups.

Clinical Outcomes

No deaths were reported in either of the two trials during the 1-month followup periods. MI diagnosis at the index visit occurred with similar frequency in CCTA and usual care patients across both trials (2.3% vs. 3.6%, pooled RD -1, 95% CI -3 to 0 events per 100 patients, I^2=0%) (Figure 5).[75,80] After the index visit and through 28 days of followup, one trial also found that MI was similar in both CCTA (0.2%) and usual care groups (0.8%) (RD -0.6, 95% CI -1.5 to 0.3 events per 100 people).[80] Across both trials, diagnosis with unstable angina at the index visit was more common in the CCTA group (9.0%) compared with the usual care group (5.4%) (pooled RD 4, 95% CI 1 to 6 per 100 people, I^2=0%) (Figure 6).[75,80] Through 28 days followup (and after the index visit), one trial reported similar incidences of unstable angina requiring PCI (0.2% vs. 0.4%; RD -0.2, 95% CI -0.9 to 0.5 per 100 people).[80] In the smaller trial, hospital admission for acute coronary syndrome at the time of the index ED visit was similar between the CCTA and usual care groups (36% vs. 32%, RD 4, 95% CI -13 to 22 per 100 patients).[75] The larger trial found that CCTA was associated with significantly fewer hospitalizations at the index visit compared with usual care (51.9% vs. 82.3%, RD -33, 95% CI -39 to -28 per 100 patients),[80] but the smaller trial found no difference between groups (RD -8, 95% CI -27 to 10 per 100 patients).[75] Considerable statistical heterogeneity across the studies for the pooled estimate (RD -22, 95% CI -47 to 2 per 100 patients, I^2=85.1%) was noted and may in part result from differences in patient characteristics between the two studies as well as available sample size in one trial (Figure 7).[75,80] The smaller trial found that CCTA was associated with fewer unnecessary hospital admissions (defined as an admission for a medical condition that should not have led hospitalization) compared with usual care (4% vs. 20%, RD -16, 95% CI -28 to -4 per 100 patients).[75] Admittance to the observation unit at the index visit was significantly less common in the CCTA group (31%) versus the usual care group (60%), with 30 fewer patients per 100 being admitted (95% CI -36 to -24 per 100).[80]

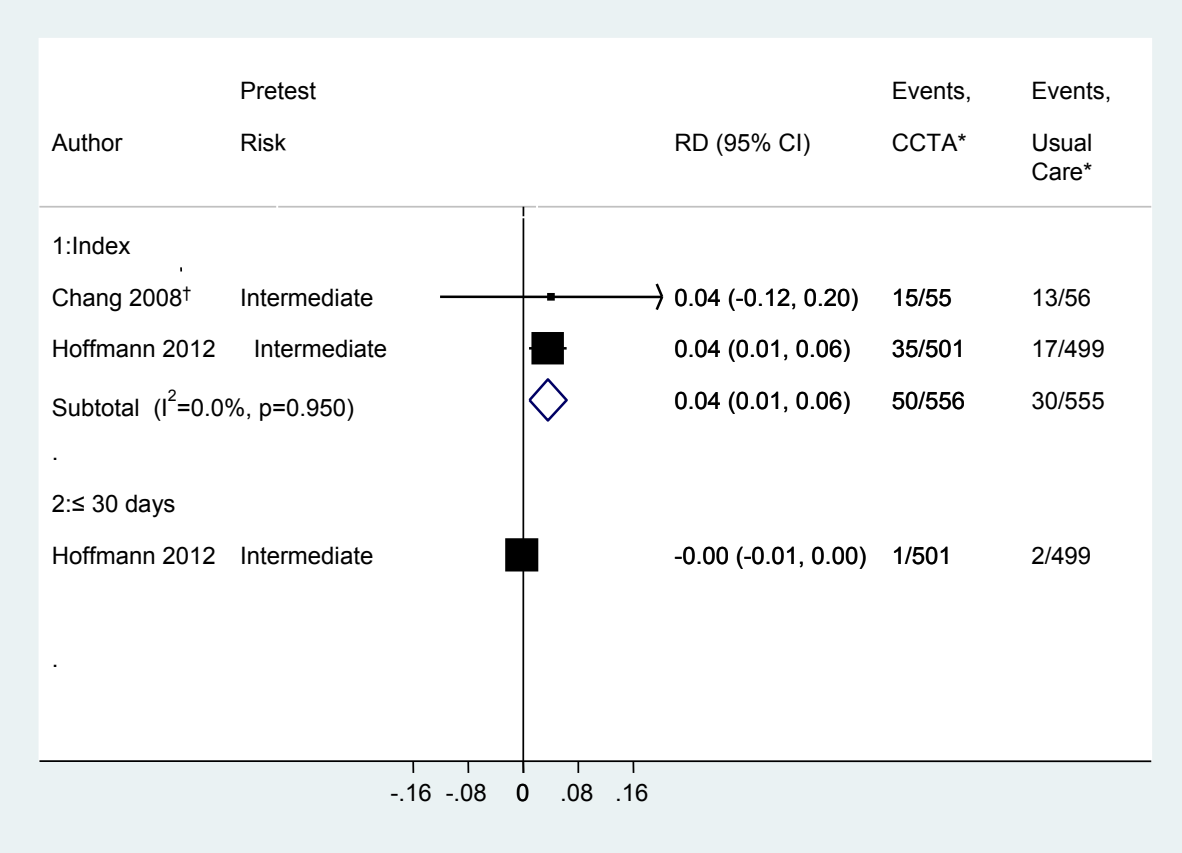
The single observational study reported no major adverse cardiovascular events in either group through 3 months followup, including death, MI, unstable angina requiring hospitalization, or development or progression of heart failure requiring hospitalization.[92,94] The study reported that hospitalization for recurrent chest pain was slightly less frequent in CCTA versus usual care patients (0% vs. 3%, RD -3, 95% CI -6 to 0.3 per 100 patients) through the 3-month followup period.

Figure 5. Meta-analysis results for risk of myocardial infarction across studies comparing CCTA with usual care in patients with intermediate pretest risk



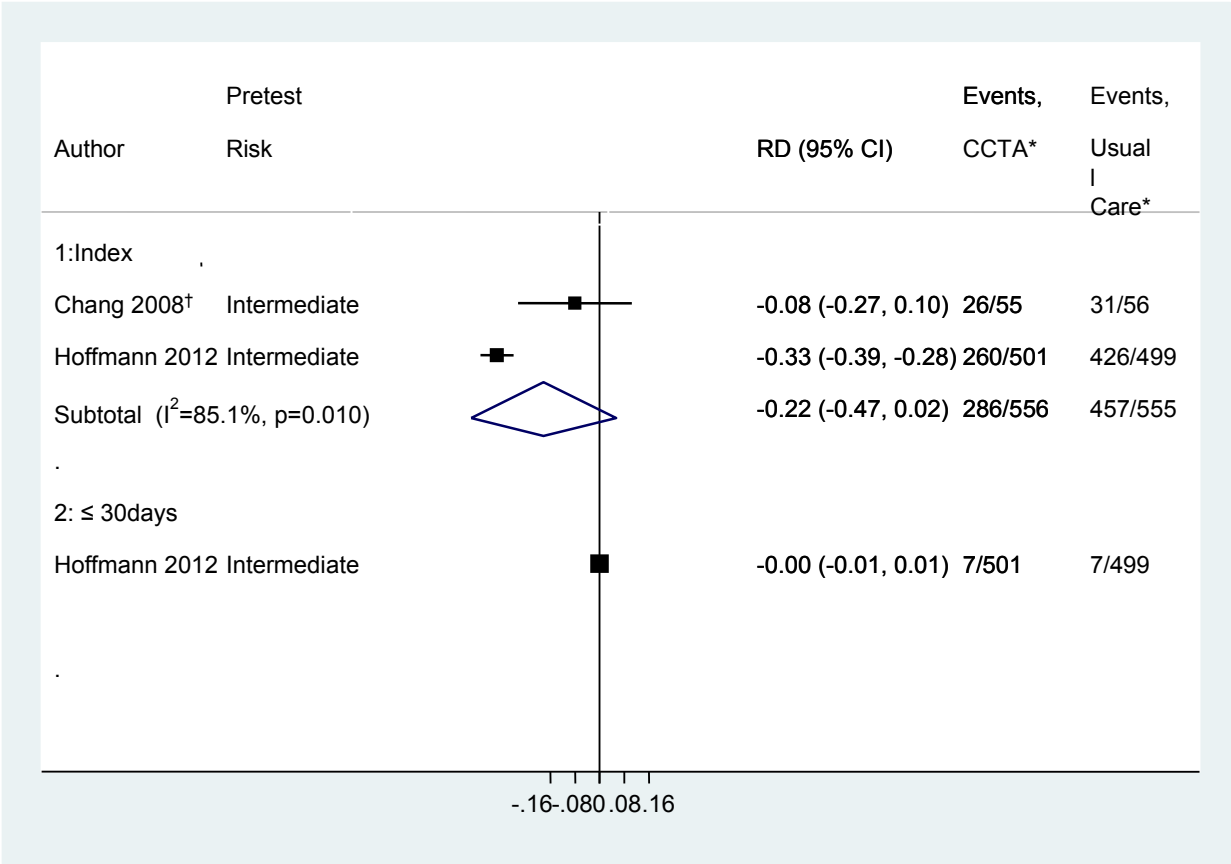
CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference
*Subgroup of intermediate-risk patients.

Figure 6. Meta-analysis results for risk of unstable angina across studies comparing CCTA with usual care in patients with intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference
*Diagnosis of unstable angina was more common following CCTA.
†Subgroup of intermediate-risk patients.

Figure 7. Meta-analysis results for risk of hospital admission across studies comparing CCTA with usual care in patients with intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference
*The large study (Hoffmann et al. 2012) showed significantly less hospitalization following CCTA testing.
†Subgroup of intermediate-risk patients.

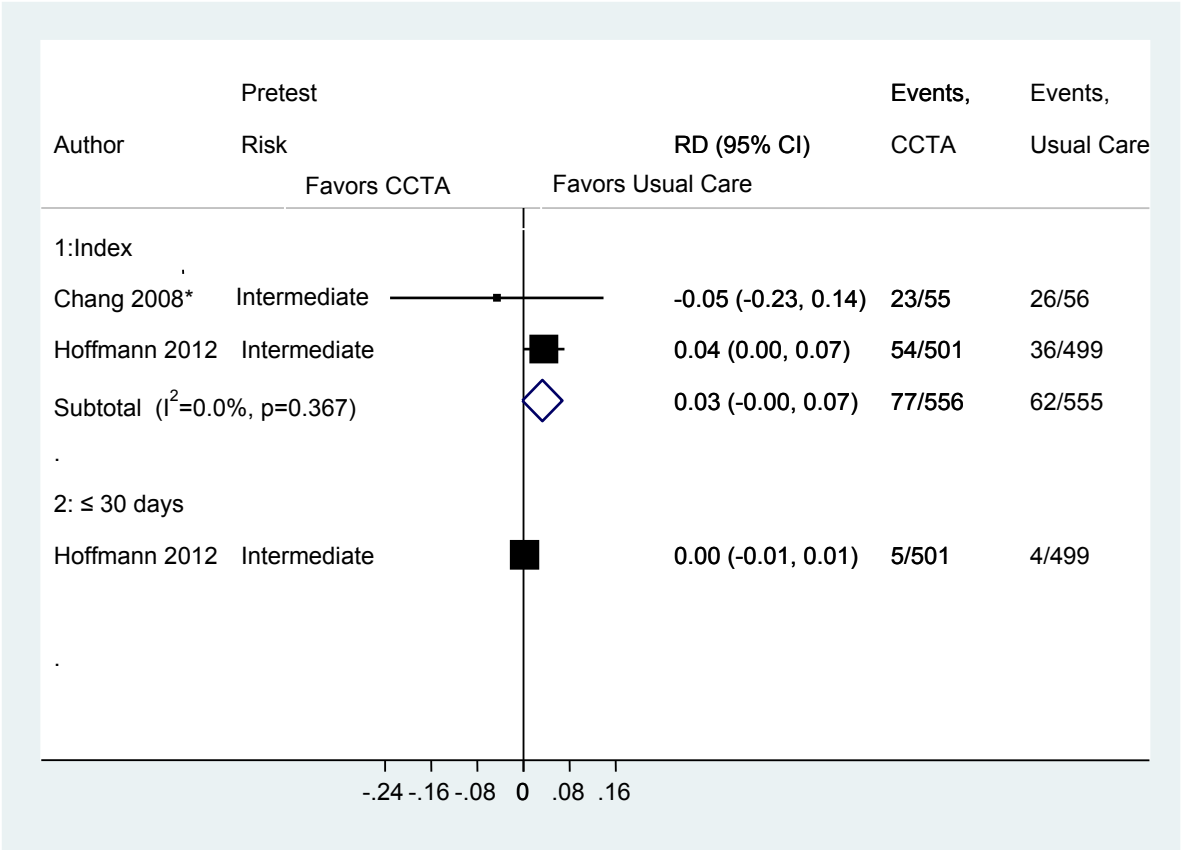
Clinical Management

Referral to ICA at the index visit occurred with similar frequency in the CCTA group compared with the usual care group based on data from both trials (13.8% vs. 11.2%, RD 3, 95% CI 0 to 7 per 100 patients, I^2=0%) (Figure 8),[75,80] as well as during the 28-day period following the index visit in the larger trial (1.0% for CCTA vs. 0.8% for usual care).[80] The latter trial reported that patients receiving CCTA testing were significantly less likely to receive any of three types of stress testing at the index ED visit compared with the usual care group: SPECT (10% vs. 25%, RD -15, 95% CI -19 to -10 per 100 patients); stress echocardiography (4% vs. 20%, RD -16, 95% CI -20 to -13 per 100 people); or exercise treadmill testing (2% vs. 29%, RD -27, 95% CI -31 to -23 per 100 patients). The protocol of that trial called for stress testing only as a second test in the CCTA group, but as the first test in the usual care group. In the 28 days after the index ED visit, percentages of patients in the CCTA and usual care groups who received these noninvasive stress tests were similar: SPECT (1.6% vs. 1.8%), stress echocardiography (0% in both groups), or exercise treadmill testing (2% vs. 3%). In the smaller trial, 50 percent of intermediate-risk usual care patients underwent additional stress testing at the time of the index ED visit, however this data was not reported for intermediate-risk CCTA patients.[75] Revascularization (PCI or CABG) at the index visit was similar between the CCTA (7.2%) and

usual care (5.6%) groups at the time of the index ED visit compared with the usual care group based on data from both trials (RD 2, 95% CI -1 to 5 per 100 patients, I^2=0%) (Figure 9).[75,80] One trial similarly reported comparable proportions of patients who had PCI at the index visit (5.0% vs. 2.8%, RD 2.0, 95% CI -0.3 to 4.3 per 100 patients) and through 28 days of followup after the index ED visit (0.6% in both groups); CABG was performed in 1.0 percent of patients in both groups at the index visit and no patients in either group received CABG during the followup period.[80]

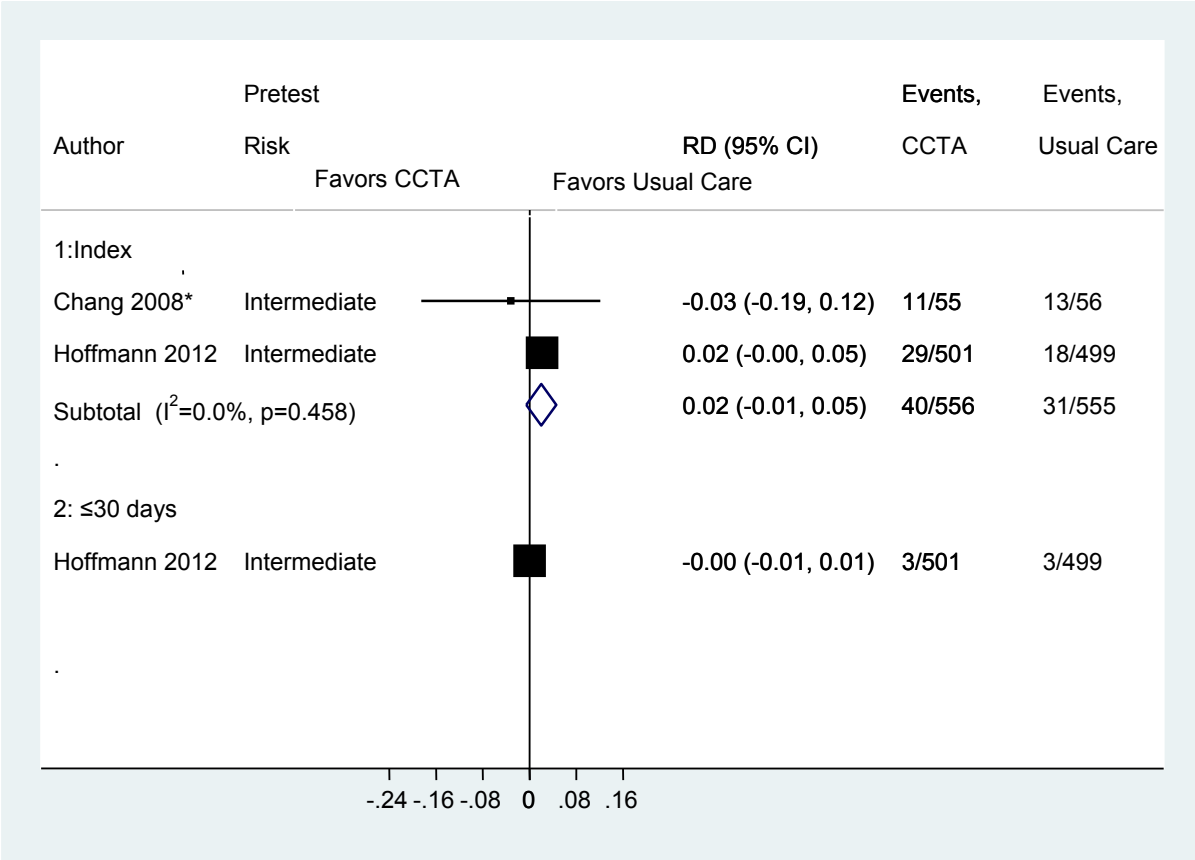
The observational study reported no statistical differences between CCTA and usual care patients in PCI (9% vs. 15%), CABG (1% vs. 2%), and intensified medical therapy (7% vs. 8%); however, the rate of referral for ICA was significantly lower following CCTA (19% vs. 87%; RR 0.22, 95% CI 0.14 to 0.33).[92,94] Of those referred, a smaller proportion of CCTA patients showed no obstructive CAD on ICA compared with patients tested via usual care (10.5% [2/19] vs. 71.3% [62/87], RR 0.15, 95% CI 0.04 to 0.55).

Figure 8. Meta-analysis results for risk of invasive coronary angiography across studies comparing CCTA with usual care in patients with intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference
*Subgroup of intermediate-risk patients.

Figure 9. Meta-analysis results for risk of any revascularization across studies comparing CCTA with usual care in patients with intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference
*Subgroup of intermediate-risk patients.

Harms of Index Test and Consequences of Testing

The larger RCT reported a similarly low incidence of periprocedural complications (not defined further) in the CCTA (0.4%) and the usual care (0%) groups.[80] In this same trial, CCTA was associated with significantly higher exposure to radiation at the index visit compared with usual care (mean 13.9 ± 10.4 vs. 4.7 ± 8.4 mSv, p<0.001). The observational study reported a mean radiation exposure of 8.7 mSv following CCTA but did not report exposure for the usual care group.[92,94]

Harms of Additional Testing

Cumulative radiation exposure (index visit plus additional testing during followup) was significantly greater following CCTA compared with usual care, as reported by one RCT (mean 14.3 ± 10.9 vs. 5.3 ± 9.6 mSv, p<0.001);[80] however, over the followup period, the effective radiation dose was similar between groups: 0.4 versus 0.6 mSv, respectively.

Differential Effectiveness or Safety in Subgroups

A prespecified analysis from a fair-quality trial (ROMICAT-II) evaluated potential differences between women and men on outcomes following CCTA versus usual care;[89] however, the primary clinical outcomes of interest for this review were not reported (e.g., death,

MI). Of the 1,000 patients included, 468 (47%) were women and 532 (53%) were men. There were multiple differences at baseline between the sexes. Compared with men, women were slightly older (56 vs. 53 years) and a greater proportion were African American (75% vs. 66%), had diabetes (48% vs. 39%), were taking beta-blocker medication (47% vs. 39%), and were diagnosed with noncardiac chest pain (93% vs. 82%) ($p<0.03$ for all); conversely, fewer women were smokers (43% vs. 55%, $p<0.01$).

Although ACS as a final diagnosis was less common in women than men (3% vs. 12%), no difference in ACS rate by randomization strategies of CCTA versus usual care were identified for women (3% vs. 3%) or men (14% vs. 10%) and no evidence of modification by sex was seen ($p=0.46$). Similarly, there was no evidence of modification by sex for any of the following outcomes: direct ED discharge, downstream testing, ICA referral, PCI use, PCI or CABG use, repeat ED visit or hospitalization for chest pain, or major adverse cardiac event at 28 days. Authors report, however, that women undergoing CCTA versus usual care had fewer hospital admissions and shorter length of hospital stays compared with men ($p=0.005$ and 0.006, respectively). Sex also modified cumulative radiation exposure: women had lower mean cumulative radiation following initial testing with CCTA compared with men at both the index visit and at 28 days followup ($p=0.003$ and 0.02, respectively). CAD prevalence and severity was lower in women compared with men, which may partially explain the results.

Functional Tests Versus Functional Tests

SPECT Versus ECG

Two fair-quality trials compared SPECT with exercise ECG in intermediate-risk patients (see Appendix E and G for details); no other studies compared different types of functional testing in this population. One large RCT (N=824) enrolled women only who were at intermediate pretest risk presenting with chest pain to various outpatient cardiology practices (43 sites) across the United States and Canada.[87] The trial was funded by a grant from GE Healthcare. The women received either SPECT (n=412) or exercise ECG (n=412); the Bruce exercise protocol was used in both test groups. Overall, groups were similar in age (median 62 years), presenting symptoms (60% typical angina), and cardiac risk factors. Outcomes were reported at 24 months for 93.7 percent of patients. Another RCT included 457 patients referred for stable chest pain to a single outpatient center in the United Kingdom; funding via grants was received from Bristol-Myers Squibb and Northwick Park Cardiac Research, as well as from an individual.[85] Results were stratified based on pretest risk; 280 patients had intermediate pretest likelihood of CAD. Patients underwent either SPECT (n=178) or exercise ECG (n=102). Treadmill exercise was employed in both groups; pharmacological stress was used in some patients receiving SPECT. Groups were similar overall in age (mean age 59 years), sex (43.5% female), and cardiac risk factors but were not compared within the intermediate-risk group. Neither study reported a baseline risk score for their population. Patients were followed for a mean of 22 months; loss to followup was not reported for this subgroup of patients but attrition was 3 percent in the overall population. Methodological shortcomings included lack of concealed allocation in both studies and lack of blinded assessment of outcomes in one.[85]

Clinical Outcomes

All clinical outcomes were reported through 24 months of followup in the trial of women. Overall mortality was similarly low in both SPECT and exercise ECG groups (1.0% vs. 0.5%),[87] as was the frequency of major adverse major adverse cardiac events (including cardiac death,

nonfatal MI, or hospitalization for acute coronary syndrome or heart failure) (2.3% SPECT vs. 1.7% exercise ECG, RD 0.54, 95% CI -1.5 to 2.6 per 100 people). Hospitalizations for chest pain (3.9% vs. 3.1%) and worsening angina frequency or stability (5% of patients in both groups) were also similar. By 12 months, 49 percent of patients in both groups were angina-free, and by 24 months a similar proportion of patients in both groups remained free from angina (64.9% SPECT vs. 60.4% ECG; RD 4.5, 95% CI -2.3 to 11.4 per 100 patients).

Clinical Management

While referral to ICA was similar between the SPECT and exercise ECG arms (5.7% vs. 6.4%, RD -0.7, 95% CI -4 to 3 per 100 people) through 24 months in the trial of women,[87] the other trial reported that a significantly smaller percentage of subjects undergoing SPECT had ICA when compared with ECG testing (10.7% vs. 43.1%, RD -32.5, 95% CI -43 to -22 per 100 people) through a mean of 22 months.[85] This latter trial used Bayesian methods to model post-test risk and reported that only 21 percent of those with intermediate pretest risk finished with intermediate post-test risk (2% SPECT vs. 53% ECG) and that those with a normal or low-risk test in either arm did not receive ICA. Based on results from the Shaw trial of women, additional testing with SPECT was done less frequently in the SPECT group than in the exercise ECG group (9.1% vs. 18.6%, RD -8.9, 95% CI -13.7 to -4.1 per 100 people); of those randomized to SPECT, this test was repeated in 9, 8, and 15 percent of women with normal, mildly abnormal, and moderately to severely abnormal results, while among those randomized to exercise ECG, the frequency of crossover to SPECT (counts as use of additional test) was 8, 25, and 43 percent respectively for women who had normal, indeterminate, and abnormal ECG results.[87] Additional testing with exercise ECG was performed in 0.3 percent of patients in both groups. In the other trial, SPECT patients had significantly less additional testing when compared with ECG testing through a mean of 22 months (0% vs. 38%, RD -38, 95% CI -48 to -29 per 100 people).[85] Revascularization was similar between SPECT and exercise ECG in the trial of women only (2.1% vs. 1.0%, RD 1.1, 95% CI -0.7 to 2.8 per 100 patients).[87] The trial of the general population reported that SPECT patients were considerably more likely to receive medical therapy than those who underwent stress ECG (89.3% vs. 18.6%, RD 70.7, 95% CI 61.9 to 79.5 per 100).[85]

Harms of Index Test and Consequences of Testing

The Shaw trial reported a mean radiation exposure of 14.0 mSv following SPECT but did not report radiation exposure for the exercise ECG group.[87]

Harms and Consequences of Additional Testing; Differential Effectiveness or Safety in Subgroups

Not reported for intermediate-risk patients.

Anatomic Tests Versus Functional Tests

CCTA Versus Functional Testing (Various)

One large, good-quality trial compared CCTA with functional testing in 10,003 outpatients at intermediate pretest risk (see Appendix E and G for details);[76] no other studies compared anatomical with functional testing in this population. Dubbed the PROMISE trial, this multicenter RCT was conducted in 193 outpatient clinics (cardiology, radiology, primary care, urgent care, and anesthesiology departments) across the United States and Canada. Outcomes

were reported at 12 months for 93.5 percent of patients; outcomes at the last followup were also reported (median of 25 [interquartile range (IQR) 18 to 34] months). CCTA scans were obtained with a 64-detector row scanner and contrast. Those randomized to functional testing could undergo one of a number of different testing modalities which were chosen prior to randomization. Functional testing modalities used included nuclear stress imaging (63.09%), stress echocardiography (21.09%), and exercise ECG (9.53%). A similar proportion of patients randomized to both CCTA and functional testing (6.25%) did not receive the assigned test (i.e., did not undergo any test or underwent a different test). The stressors used for nuclear imaging and echocardiography were not reported.

For inclusion, patients were required to have new or worsening symptoms consistent with suspected CAD, no history of MI, and no history revascularization or testing within the past 12 months. In general, males were required to be 55 years or older and females 65 years or older, although exceptions were made for slightly younger patients with specific risk factors. The two groups were well-balanced in terms of baseline characteristics and cardiac risk factors (mean of 2.4 ± 1.1 risk factors per patient). Mean age was 60.8 ± 8.3 years and 52.7 percent of patients were female. Racial or ethnic minorities comprised 22.6 percent of the population. Pretest risk for CAD was intermediate (10%–90%) in 92.6 percent of patients (and was low [<10%] in 2.5% and high [>90%] in 4.9%). Overall, the mean pretest risk of CAD was 53.3 percent ± 21.4 percent based on a combined Diamond and Forrester and Coronary Artery Surgery Study score. Presenting symptoms included chest pain (72.7%) and shortness of breath on exertion (14.9%). Angina was atypical in the majority of patients (77.7%), with fewer presenting with typical (11.7%) or nonanginal pain (10.6%). There were no apparent methodological shortcomings.

Clinical Outcomes

There was no difference in the risk of all-cause death between the CCTA and functional testing groups through 12 months (0.42% vs. 0.64%) and a median of 25 months (1.48% vs. 1.50%) followup.[76] Similarly, risk of nonfatal MI was similar between groups through 12 months (0.36% vs. 0.54%, RD -0.18, 95% -0.44 to 0.08 per 100 people) and a median of 25 months (0.60% vs. 0.80%, RD -0.20, 95% CI -0.53 to 0.13 per 100 people). However, the composite risk of death or nonfatal MI was significantly lower in the CCTA group through 12 months (0.78% vs. 1.14%, adjusted hazard ratio (HR) 0.66, 95% CI 0.44 to 1.00, p=0.049) although the difference was no longer significant by a median of 25 months (2.08% vs. 2.24%). The primary composite endpoint (defined as all-cause death, nonfatal MI, hospitalization for unstable angina, or a major procedural complication [e.g., stroke, major bleeding, anaphylaxis, or renal failure requiring dialysis]) and the secondary endpoint (defined as the primary endpoint or catheterization showing no obstructive CAD) occurred at a similar rate in both groups. While there was no difference in hospitalization for unstable angina between groups through 12 months (0.98% vs. 0.67%), it was more common in the CCTA group through a median of 25 months (1.22% vs. 0.82%, RD 0.40, 95% CI 0.01 to 0.80 per 100 patients). In contrast, hospitalization for any cardiovascular reason other than unstable angina was less common in the CCTA group through a median of 25 months (0% vs. 0.10%, p=0.0255). There was no difference between groups at either time point in composite outcome of death, nonfatal MI, or hospitalization for unstable angina. While the study reported that a similar percentage of patients in each test group tested positive (abnormal) (10.68% vs. 1.16%), clinical outcomes were not stratified according to test result.

Clinical Management

Although more patients in the CCTA group underwent ICA within 90 days compared with the functional testing group (12.19% vs. 8.11%, RD 4.08, 95% CI 2.90 to 5.26 per 100 people), the ICA results showed no obstructive CAD (i.e., false positives) in fewer CCTA patients (27.9% vs. 52.5% of patients who underwent ICA; p<0.0001). Moreover, more CCTA patients underwent revascularization within 90 days than functional testing patients (6.22% vs. 3.16%, RD 3.07, 95% CI 2.24 to 3.90 per 100 patients); similar results were found when considering the 90-day risk of CABG alone (1.44% vs. 0.76%, RD 0.68, 95% CI 0.27 to 1.09 per 100 people) and PCI alone (4.8% vs. 2.4%, RD 2.4, 95% CI 1.7 to 3.1 per 100 people).[76]

Harms of Index Test and Consequences of Testing

Douglas et al. reported no difference between CCTA and functional imaging groups in the risk of major procedural complications, which was a component of the primary outcome and included stroke, major bleeding, anaphylaxis, or renal failure requiring dialysis (0.1% in both groups) throughout the entire followup period.[76] There was similar risk of procedural stroke (0.02% vs. 0.04%) and major bleeding (0.1% in both groups) between groups, and no instances of anaphylaxis or renal failure requiring dialysis. Exercise-induced hypotension, stress-induced symptoms not resolved within 20 minutes, ventricular tachycardia, and hemodynamic instability were rare, occurring in no CCTA patients and less than 0.1 percent of functional testing patients; it was unclear whether these events occurred periprocedurally or at a later time point. There were no cases of rapid atrial fibrillation that did not slow or convert. Mild contrast reactions were significantly more common in the CCTA group than in the functional testing group (0.4% vs. 0%, RD 0.44 per 100 people, p<0.0001). The study reported a total of 37 mild safety events in the CCTA group and 21 in the functional testing group, making these events significantly more common for CCTA patients (0.74% vs. 0.42%, RD 0.32, 95% CI 0.02 to 0.62 per 100 people, p=0.0344).

Harms of Additional Testing

In the PROMISE trial (Douglas et al.), cumulative radiation exposure through 90 days was higher in the CCTA group compared with the functional testing group (mean 12.0 ± 8.5 vs. 10.1 ± 9.0 mSv [mean difference 3.0, 95% CI 2.7 to 3.3]).[76]

Differential Effectiveness or Safety in Subgroups

Douglas et al. reported that none of the prespecified subgroups modified the primary composite outcome (all-cause death, nonfatal MI, hospitalization for unstable angina, or a major procedural complication [e.g., stroke, major bleeding, anaphylaxis, renal failure requiring dialysis]), with results across subgroups consistent with those for the entire study population. Subgroups examined included age (<65 vs. ≥65 years), sex, race (white vs. nonwhite), pretest risk assessment (≤30% vs. 31-70% vs. >70%), CAD equivalence, and pretest probability of CAD (low [<10%] vs. intermediate [10-90%] vs. high [>90%]).[76]

CCTA Versus SPECT

One fair-quality trial (PROSPECT)[88] evaluated the impact of testing with CCTA versus SPECT in 400 intermediate-risk patients admitted to a telemetry-monitored ward (see Appendix E and G for details). No other studies compared CCTA with SPECT alone in this population. PROSPECT was a single-center trial conducted at an inner-city hospital in the United States. Twelve-month (or longer) outcomes were available for 95.3 percent of patients. Two-hundred

patients were randomized to each testing group. In the CCTA group, 93.5 percent underwent testing as randomized; 64-row scanning with contrast was used. In the SPECT group, 94.5 percent received testing as randomized. The preferred stressor was exercise, while those unable to exercise received pharmacological stress with or without low-level exercise. The percentage of patients who received each type of stress was not reported.

Inclusion criteria were admittance to a telemetry screening ward for chest pain, absence of known CAD or acute MI, one or more intermediate-risk criteria for short-term death, or MI and no cardiac testing or catheterization within the previous 6 months. The groups were well-balanced in terms of baseline characteristics. Mean age was 56.6 ± 11.2 years and 62.8 percent of patients were female. Racial or ethnic minorities comprised the majority of the population (94.8%). Pretest risk was intermediate (37%) based the Diamond and Forrester prediction rule; the mean TIMI score was 1.3 ± 1.0. Symptoms at presentation included retrosternal pain in 69.5 percent, exertional pain in 40.0 percent, pain for longer than 20 minutes in 62.0 percent, and new pain on exertion within the past 2 weeks in 37.8 percent. Methodological limitations were lack of blinding for all outcomes except revascularization and absence of a prespecified definition of a positive test. The authors recognized both limitations and noted that the trial was designed to mimic real-life practice wherein treatment decisions are made based on factors besides imaging results alone.

Clinical Outcomes

Through a median of 24.5 months, all-cause mortality occurred in slightly fewer CCTA than SPECT patients, though the difference did not reach statistical significance (0.5% vs. 3.0%, RD -2.5, 95% CI -5.1 to 0.06 per 100 people). The percentage of patients who had a nonfatal MI or stroke was not clearly reported for both treatment groups. One patient in the CCTA group had a nonfatal MI and died at a later time. Whether the death was MI- or cardiac-related was not reported. The composite risk of nonfatal MI, cardiac arrest, and stroke was the same in both groups (4.5% vs. 4.5%). No details were reported for events in the CCTA group and in the SPECT group, two patients had two strokes each, and no details were reported for the remaining patients. Chest pain was described as “same” or “worse” in a similar percentage of patients in the CCTA versus SPECT groups at 6 to 12 months (15.8% vs. 12.7%, RD 3.0, 95% CI -4.2 to 10.3 per 100 people) and 36 percent of patients in both groups continued to have chest pain during this time period. Cardiovascular rehospitalization through a median of 40.4 months was needed in fewer CCTA versus SPECT patients, although the difference did not achieve statistical significance (25.0% vs. 31.0%, RD -5.5, 95% CI -14.3 to 0.03 per 100 people). Cardio-related ED visits (21.0% vs. 20.0%) were similar between groups through a median of 40.4 months.

Clinical Management

Test results were not reported. There was no difference between CCTA and SPECT groups in the percentage of patients who underwent ICA within 12 months (15.0% vs. 16.0%, RD 1.0, 95% CI -8.1 to 6.1 per 100 people). A similar percentage of CCTA and SPECT patients who underwent ICA did not undergo revascularization (7.5% vs. 10.0%, RD 2.5, 95% CI -2.2 to 7.2 per 100 patients). Although there was no difference between groups in revascularization through 12 months (7.5% vs. 6.0%, RD 1.5, 95% CI -3.4 to 6.4 per 100 patients) or in PCI through 12 months (4.0% vs. 5.5%, RD -1.5, 95% CI -5.7 to 2.7 per 100 patients), significantly more CCTA patients underwent CABG compared with SPECT patients through 12 months (3.5% vs. 0.5%, RD 3.0, 95% CI 0.3 to 5.7 per 100 people). Additional noninvasive testing was performed in 22.5 percent of patients in both the CCTA and SPECT groups, including myocardial perfusion

imaging (MPI) (15.0% vs. 13.0%), stress echocardiography (6.5% vs. 7.0%), and CCTA (1.0% vs. 2.5%). There were no differences between the CCTA and SPECT groups in new prescriptions for aspirin (39.5% vs. 34.0%), statins (25.0% vs. 18.0%), or in prescriptions for increased statin dosages (3.0% in both groups).

Harms of Index Test and Consequences of Testing

No major complications were attributed to the imaging procedure. Thirty-day death, MI, and stroke were not reported. Periprocedural chest pain, shortness of breath, or palpitations occurred in significantly fewer CCTA versus SPECT patients (0.5% vs. 15.9%, RD -15.4, 95% CI -20.8 to -10.1 per 100 people), while there were no differences between groups in "general" adverse reactions (including headache, nausea, dizziness, or feeling of warmth) (24.2% vs. 24.5%) or in rash or pruritus (1.6% vs. 0%, p=0.25). There were no cases of post-test renal dysfunction. Radiation exposure from the initial test was lower in the CCTA group compared with the functional testing group (9.6 [IQR, 6.2 to 23] vs. 27 [IQR, 19 to 27] mSv, mean difference -17.4, 95% CI NR, p<0.001).

Harms of Additional Testing

Cumulative cardiac radiation exposure through 12 months was lower in the CCTA group compared with the functional testing group (12 [IQR 6.4 to 26] vs. 27 [IQR 19 to 27] mSv, mean difference -15, 95% CI NR, p<0.001); similar results were found through the entire followup period (median of 40.4 months) (13 [IQR, 6.9 to 27] vs. 27 [IQR 19 to 27] mSv, mean difference -14, 95% CI NR, p<0.001).

Differential Effectiveness or Safety in Subgroups

Not reported.

Noncomparative Studies: Anatomical

No noncomparative studies of functional testing in patients at intermediate risk met the inclusion criteria that reported outcomes of interest. For anatomic testing in this population, only studies of coronary artery calcium scoring were identified.

Calcium Scoring

Two noncomparative studies of calcium scoring during CCTA in patients at intermediate pretest risk reported on predictive accuracy.[123,125] One study was conducted in a single center outpatient setting (N=341) and the other included data from an international, multicenter registry (N=10,037). The study populations differed, respectively, in terms of mean age (62 vs. 57 years) and sex (33% vs. 43% female), as well as several cardiac risk factors. The followup period was 24 months in both studies. In terms of test-positive patients, the frequency of any cardiac event was substantially higher in both studies (5 and 8 per 100 people) compared with those who tested negative (0 and 1 per 100 people). The registry study also reported a higher risk of both mortality (1.8% vs. 0.4%) and MI (1.1% vs. 0.2%) in those who tested positive (see Appendix F for details).

Table 9. Summary of findings and strength of evidence: Intermediate pretest risk

Outcome[*]	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	CCTA vs. usual care[†]	2 RCTs (N=1098)[‡] 1 observational study (N=200)	ED	There is low-strength evidence that a difference in mortality was not found. At ED visit through 28 to 30 days, there were no deaths in either group (2 RCTs). Through 3 months followup, there were no deaths in either group (observational study).	Low
	SPECT vs. exercise ECG	1 RCT (N=824 women)	NR	There is low-strength evidence that a difference in mortality was not found. Through 24 months, overall mortality was similarly low in both groups (1.0% vs. 0.5%).	Low
	CCTA vs. functional testing	1 RCT (N=10,003)	Outpatient	Mortality was similar between the CCTA and functional testing groups through 12 months (0.42% vs. 0.64%) and a median of 25 months (1.48% vs. 1.50%) followup.	Moderate
	CCTA vs. SPECT	1 RCT (N=400)	Telemetry	There is low-strength evidence that a difference in mortality was not found through a median of 24.5 months (0.5% vs. 3.0%, RD -2.5, 95% -5.1 to 0.06 events per 100 people).	Low
Myocardial Infarction	CCTA vs. usual care[†]	2 RCTs (N=1098)[‡] 1 observational study (N=200)	ED	Strength of evidence is low that a difference in diagnosis of MI was not found (2.3% vs. 3.6%, pooled RD -1, 95% CI -3 to 0 events per 100 patients, I^2=0%) (2 RCTs) at the index ED visit; or after index visit through 28 days (0.2% vs. 0.8%, RD -0.6, 95% CI -1.5 to 0.3 events per 100 people) in one trial (N=987). The observational study reported no MIs in either group through 3 months followup.	Low
	CCTA vs. functional testing	1 RCT (N=10,003)	Outpatient	Nonfatal MI was similarly rare between groups through 12 months (0.36% vs. 0.54%, RD -0.18, 95% -0.44 to 0.08 per 100 people) and a median of 25 months (0.60% vs. 0.80%, RD -0.20, 95% CI -0.53 to 0.13 per 100 people).	Moderate
Heart Failure	CCTA vs. usual care[†]	1 observational study (N=200)	ED	Through 3 months followup, there was no development or worsening of heart failure that required hospitalization in either group. Definitive conclusions are not possible.[§]	Insufficient

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Invasive Coronary Angiography Referral	CCTA vs. usual care†	2 RCTs (N=1098)‡	ED	At the index visit, ICA referral was similar in the testing groups (13.8% vs. 11.2%, RD 3, 95% CI 0 to 7 per 100 patients, I^2=0%, p=NS). Through 28 days followup (after the index visit), there was no difference between groups (1.0% vs. 0.8%) in one RCT (N=987).	Low
	SPECT vs. exercise ECG	2 RCTs (N=824 women in one trial; n=280 in intermediate-risk subgroup in other trial)	NR (trial of women) Outpatient (general population)	One trial of women only reported identical referral rates for ICA in both groups (6%) through 24 months. The other trial (general population) found that SPECT was associated with a significantly lower risk of ICA (10.6% vs. 43.1%, RD -32, 95% CI -43 to -22 per 100 people) through a mean of 22 months followup.	Low
	CCTA vs. functional testing	1 RCT (N=10,003)	Outpatient	ICA within 90 days was significantly more common in the CCTA group than the functional testing group (12.19% vs. 8.11%, RD 4.08, 95% CI 2.90 to 5.26 per 100 people).	High
	CCTA vs. SPECT	1 RCT (N=400)	Telemetry	ICA within 12 months was similar between the CCTA and SPECT groups (15.0% vs. 16.0%, RD 1.0, 95% CI -8.1 to 6.1 events per 100 people).	Low
Revascularization	CCTA vs. usual care†	2 RCTs (N=1098)‡	ED	At the index visit, revascularization was similar between CCTA (7.2%) and usual care(5.6%) (pooled RD 2, 95% CI -1 to 5 per 100 patients, I^2=0%) (2 RCTs).	Low
	SPECT vs. exercise ECG	1 RCT (N=824 women)	NR	Similar over 24 months of followup in the SPECT (2.0%) and exercise ECG groups (1.0%) in one trial of women only (RD 1.1, 95% CI -0.7 to 2.8 per 100 patients).	Low
	CCTA vs. functional testing	1 RCT (N=10,003)	Outpatient	Significantly more CCTA patients underwent revascularization within 90 days than functional testing patients (6.22% vs. 3.16%, RD 3.07, 95% CI 2.24 to 3.90 per 100 people).	High
	CCTA vs. SPECT	1 RCT (N=400)	Telemetry	No difference in revascularization rates through 12 months between CCTA and SPECT groups (7.5% vs. 6.0%, RD 1.5, 95% CI -3.4 to 6.4 events per 100 patients).	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Percutaneous Coronary Intervention	CCTA vs. usual care†	1 RCT (N=987) 1 observational study (N=200)	ED	Similar rates of PCI at the index ED visit (5% vs. 3%) (1 RCT), through 28 days (0.6% vs. 0.6%) (1 RCT), and through 3 months (9% vs. 15%) (1 observational study).	Low
	CCTA vs. functional testing	1 RCT (N=10,003)	Outpatient	More common following CCTA vs. functional testing through 90 days (4.8% vs. 2.4%, RD 2.4, 95% CI 1.7 to 3.1 per 100 people).	High
	CCTA vs. SPECT	1RCT (N=400)	Telemetry	No difference in PCI rates through 12 months between CCTA and SPECT groups (4.0% vs. 5.5%, RD -1.5, 95% CI -5.7 to 2.7 events per 100 patients).	Low
Coronary Artery Bypass Graft	CCTA vs. usual care†	1 RCT (N=987) 1 observational study (N=200)	ED	Similar between groups at the index visit (1% in both groups) (1 RCT), through 28 days (0% in both groups) (1 RCT), or through 3 months (1% vs. 2%) (1 observational study).	Low
	CCTA vs. functional testing	1 RCT (N=10,003)	Outpatient	More common following CCTA vs. functional testing through 90 days (1.44% vs. 0.76%, RD 0.68, 95% CI 0.27 to 1.09 per 100 people).	High
	CCTA vs. SPECT	1 RCT (N=400)	Telemetry	CABG was more common following CCTA vs. SPECT through 12 months (3.5% vs. 0.5%, RD 3.0, 95% CI 0.3 events to 5.7 per 100 people).	Low
Additional Testing	CCTA vs. usual care†	1 RCT (N=987)	ED	Through 28 days (and after the index visit) similar frequency of additional noninvasive testing: SPECT (1.6% vs. 1.8%); stress echocardiography (0% in both groups) or exercise treadmill testing (2% vs. 3%).	Low
	SPECT vs. exercise ECG	2 RCTs (N=824 women in one trial; n=280 in intermediate-risk subgroup in other trial)	NR (trial of women) Outpatient (general population)	SPECT was associated with a significantly lower risk of additional noninvasive testing in both trials; this included stress testing with or without imaging in one RCT of women only (9.4% vs. 18.6%; RD -9, 95% CI -14 to -4 per 100 people). The other trial reported additional stress testing in no SPECT patients and 38% of exercise ECG patients (RD -38, 95% CI -48 to -29 per 100 people).	Moderate (trial of women) Low (subgroup of general population)
	CCTA vs. SPECT	1 RCT (N=400)	Telemetry	Additional noninvasive testing was performed in 22.5% of patients in both the CCTA and SPECT groups (RD 0, 95% CI -8.2 to 8.2 events per 100 patients), and included myocardial perfusion imaging (15.0% vs. 13.0%), stress echocardiography (6.5% vs. 7.0%), and CCTA (1.0% vs. 2.5%).	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Hospitalization (Cardiac related)	CCTA vs. usual care†	1 RCT (N=987) 1 observational study (N=200)	ED	Strength of evidence is low that hospitalizations were similar at the time of ED index visit (pooled RD -22, 95% CI -47 to 2 per 100 patients, I^2=85.1%); the larger trial (N=987) found fewer hospitalizations with CCTA vs. usual care(51.9% vs. 82.3%, RD -33, 95% CI -39 to -28 per 100 patients) but the smaller trial (N=111) found no difference between groups. The observational study found that through 3 months, hospitalization for recurrent chest pain was similar (0% vs. 3%, RD -3, 95% CI -6 to 0.3 per 100 patients, p=NS).	Low
	SPECT vs. exercise ECG	1 RCT (N=824 women)	NR	Through 24 months, hospitalization for chest pain was similarly low between groups (3.9% vs. 3.1%, RD 0.8, 95% CI -1.8 to 3.4).	Low
	CCTA vs. functional testing	1 RCT (N=10,003)	Outpatient	Through a median of 25 months, no difference was found between groups in the risk of cardiac hospitalization (1.22% vs. 0.92%, RD -0.30, 95% CI -0.10 to 0.71 per 100 people), and hospitalization for unstable angina was similar but significantly more common in CCTA patients (1.22% vs. 0.82%, RD 0.40, 95% CI 0.01 to 0.80 per 100 people).	Moderate
	CCTA vs. SPECT	1 RCT (N=400)	Telemetry	Cardiac rehospitalization occurred in fewer CCTA vs. SPECT patients through a median of 40.4 months, although the difference did not achieve statistical significance (25.0% vs. 31.0%, RD -5.5, 95% CI -14.3 to 0.03 events per 100 people)	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Harms of the Index Test	CCTA vs. functional testing	1 RCT (N=10,003)	Outpatient	For major procedural complications, there were no differences between groups (procedural stroke (0.02% vs. 0.04%); major bleeding (0.1% in both groups); no cases of anaphylaxis or renal failure requiring dialysis). Overall, minor side effects (e.g., stress-induced symptoms, mild contrast reactions) occurred at a similar rate between groups although the difference was statistically significant (0.74% vs. 0.42%, RR 1.77, 95% CI 1.05 to 3.01).	Moderate
	CCTA vs. SPECT	1 RCT (N=400)	Telemetry	No major complications were attributed to the imaging procedure; 30-day death, MI, and stroke were not reported. The composite of periprocedural chest pain, shortness of breath, or palpitations occurred in significantly fewer CCTA vs. SPECT patients (0.5% vs. 15.9%, RD -15.4, 95% CI -20.8 to -10.1 per 100 people), while there were no differences between groups in minor adverse reactions (including headache, nausea, dizziness, or feeling of warmth) (24.2% vs. 24.5%) or in rash or pruritus (1.6% vs. 0%, p=0.25). There were no cases of post-test renal dysfunction	Low

CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ED = emergency department; ICA = invasive coronary angiography; MI = myocardial infarction; NS = not statistically significant; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SPECT = single photon emission computed tomography

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Usual care varied by study and included consisted of the standard evaluation strategy used at each ED (1 RCT), a conventional diagnostic strategy using serial ECGs and cardiac biomarkers (1 RCT), and repeated biomarker measurements, stress testing (e.g., exercise ECG, stress echocardiography, SPECT), and clinical observation (observational study).

‡Number of patients includes the 987 patients in the Hoffman trial and the subset of 111 patients who were at intermediate pretest risk in the Chang trial.[75,80]

§Definitive conclusions are not possible because of study limitations and/or imprecision in observational studies.

Low to Intermediate Pretest Risk of Coronary Artery Disease

Key Points

Evidence for all primary outcomes and comparators not listed was insufficient to draw conclusions because of study limitations and/or imprecision in the observational study or because of lack of evidence.

CCTA Versus Usual Care

- In low- to intermediate-risk patients presenting to the ED, there is low-strength evidence showing no difference between groups in mortality or MI diagnosis at the index visit or through 1 month based on one fair-quality trial. Moderate-strength evidence from the same trial suggests that CCTA patients were less likely to be hospitalized at the index ED visit but cardiac-related hospitalizations through 1 month were similar. The CCTA groups were less likely to undergo additional testing at the index and 1-month followup visits (1 fair-quality trial) and through 3-months followup (1 poor-quality trial) (moderate [1 month] and low [3 months] strength of evidence). While ICA referrals were similar for the groups at the index ED visit and through 1- to 3-month followup, there were slightly more revascularization procedures in the CCTA group at the index visit in one large fair-quality trial but no difference through the followup period across two trials (low strength of evidence).

CCTA Versus Exercise ECG

- In low- to intermediate-risk patients, there was low-strength evidence of no differences in mortality or MI between groups through 12 months based on one trial of ED patients and one observational study of outpatients (both fair quality). The 12-month rate of referral to ICA and revascularization was significantly greater following CCTA than exercise ECG based on data from the trial of ED patients (low strength of evidence).

CCTA Versus SPECT

- In low- to intermediate-risk patients presenting to the ED, there was low-strength evidence from two trials (1 good- and 1 fair-quality) that no difference was found between groups in mortality through 6 months. There was moderate-strength evidence that there was no difference in MI (both RCTs) or cardiac-related hospitalizations (1 good-quality RCT) through 6 months; one fair-quality observational study of outpatients also reported no difference in mortality or cardiac-related hospitalizations between groups through a mean of 30 months. Together, the trials of ED patients reported that ICA referrals were similar between groups at both the index ED test and through 6 months (low strength of evidence). Additional noninvasive testing was more common following CCTA at the index visit (high strength of evidence from two trials); additional noninvasive testing through 6 months was similar (low strength of evidence from 1 trial). Moderate-strength evidence from both trials of ED patients suggested similar referral for revascularization, including PCI and CABG evaluated separately, at the index visit and through 6 months.

Detailed Synthesis

A total of 15 studies were identified in populations with low to intermediate pretest risk of CAD and eight (9 publications) compared CCTA with usual care (2 RCTs,[81,83] 1 retrospective observational[107]), SPECT (2 RCTs,[77,78] 1 retrospective observational[90]), and exercise ECG (1 RCT,[79] 1 retrospective observational[100,106]) (Table 10); seven additional noncomparative studies (2 of which contained data for 2 different tests) reported on the predictive accuracy of stress echocardiography (2 studies),[110,114] exercise ECG (4 studies),[109-111,116] and calcium scoring (3 studies).[111,120,122]

Anatomic Tests Versus Standard of Care

CCTA Versus Usual Care

Two RCTs, one fair quality[81] and one poor quality,[83] compared CCTA with usual care in patients with low to intermediate pretest risk presenting with chest pain to the ED in the United States (see Appendix E and G for details).[81,83] No other studies compared anatomical testing with usual care in this population. In one large multicenter trial conducted across five EDs, patients received testing with 64-slice (or higher) CCTA with contrast (n=908) or usual care (n=462) consisting of traditional "rule out" approaches at the discretion of the patients' treating physician (64% underwent diagnostic testing, primarily stress testing with imaging).[81] Outcomes were reported at the index visit and at 1 month; only 84.5 percent of patients randomized to CCTA actually underwent the test. This trial was supported by the Commonwealth of Pennsylvania Department of Health and the American College of Radiology Imaging Network Foundation. A small RCT was conducted in a single ED and all patients received standard treatment (i.e., 12-lead ECG, coronary biomarkers, continuous ECG monitoring, medication, cardiology consultation, and additional cardiac testing as required) with those randomized to the intervention group also undergoing 64-slice CCTA (n=30 in both groups).[83] Outcomes were reported for all patients over a 3-month followup period. This trial received grants from the National Center for Research Resources. Within each trial, the CCTA and usual care groups were similar in age and sex; cardiac risk factors were also similar between groups in one study[81] but not reported in the second.[83] Only one of the trials reported baseline risk scores; 51, 36, and 13 percent of the overall population had a TIMI risk score of 0, 1, and 2 or higher, respectively.[81] Across trials, mean ages (49 vs. 51 years) and the proportion of females (53% vs. 50%) were similar. The trial by Litt et al. 2012 enrolled more African Americans (60% vs. 47%) compared with Miller et al. 2012 trial. Methodological shortcomings included unclear allocation concealment and unclear blinding of outcomes assessment in both studies and no reporting of or adjustment for standard cardiac risk factors in one study.[83]

One fair-quality retrospective observational study compared CCTA with usual care in 1,788 patients at low to intermediate risk (no details on risk scores reported)[107] (see Appendix E for details). The study was conducted in a single ED in the United States and funding was not reported. Patients received CCTA or usual care at the discretion of the ED physician, depending on CCTA availability and clinical suitability. Data for the study were abstracted from hospital discharge and followup records and patients were matched for analysis by propensity scores. All patients were initially evaluated with 12-lead ECG and serum troponin I level. Patients then received CCTA (n=894) or usual care (n=894) to include cardiac monitoring in the ED with serial ECGs and serial troponin I levels and stress testing at the discretion of the clinician. Patents in the two groups were similar in mean age (49 years), proportion that was female (52%),

and in all cardiac risk factors. Methodological shortcomings included unclear blinding of outcomes assessment.

Clinical Outcomes

In the larger trial, no deaths were reported for CCTA or usual care patients during the 30-day followup period.[81] The same trial found similar percentages of patients with a MI diagnosis at the index ED visit (1.0% vs. 0.9%, RD 0.1, 95% CI -0.9 to 1.2 per 100 people) and through 30 days (1.1% in both groups). At the index visit, diagnosis with acute coronary syndrome without MI was also similar between CCTA and usual care groups (3.1% vs. 1.5%, RD 1.6, 95% CI -0.01 to 3.2 per 100 patients); CCTA was associated with significantly more positive diagnoses for CAD (9.0% vs. 3.5%, RD 5.6, 95% CI 3.1 to 8.1 per 100 patients).[81] The CCTA group was less likely than the usual care group to be admitted to the hospital or observation unit at the index ED visit (50% vs. 77%, RD -26.8, 95% CI -31.9 to -21.8 per 100), with similar incidences between the groups of cardiac-related hospital admissions after the index visit (3.1% vs. 2.4%, RD 0.7, 95% CI -1.1 to 2.6).[81] In the smaller trial, the CCTA group was less likely to be hospitalized (for presumably any reason) during the 90-day followup period compared with the usual care group (20% vs. 53%, RD -33, 95% CI -56 to -10 per 100 people), but it was not clear whether or not this included admissions at the time of the index visit.[83] This same trial found that ED visits within 90 days were less common in the CCTA group compared with the usual care group, though the results did not reach statistical significance (17% vs. 33%, RD -17, 95% CI -38 to 5 per 100 people),[83] while similar proportions of CCTA and usual care patients had revisits to the ED during 30 days of followup as reported in the larger trial (8.0% vs. 7.2%, RD 0.5, 95% CI -2.5 to 3.5).[81] The smaller trial found no significant difference between the CCTA and usual care groups in change in quality of life, as measured by either the SF-12 Physical Component Score or the SF-12 Mental Component Score.[83]

The single observational study reported no deaths in either group within 30 days of the index visit.[107] The risk of acute MI was not statistically different between the CCTA and the usual care groups over 30 days (0.3% vs. 0.6%, adjusted OR [CCTA as referent] 4.3, 95% CI 0.3 to 71.4, p=0.31); all MIs occurred during the index visit. Patients in the usual care group were significantly more likely to be hospitalized at the index visit compared with those who underwent CCTA initially (40% vs. 14%; adjusted OR 5.5, 95% CI 3.8 to 8.0, p<0.001). The likelihood of returning to the ED for any cause within 30 days of the index visit was similar following usual care compared with CCTA (3.6% vs. 1.3%; adjusted OR 8.5, 95% CI 0.4 to 180, p=0.17); however, among patients that returned to the ED, those in the usual care group were significantly more likely to return for chest pain (2.2% vs. 0.6%; adjusted OR 5.1, 95% CI 1.3 to 20.3, p=0.02).

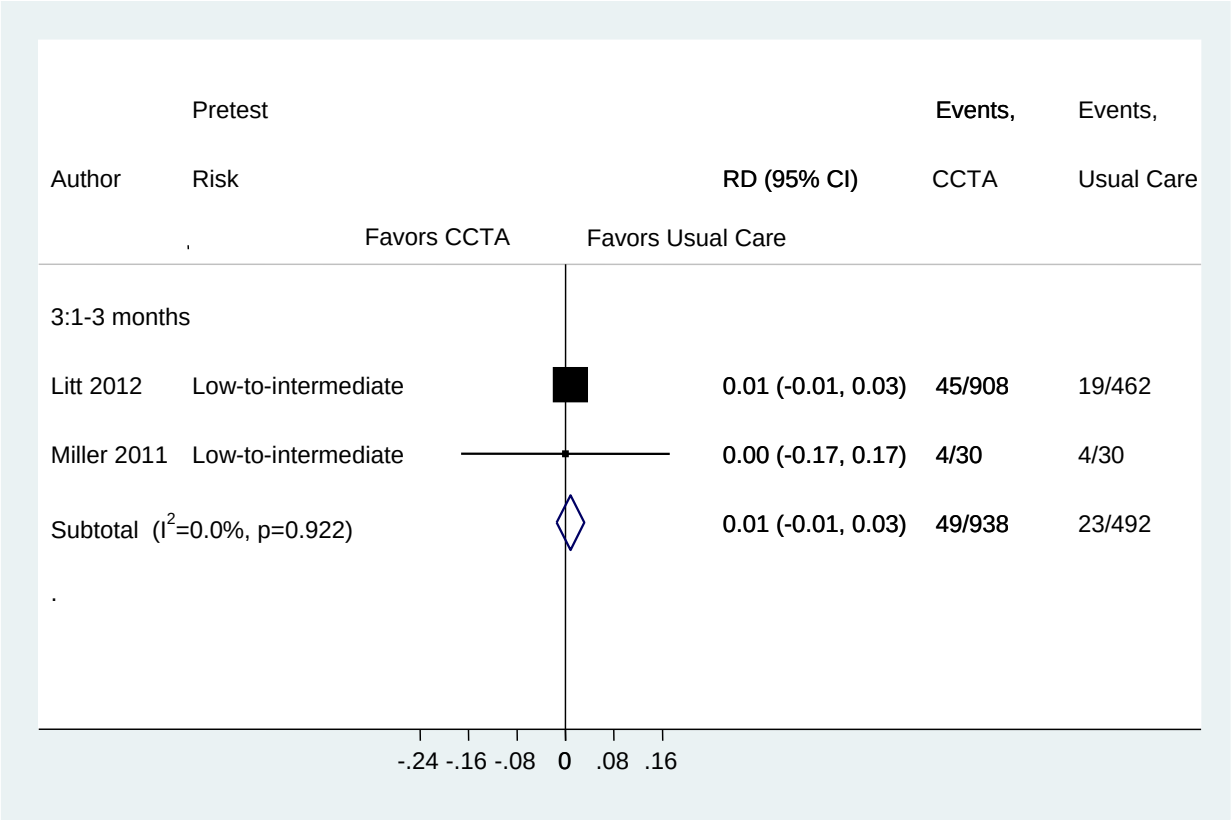
Clinical Management

ICA referral was similar between CCTA and usual care patients at both the index ED visit (4.1% vs. 3.9%) as reported by the larger trial (4.1% vs. 3.9%),[81] and during the 30- and 90-day followup periods as reported by both trials (pooled, 5.2% vs. 4.7%, RD 1, 95% CI -1 to 3 per 100 people, I^2=0%) (Figure 10).[81,83] However, ICA results showed fewer false positives (i.e., no obstructive CAD) in patients referred following CCTA compared with usual testing at the index ED visit (24% vs. 56%) and at 30 days (29% vs. 53%) in the larger trial,[81] and during 90 days of followup (25% vs. 75%) in the smaller trial.[83] The larger trial found that CCTA testing was associated with less stress testing than usual care at the index ED visit (13.7% vs. 57.8%, RD -44.1, 95% CI -49.2 to -39.1 per 100 people) and less additional noninvasive testing of any type

within 30 days in the CCTA group (23.1% vs. 66.4%, RD -43.3, 95% CI -48.4 to -38.1 per 100 people). While stress testing through 30 days of followup was done in fewer CCTA patients (16.9% vs. 59.8%, RD -42.9, 95% CI -48.0 to -37.8 per 100 people), a similar number of patients in the CCTA and usual care groups received resting echocardiogram within 30 days (6.2% vs. 6.6%).[81] The smaller trial of 60 patients found that through 90 days of followup, the CCTA group had less additional noninvasive testing (33% vs. 60%, RD -27, 95% CI -51 to -2), which included exercise stress testing (7% vs. 20%), nuclear perfusion testing (10% vs. 20%), transthoracic echocardiography (7% vs. 17%), and stress echocardiography (10% vs. 3%).[83] CCTA was associated with slightly more revascularization procedures at the time of the index visit, as reported by the larger trial (2.5% vs. 0.9%, RD 1.7, 95% CI 0.3 to 3.0 per 100 people),[81] while revascularization was similar between the CCTA and usual care groups during the 30- and 90-day followup periods, as reported across both trials (pooled, 2.7% vs. 1.2%, RD 1, 95% CI 0 to 3 per 100 people, I^2=0) (Figure 11).[81,83] There were no significant differences between the CCTA group and the usual care group in prescription or use of medications (aspirin, thienopyridines, or statins) at either the index visit or during 30 days of followup in the larger trial.[81] There were also no differences between the two groups in the likelihood of having a followup visit with a cardiologist[81,83] or with a primary care or other physician.[83]

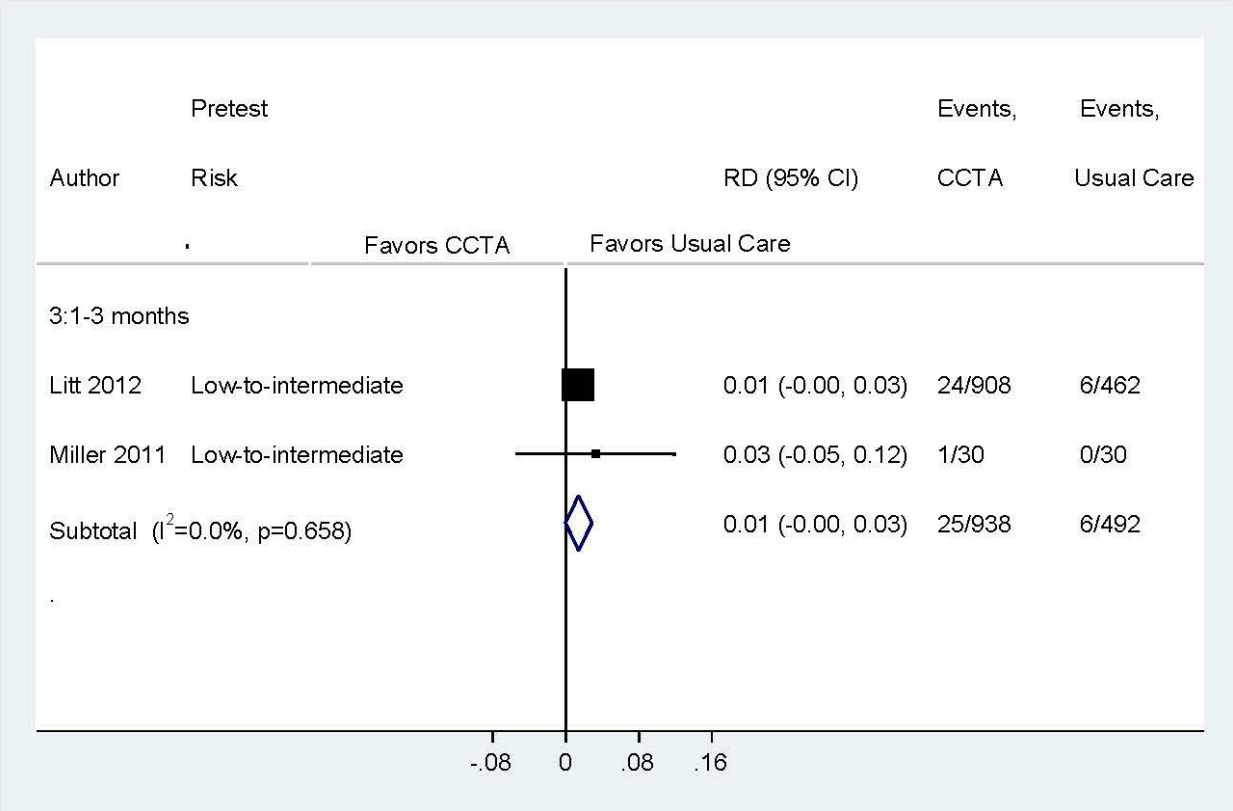
In the single observational study, the usual care group was significantly more likely to be referred for subsequent ICA (3.0% vs. 0.9%, adjusted OR 7.2, 95% CI 2.5 to 20.6, p<0.0001) or stress testing (20.6% vs. 3.7%, adjusted OR 6.1, 95% CI 3.8 to 9.8, p<0.001) compared with the CCTA group.[107] There was no significant difference between the groups in the proportion receiving revascularization, either PCI or CABG (usual care 2.1% vs. CCTA 2.6%, adjusted OR 2.1, 95% CI 0.7 to 6.1, p=0.19).

Figure 10. Meta-analysis results for risk of invasive coronary angiography across studies comparing CCTA with usual care in patients with low to intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference

Figure 11. Meta-analysis results for risk of revascularization across studies comparing CCTA with usual care in patients with low to intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference

Harms of Index Test and Consequences of Testing

The larger trial reported a similarly low incidence of bradycardia (presumed to be related to the medication to control heart rate) following CCTA (0.1%) and usual care (0.2%).[81] The single observational study reported the overall median dose of radiation in the CCTA group only, which was 5.88 mSv (95% CI 5.2 to 6.4).[107]

Harms of Additional Testing, Differential Effectiveness or Safety in Subgroups

Not reported for low- to intermediate-risk patients.

Anatomic Tests Versus Functional Tests

CCTA Versus Exercise ECG

Two fair-quality studies, including one trial and one retrospective observational study, compared 64-slice dual source CCTA with exercise ECG in patients at low to intermediate pretest risk (see Appendix E and G for details).[79,100] An additional publication was also found that provided data on extracardiac findings on CCTA from the observational study.[106] Exercise ECG followed the Bruce protocol in the trial and a "standardized protocol" in the observational study. Patients enrolled in the RCT (N=562) presented to a single ED in Australia with acute, undifferentiated chest pain.[79] This trial was supported by various grants (Queensland Emergency Medicine Research Foundation, Smart Future Fellowship Early Career Grant, and the Washington–Queensland Trans-Pacific Fellowship fund). In the observational study (N=498),

patients with stable angina were referred from primary care to one of two clinics in Denmark based on geographic location, with one clinic using CCTA and the other exercise ECG as the primary initial test for CAD.[100] The source of funding was not reported for this study. Within each study, patients in the CCTA and exercise ECG groups were similar in age, sex, and cardiac risk factors. Across the trial and the observational study, mean ages (52 vs. 55 years) and sex (female 42% vs. 48%) were similar, respectively; however, the two populations differed regarding symptoms and various cardiac risk factors, respectively, including typical angina (90% vs. 14%), hypertension (31% vs. 56%), hyperlipidemia (25% vs. 83%), and smoking (23% vs. 48%). In the observational study, the mean overall baseline risk score (according to Diamond and Forrester) was 26 ± 23 percent and did not differ between test groups; the trial did not report baseline risk scores for its population. Both studies reported outcomes at 12 months, and the trial also reported outcomes at 1 and 6 months. Methodological shortcomings included unclear randomization sequence generation and allocation concealment in the RCT and unclear blinding of outcomes assessment in both studies.

Clinical Outcomes

In the trial of ED patients, there were no deaths through 30 days and similar mortality rates between CCTA and exercise ECG groups through 12 months (0.6% vs. 0.4%, RD 0.2, 95% CI -1.0 to 1.4 per 100 people).[79] None of the deaths were cardiac-related. At the index visit, MI diagnosis occurred at a similar rate in CCTA and exercise ECG groups (1.9% vs. 1.7%, RD 0.2, 95% CI -2.0 to 2.4 per 100 people) and there were no additional MIs through 30 days in either group.[79] Unstable angina was similar between groups at the index visit (3.4% vs. 1.3%, RD 2.2, 95% CI -0.3 to 4.6 per 100 people) and no additional cases were reported through 30 days. Through 12-month followup, hospitalizations for any reason (10.2% vs. 10.8%) and ED visits for recurrent chest pain or cardiac symptoms (12.5% vs. 10.5%) were similar between groups. However, the length of stay in the ED was significantly shorter in the CCTA group compared with the exercise ECG group (13.5 vs. 19.7 hours; p=0.003). Outcomes in the observational study of outpatients were similar, with no deaths through 12 months, and no difference in the risk of MI between CCTA and exercise ECG groups (0% vs. 1.2%, unadjusted p=0.08) through the same followup period.[100]

Clinical Management

While the trial found that CCTA was associated with more ICA referrals through 12 months (9.0% vs. 2.3%, RD 4.8, 95% CI 0.8 to 8.9 per 100 people), the observational study reported the opposite, although the results did not reach statistical significance (17.5% vs. 22.7%; unadjusted RR 0.7, 95% CI 0.54 to 1.1). Through 12 months, CCTA was associated with significantly more people undergoing revascularization compared with exercise ECG (4.3% vs. 1.3%, RD 3.1, 95% CI 0.5 to 5.7 per 100 people)[79] in the RCT. In terms of the patients who tested positive after CCTA (n=31) and exercise ECG (n=65), the observational study found that CCTA patients were more likely to undergo revascularization through 12 months (45% vs. 17%, unadjusted RR 2.7, 95% CI 1.4 to 5.2), including PCI (29% vs. 15%, unadjusted RR 1.9, 95% CI 0.9 to 4.2, p=NS) and CABG (16% vs. 2%, unadjusted RR 11, 95% CI 1 to 86).[100] Additional noninvasive testing was done in significantly fewer CCTA patients in the observational study (4.8% vs. 13.4%, unadjusted RR 0.4, 95% CI 0.2 to 0.7).[100]

Harms of Index Test and Consequences of Testing

The mean radiation exposure with index CCTA was reported by both studies: 3.8 mSv (95% CI 3.5 to 4.1 mSv) in the trial[79] and 7.5 ± 3.6 mSv in the observational study.[100] The incidence of extracardiac findings on CCTA, as reported in a subsequent publication of the observational study,[106] was 17.5 percent (44/251 patients). One-fourth of these patients (n=11) had additional testing (7 chest CT scans, 4 chest x-rays, 3 hepatic ultrasounds, 1 mammogram, 1 transesophageal echocardiogram, and 1 pulmonary scintigraphy), and in two patients malignancies were diagnosed and treated (one breast lumpectomy with adjuvant radiotherapy and one lung lobectomy).

Harm of Additional Testing

Radiation dose was also reported for index testing plus downstream diagnostic tests in a fair-quality retrospective cohort, with the CCTA group having significantly greater exposure compared with exercise ECG regardless of initial test result (range of means for positive, negative, and inconclusive test results: 7.8 to 13 vs. 0.7 to 5.4, $p<0.001$ for all comparisons), but not when downstream revascularization was considered in test-positive patients (28 [CCTA] vs. 32 [exercise ECG], $p=0.61$) (Appendix G, Table G4).

Differential Effectiveness or Safety in Subgroups

No analyses related to differential effectiveness or safety of CCTA versus exercise ECG with regard to patient characteristics or other factors were provided in either study.

CCTA Versus SPECT

Two trials, one good quality[77] and one fair quality,[78] and one fair-quality observational study[90] compared CCTA with SPECT in patients with low to intermediate risk (see Appendix E and G for details).

Goldstein et al. conducted two trials of patients presenting to the ED with acute chest pain; one trial published in 2007 enrolled 203 patients[78] and the other, published in 2011, enrolled 749 patients[77] (the enrollment periods did not overlap). Although Goldstein et al. 2007 specified that patients be at very low to low pretest risk and Goldstein et al. 2011 included patients at low to intermediate pretest risk, the median TIMI scores were identical in both studies (1.0). Because of this, and because demographics and outcomes were similar across both studies, they are analyzed here together as trials of low- to intermediate-risk patients. The 2007 trial collected data from a single ED,[78] while the 2011 trial was multicenter (16 EDs).[77] Both trials were conducted in the United States and received funding via research grants from the Minestrelli Advanced Cardiac Research Imaging[78] and Bayer Pharmaceuticals.[77] CCTA scans were obtained with a 64-slice CT in the earlier trial or a 64- to 320-slice CT scanner in the other. The 2007 trial employed exercise stress SPECT while the 2011 trial used either exercise or pharmacological stress, though the percentage of patients who received each type of stress was not reported. No patients had a history known CAD. Aside from the 2007 trial having slightly younger (mean age 48 vs. 51 years) and fewer male patients (43% vs. 57%) in the CCTA group than the SPECT group, the trials had similar baseline characteristics and cardiac risk factors (i.e., hypertension, dyslipidemia, diabetes, smoking) between groups. Mean age was 50 years in both trials, and males comprised 49.5 percent (2007) and 46.1 percent (2011) of patients. The 2007 trial had considerably more patients with a family history of CAD (41.6%) than did the 2007 study (30.3%). Outcomes were reported through 6 months, with complete followup of 97.0 and 89.7 percent, respectively. The 2011 trial had no apparent methodological shortcomings.[77] However,

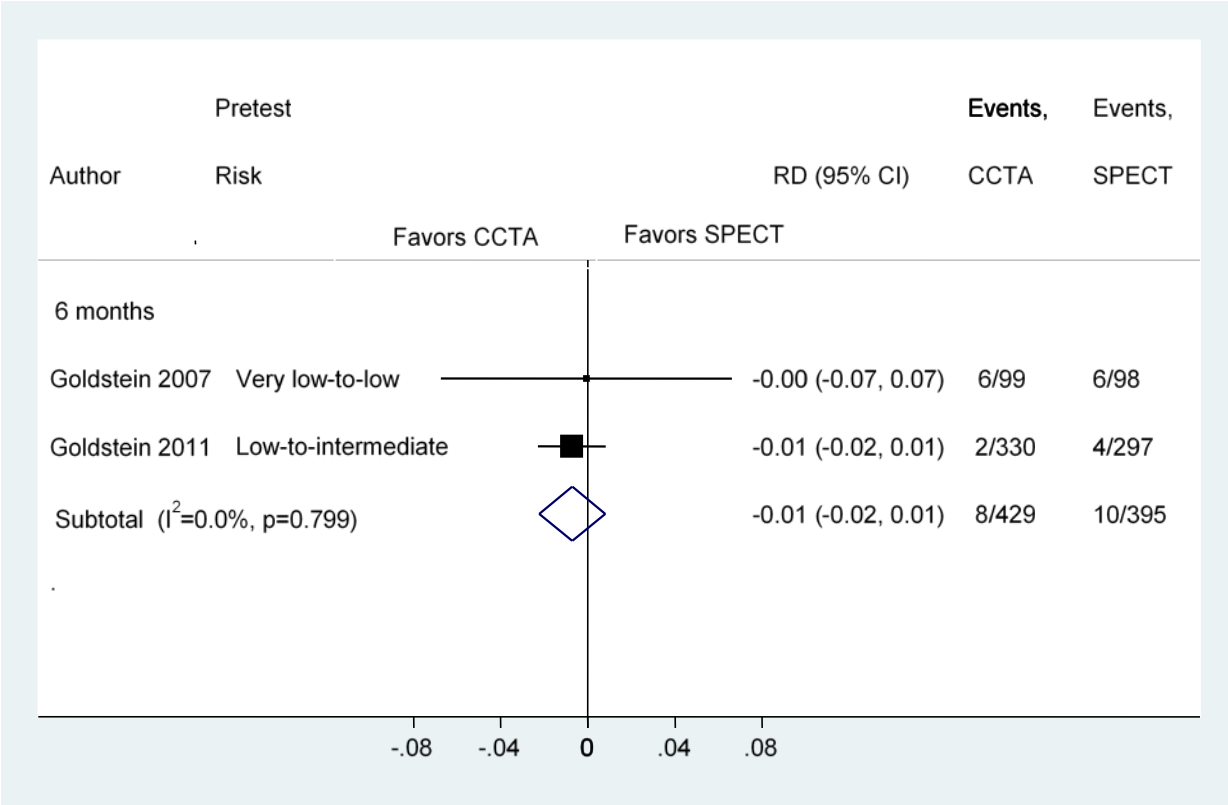
the 2007 trial had several methodological shortcomings including unclear methods for allocation concealment, lack of analysis according to allocated treatment assignment, lack of blinded outcomes assessment, and significant baseline differences between groups that were not controlled for.[78]

Cheezum et al. retrospectively enrolled 252 consecutive patients who had undergone exercise stress (72%) or pharmacologic stress (28%) SPECT who were then matched by age and sex to 241 patients who underwent 64-slice CCTA. All patients were at intermediate risk presenting with chest pain (89%) or dyspnea (11%) to a single center in the United States (90.0% were outpatients).[90] According to Diamond-Forrester, the overall pretest risk was very low (<5%) in 3 percent, low (5%–10%) in 14.5 percent, and intermediate (10%–90%) in 82.5 percent of the population. No patient had a history of CAD. The majority of patient characteristics were similar between groups; the mean age was 53 years, and 44.5 percent of patients were female. Patients were followed for a mean of 30 ± 7 months, with complete followup in 97.2 percent of patients. The only methodological shortcoming was lack of blinded outcomes assessment.

Clinical Outcomes

No patients died through 6 months followup in either trial. The 2007 trial reported no MI events in either group at any time through 6 months.[78] In contrast, the 2011 trial reported a total of six MI events at the index visit; although the cause and precise timing of these events was not reported, they were not detected by resting ECG or serum biomarker testing within the first 4 hours of evaluation (otherwise the patients would have been excluded) and thus occurred or were detected after study enrollment. CCTA and SPECT patients had a similar risk of MI diagnosis at the index ED visit (0.3% vs. 1.5%, RD -1.2%, 95% CI -2.6 to 0.19); no additional MI events occurred in either group after the index visit through 6-month followup.[77] The 2011 trial reported no repeat cardiovascular hospitalizations in either group through 6 months.[77] Both trials reported a similar occurrence of repeat ED visits for cardiovascular causes between the CCTA and SPECT groups through 6 months (1.9 vs. 2.5 per 100 people; pooled RD -1, 95% CI -2 to 1) (Figure 12); these visits occurred in fewer patients in the 2011 trial (0.6% vs. 1.3%, RD -0.7, 95% CI -2.3 to 0.8)[77] than in the 2007 trial (6% in both groups).[78] Repeat cardiovascular office visits occurred in 2 percent of patients in both groups in the 2007 trial. Test results were normal in fewer CCTA patients than SPECT patients in both the 2011 trial (82.2% vs. 89.9%, RD -7.7%, 95% CI -12.8 to -2.6) and in the 2007 trial (68% vs. 95%, RD -27%, 95% CI -37 to -17). The 2007 trial reported that the diagnosis was “clinically correct” in a similar percentage of patients between groups (95% vs. 91%, RD 4%, 95% CI -3 to 11) according to either a definitive diagnosis made during ICA or by the occurrence of a major adverse cardiac event including cardiac death, acute MI, or unstable angina through 6-month followup.[78] Clinical outcomes for test-positive versus test-negative patients were not reported by either trial.

Figure 12. Meta-analysis results for risk of repeat cardiovascular emergency department visits across studies comparing CCTA with SPECT in patients with low to intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference; SPECT = single-positron emission tomography

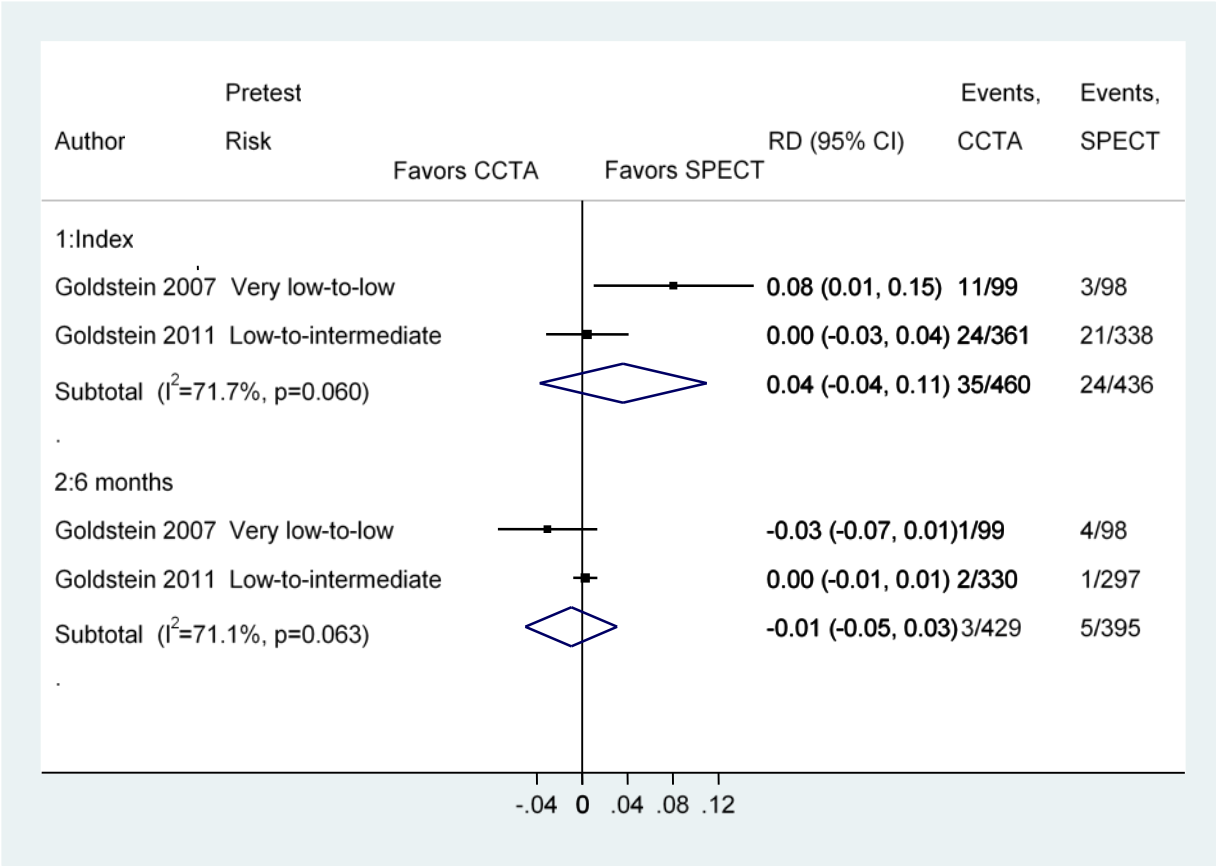
The observational study reported all events through a mean of 30 ± 7 months.[90] There were no cardiovascular deaths in either group; 2.4 percent of patients in both groups died of other unknown causes through the followup period, as identified upon medical record review. The risk of the composite major adverse cardiac event outcome (cardiac death, MI, acute coronary syndrome, or revascularization) was similar between CCTA and SPECT patients (0.4% vs. 0.9%). Cardiovascular hospitalization occurred at a similar rate in the CCTA and SPECT groups (6.6% vs. 4.3%) as did cardiovascular ED visits (13.1% vs. 14.0%). Clinical outcomes were not stratified by test results.[90]

Clinical Management

ICA referral rates were similar between CCTA and SPECT groups in both trials at the index visit (7.6% vs. 5.5%, pooled RD 4, 95% CI -4 to 11 per 100 people, I^2=71.7%) as well as through 6-month followup (0.7% vs. 1.3%, pooled RD -1, 95% CI -5 to 3 per 100 people, I^2=71.1%) (Figure 13).[77,78] In the smaller 2007 trial, of those referred for ICA the results showed a similar proportion of false positives (i.e., no obstructive CAD) between groups (CCTA 25% vs. SPECT 29%, respectively).[78] At the index ED visit, 10.7 percent (2011 trial) and 24 percent (2007 trial) of patients in the CCTA group underwent additional testing with SPECT, while 1.8 percent (2011 trial) of patients in the SPECT group underwent additional testing with CCTA at this initial visit. Overall, additional noninvasive testing at the index visit occurred more

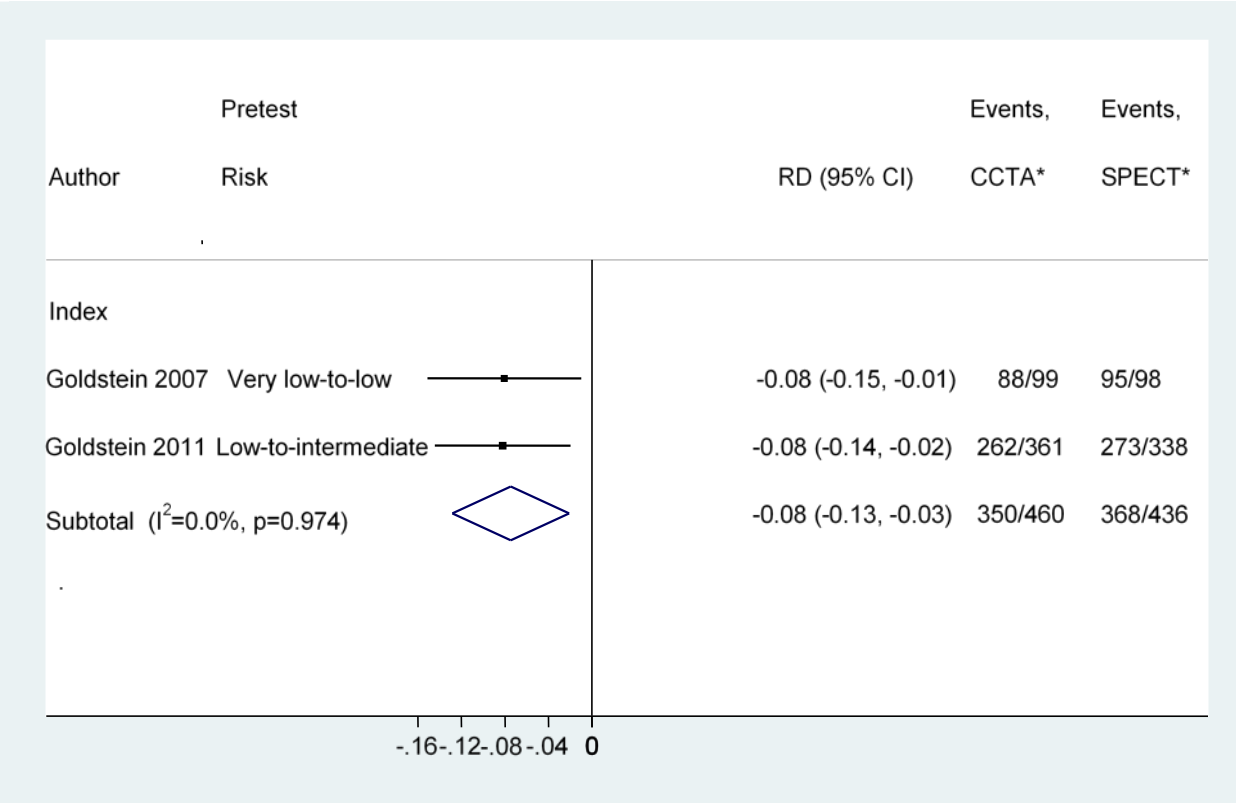
commonly in the CCTA group, with the larger 2011 trial reporting 10.2 percent for CCTA and 0.9 percent for SPECT (RD 9.4, 95% CI 6.1 to 12.7 per 100 patients) and the smaller 2007 trial reporting 24 percent for CCTA and 0 percent for SPECT (RD 24 per 100 people, p<0.001). The smaller trial found that after the index visit through 6-month followup, additional SPECT was done similarly across both groups (1% vs. 3%).[78] Across both studies, fewer CCTA patients were discharged home from the ED at the index visit (76.1% vs. 84.4%, pooled RD -8, 95% CI -13 to -3 per 100 patients, I^2=0%) (Figure 14); in general, discharge occurred upon normal test results.[77,78] Across both trials, CCTA and SPECT groups were similar regarding revascularization at the index ED visit (3.9% vs. 2.1%, pooled RD 2, 95% CI 0 to 4 per 100 people, I^2=3.8%) and after the index visit through 6 months (0.5% vs. 0%, pooled RD 0, 95% CI 0 to 1 per 100 people, I^2=3.8%) (Figure 15); this effect was consistent for both PCI and CABG evaluated separately at the index ED visit (PCI: 2.5%–3% vs. 1.0%–2.4%; CABG: 1.1%–2.0% vs. 0%) and through 6-month followup (PCI: 0.3%–1.0% vs. 0%; CABG: 0% in both groups).[77,78]

Figure 13. Meta-analysis results for risk of referral for invasive coronary angiography across studies comparing CCTA with SPECT in patients with low to intermediate pretest risk



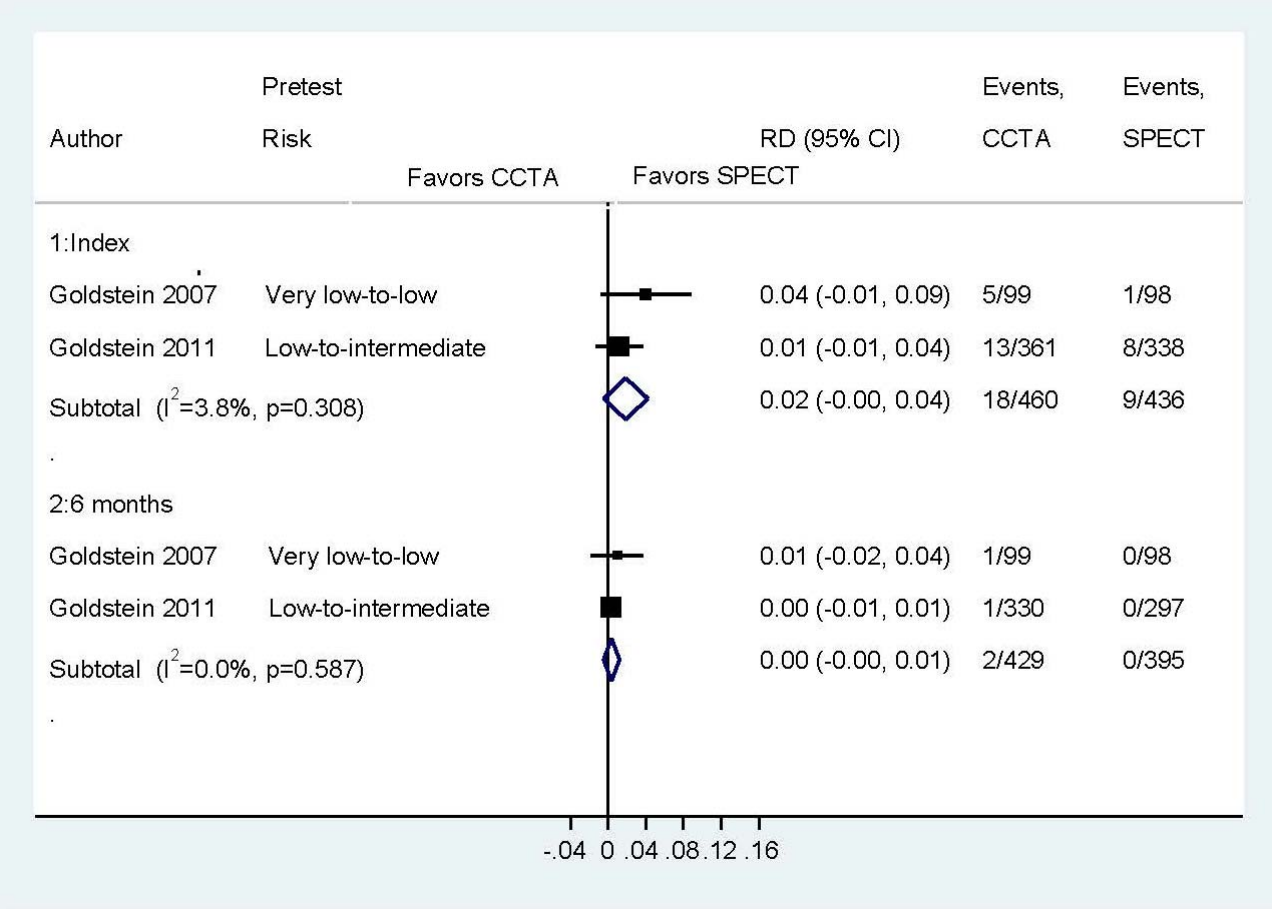
CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference; SPECT = single-positron emission tomography

Figure 14. Meta-analysis results for discharge to home following index visit across studies comparing CCTA with SPECT in patients with low to intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference; SPECT = single-positron emission tomography
*Fewer patients were discharged home following initial testing with CCTA.

Figure 15. Meta-analysis results for risk of revascularization across studies comparing CCTA with SPECT in patients with low to intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference; SPECT = single-positron emission tomography

The observational study reported all events through a mean of 30 ± 7 months.[90] CCTA patients were less likely than SPECT patients to undergo ICA (3.3% vs. 8.1%, RR 0.4, 95% CI 0.2 to 0.9) or additional testing with CCTA (0.4% vs. 4.7%, RR 0.1, 95% CI 0.01 to 0.7). Also, of those patients referred for ICA, there were fewer false positives (i.e., no obstructive CAD) after CCTA versus SPECT (33% vs. 60%). However, the groups were similar in regards to other types of noninvasive test utilization, including SPECT (5.7% vs. 6.0%), exercise echocardiography (1.2% vs. 0.9%), and exercise ECG (2.5% vs. 2.1%). Overall, CCTA patients were slightly less likely to need additional testing than SPECT patients although this difference did not reach statistical significance (11.5% vs. 17.0%, RR 0.7, 95% CI 0.4 to 1.1).[90]

Harms of Index Test and Consequences of Testing

There were no test complications in either group, as reported by the 2007 Goldstein trial.[78] The 2011 Goldstein trial noted that radiation exposure at the index visit was significantly lower in the CCTA group compared with the SPECT group (median 11.5 vs. 12.8 mSv, p=0.02).[77] In the observational study, incidental findings requiring further investigation following CCTA occurred in 7.1 percent of patients. In the 252 patients who received CCTA, pulmonary nodule (≥4 mm) was found in five patients; hepatic cyst in three patients; liver hemangioma, fatty liver,

and mediastinal lymphadenopathy in two patients each; and pulmonary embolism, thoracic aortic aneurysm, esophageal thickening, and pleural thickening in one patient each.

Harms of Additional Testing

No harms of additional testing were reported in any of the three studies.

Harms of Additional Testing Differential Effectiveness or Safety in Subgroups

Not reported for this patient population.

Noncomparative Studies: Anatomical

Calcium Scoring

Three noncomparative studies of calcium scoring in patients at low to intermediate pretest risk reported on predictive accuracy. One study was conducted in an outpatient setting (N=422),[111] one in the ED (N=263),[122] and the setting was unclear in the third study of patients who were referred for invasive coronary angiography (N=2088).[120] Of note, this latter study excluded patients who underwent elective revascularization within 60 days after index CT to control for procedure-driven events. Patients presenting to the ED were younger, more likely male, and, with the exception of smoking which was higher in this population, had fewer cardiac risk factors than patients in the other studies. Mean ages ranged from 47.3 to 58.6 years across studies and a slight majority of patients were male (49.3%–60%). In terms of test-positive patients, in all studies, the frequency of cardiac events was higher compared with test-negative patients. Across the two non-ED studies with mean followups of 2.5 years, the frequency of any cardiac event was 5 and 11 per 100 people (vs. 1 per 100 people in both), mortality was 2 per 100 people in both (vs. 0 and 1 per 100 people), and MI was 1 and 2 per 100 people (vs. 0 events); in the ED study, over 5 years followup, the frequency of any cardiac event was 20 per 100 people compared with no events (see Appendix F for details).

Noncomparative Studies: Functional

Stress Echocardiography

Two noncomparative studies of stress echocardiography in patients at low to intermediate pretest risk reported on predictive accuracy. One study was a conducted in an outpatient setting and used treadmill exercise only (N=7236)[114] while the other was conducted in an ED and employed exercise (72%) or dobutamine (28%) as a stressor (N=108).[110] The mean age of both study populations was 54 ± 12 years. Compared with the ED study, the outpatient study enrolled fewer females (30% vs. 50%), had more patients with hyperlipidemia (59% vs. 31%), and included patients with known CAD (10% vs. 0%). In terms of test-positive patients, regardless of setting, the frequency of cardiac events was greater compared with test-negative patients. In the outpatient setting, over a mean followup of 4.8 years, higher annualized mortality rates per person year of followup were reported: ischemia (0.53, 95% CI 0.33 to 0.80) and fixed wall motion abnormality (0.93, 95% CI 0.56 to 1.31) versus normal (0.30, 95% CI 0.24 to 0.37). In the ED setting, the frequency of any cardiac event over a mean followup period of 1 year was 75 per 100 people compared with no events (see Appendix F for details).

Stress ECG

Four noncomparative studies of stress ECG in patients at low to intermediate pretest risk reported on predictive accuracy. Three studies employed exercise stress (treadmill or bicycle)[109,111,116] and one used either exercise or dobutamine stress.[110] One study was conducted in an outpatient setting, one in an ED, and the setting was unclear in the remaining two studies. Samples sizes ranged from 108 to 2,977, mean ages ranged from 50 to 61 years, and the majority of populations were male (51%–60%). The proportion of patients with relevant cardiac risk factors varied across the studies. As compared with a negative result, a positive stress ECG was associated with a higher frequency of any cardiac event across three of the studies (N=5,353), with followup ranging from 1 to 3 years (2 to 30 per 100 people vs. 1 to 3 per 100 people). Of note the largest event rate (30%) in those who tested positive was seen in the study conducted in the ED at 1 year of followup. In the fourth study (N=422),[111] the frequency of cardiac events over a mean 2.6 years was similar between groups (5 and 4 per 100 people) as was mortality (0 for both) and MI (1 per 100 people for both) (see Appendix F for details).

Table 10. Summary of findings and strength of evidence: Low to intermediate pretest risk

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	CCTA vs. usual care†	1 RCT (N=1,392) 1 observational study (N=1,788)	ED	There is low-strength evidence that a difference in mortality was not found. In both studies, no deaths occurred in either group through 1 month.	Low
	CCTA vs. exercise ECG	1 RCT (N=562) 1 observational study (N=498)	ED (RCT) Outpatient (observational)	There is low-strength evidence that a difference in mortality was not found. No deaths through 1 month. Through 12 months, no difference between groups in mortality (0.6% vs. 0.4%, RD 0.2, 95% CI -1.0 to 1.4 per 100 people) were reported; the observational study reported no deaths.	Low
	CCTA vs. SPECT	2 RCTs (N=952) 1 observational study (N=252)	ED (RCTs) Inpatient or outpatient (observational)	There is low-strength evidence that a difference in mortality was not found. No deaths through 6 months (2 RCTs) or through a mean of 30 months (observational study).	Low
Myocardial Infarction	CCTA vs. usual care†	1 RCT (N=1,392) 1 observational study (N=1,788)	ED	A difference in diagnosis of MI was not found at the ED index visit (1.0% vs. 0.9%) in the RCT or through 1 month in both the RCT (1.1% in both groups) and the observational study (0.3% vs. 0.6%).	Low
	CCTA vs. exercise ECG	1 RCT (N=562) 1 observational study (N=498)	ED (RCT) Outpatient (observational)	A difference in diagnosis of MI was not found at index visit (1.9% vs. 1.7%, RD 0.2, 95% CI -2.0 to 2.4 per 100 people) and there were no additional MIs through 1 month. Through 12 months, MI occurred at a similar rate between groups (0% vs. 1.2%, p=0.08) based on the observational study.	Low
	CCTA vs. SPECT	2 RCTs (N=952)	ED	No difference in MI diagnosis was found between groups at the index visit (0.3% vs. 1.5%, RD -1.2%, 95% CI -2.6%–0.19%) (1 RCT, N=749) or through 6 months (0% in both groups) (both RCTs).	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Invasive Coronary Angiography referral	CCTA vs. usual care†	2 RCTs (N=1452) 1 observational study (N=1,788)	ED	Referral for ICA was similar between groups at the time of index ED visit (1 RCT, N=1392) (4.1% vs. 3.9%) and through 1- to 3-months (2 RCTs) (pooled 5.2% vs. 4.7%, RD 1, 95% CI -1 to 3 per 100 people). In the observational study, up to 1 month post ED visit, ICA referral was less common with CCTA (1% vs. 3%); although authors report statistical significance (p<0.001), clinical significance is unclear.	Low
	CCTA vs. exercise ECG	1 RCT (N=562)	ED	CCTA associated with more ICA referrals through 12 months (9.0% vs. 2.3%, RD 4.8, 95% CI 0.8 to 8.9 per 100 people).	Low
	CCTA vs. exercise ECG	1 observational study (N=498)	Outpatient	There were fewer ICA referrals in the CCTA group through 12 months (17.5% vs. 22.7%; unadjusted RR 0.7, 95% CI 0.54 to 1.1, p=NS). Definitive conclusions are not possible.‡	Insufficient
	CCTA vs. SPECT	2 RCTs (N=952)	ED	ICA referral rates were similar at the index ED visit (7.6% vs. 5.5%, pooled RD 4, 95% CI -4 to 11 per 100 people, I^2=71.7%) and through 6 months (0.7% vs. 1.3%, pooled RD -1, 95% CI -5 to 3 per 100 people, I^2=71.1%).	Low
	CCTA vs. SPECT	1 observational study (N=252)	Inpatient or outpatient	CCTA patients were less likely than SPECT patients to undergo ICA (3.3% vs. 8.1%, RR 0.4, 95% CI 0.2 to 0.9) through a mean of 30 months. Definitive conclusions are not possible.‡	Insufficient

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Revascularization	CCTA vs. usual care†	2 RCTs (N=1452) 1 observational study (N=1,788)	ED	At the index visit, CCTA was associated with slightly more revascularization procedures (2.5% vs. 0.9%, RD 1.7, 95% CI 0.3 to 3.0 per 100 people) in one trial (N=1392). Through 1- to 3-month followup, revascularization was similar between CCTA and usual care groups (pooled, 2.7% vs. 1.2%, RD 1, 95% CI 0 to 3 per 100 people) based on both trials and the observational study (3% vs. 2%).	Low
	CCTA vs. exercise ECG	1 RCT (N=562)	ED	Revascularization was significantly more common in CCTA vs. exercise ECG through 12 months (4.3% vs. 1.3%, RD 3.1, 95% CI 0.5 to 5.7 per 100 people).	Low
	CCTA vs. exercise ECG	1 observational study (n=96 subset of test-positive patients)	Outpatient	Revascularization was more common following positive CCTA than positive exercise ECG through 12 months (45% vs. 17%, unadjusted RR 2.7, 95% CI 1.4 to 5.2). Definitive conclusions are not possible.‡	Insufficient
	CCTA vs. SPECT	2 RCTs (N=952)	ED	Revascularization at the ED index visit (3.9% vs. 2.1%, pooled RD 2 per 100 people, 95% CI 0 to 4) and after this visit through 6 months (0.5% vs. 0%, pooled RD 0, 95% CI 0 to 1 per 100 people) was similar between groups.	Moderate
Percutaneous Coronary Intervention	CCTA vs. usual care†	1 RCT (N=60)	ED	Similarly low rates between groups over 3 months followup (CCTA 3% vs. usual care 0%); unclear if this estimate includes the index visit.	Low
	CCTA vs. exercise ECG	1 observational study (n=96 subset of test-positive patients)	Outpatient	More patients who tested positive with CCTA underwent PCI through 12 months compared with those who tested positive with exercise ECG (29% vs. 15%, unadjusted RR 1.9, 95% CI 0.9 to 4.2, p=NS). Definitive conclusions are not possible.‡	Insufficient
	CCTA vs. SPECT	2 RCTs (N=952)	ED	Across both trials, PCI use was similar at the index visit 2.5%–3% vs. 1.0%–2.4%, RD 0.13 to 2.0 per 100 people, p=NS) and through 6 months (0.3%–1.0% vs. 0%, RD 0.3 to 1.0 per 100 people, p=NS).	Moderate

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Coronary Artery Bypass Graft	CCTA vs. usual care†	1 RCT (N=60)	ED	A difference in CABG use was not found. No CABG procedures reported in either group through 3 months.	Low
	CCTA vs. exercise ECG	1 observational study (n=96 subset of test-positive patients)	Outpatient	Those who tested positive after CCTA were more likely to undergo CABG through 12 months than those who tested positive with exercise ECG (16% vs. 2%, unadjusted RR 11, 95% CI 1 to 86). Definitive conclusions are not possible.‡	Insufficient
	CCTA vs. SPECT	2 RCTs (N=952)	ED	A difference in referral for CABG was not found at the ED index visit (1.1%–2.0% vs. 0%) or after this visit through 6 months (0% in both groups).	Moderate
Additional Testing	CCTA vs. usual care†	2 RCTs (N=1452) 1 observational study (N=1,788)	ED	At the ED index visit, CCTA testing was associated with less stress testing than usual care (13.7% vs. 57.8%, RD -44.1, 95% CI -49.2 to -39.1 per 100 people) (1 RCT, N=1392). During the followup period, additional noninvasive testing was done in fewer patients in the CCTA group through 1 month (23.1% vs. 66.4%, RD -43.3, 95% CI -48.4 to -38.1 per 100 people) in one RCT (N=1392) and the observational study (4% vs. 21%, p<0.001), and through 3 months (33% vs. 60%, RD -27, 95% CI -51 to -2) in the second RCT (N=60).	Moderate (30 days) Low (90 days)
	CCTA vs. exercise ECG	1 observational study (N=498)	Outpatient	Additional noninvasive testing was less common following CCTA than exercise ECG through 12 months (4.8% vs. 13.4%, unadjusted RR 0.4, 95% CI 0.2 to 0.7). Definitive conclusions are not possible.‡	Insufficient
	CCTA vs. SPECT	2 RCTs (N=952)	ED	At the index visit, additional noninvasive testing was more commonly done in the CCTA group, with the larger trial reporting 10.2% for CCTA and 0.9% for SPECT (RD 9.4, 95% CI 6.1 to 12.7 per 100 patients) and the smaller trial reporting 24% for CCTA and 0% for SPECT (RD 24 per 100 people, p<0.001). There were no significant differences between groups in additional testing through 6 months as reported by one trial (1% vs. 3%).	High (index visit) Low (6 months)

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
	CCTA vs. SPECT	1 observational study (N=252)	Inpatient or outpatient	A difference was not found for additional testing at a mean of 30 months including SPECT (5.7% vs. 6.0%), exercise echocardiography (1.2% vs. 0.9%), or exercise ECG (2.5% vs. 2.1%). Definitive conclusions are not possible.‡	Insufficient
Hospitalization (Cardiac related)	CCTA vs. usual care†	1 RCT (N=1392)	ED	One trial (N=1392) reported that the CCTA group was significantly less likely to be hospitalized or admitted for observation at the ED index visit (50% vs. 77%, RD -26.8, 95% CI -31.9 to -21.8 per 100 people). During followup, 1-month rates of cardiac hospitalization were similar between groups (3% vs. 2%).	Moderate
	CCTA vs. SPECT	1 RCT (N=749) 1 observational study (N=252)	ED (RCT) Inpatient or outpatient (observational)	Frequency of hospitalization was similar between groups The RCT reported no cardiovascular hospitalizations through 6 months and the observational study reported similar results between groups (6.6% vs. 4.3%) through a mean of 30 months.	Moderate
Harms of Index Test	CCTA vs. usual care†	1 RCT (N=1392)	ED	A difference in bradyarrhythmia was not found; it occurred in one patient in each group (0.1% vs. 0.2%).	Low
	CCTA vs. SPECT	1 observational study (N=252)	Inpatient or outpatient	Incidental findings requiring further investigation occurred following CCTA in 7.1% of patients. Definitive conclusions are not possible.‡	Insufficient

CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; CI = confidence interval; ED = emergency department; ICA = invasive coronary angiography; MI = myocardial infarction; NS = not statistically significant; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SPECT = single-photon emission computed tomography

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Usual consisted of traditional "rule out" approaches at the discretion of the patients' treating physician (64% underwent diagnostic testing, primarily stress testing with imaging) in one trial (N=1392) and standard treatment (12-lead ECG, coronary biomarkers, continuous ECG monitoring, medication, cardiology consultation, and additional cardiac testing as required) in the other trial (N=60).

‡Definitive conclusions are not possible because of study limitations and/or imprecision in observational studies.

Intermediate to High Pretest Risk of Coronary Artery Disease

Key Points

Evidence for all primary outcomes and comparators not listed was insufficient to draw conclusions because of study limitations and/or imprecision in the observational study or because of lack of evidence.

CCTA Versus SPECT

- In intermediate- to high-risk patients, there was insufficient evidence from one small poor-quality trial with a mean 1.8 months of followup without any deaths or MIs found. Strength of evidence was low that cardiac hospitalizations occurred at a similar rate between groups. CCTA was associated with more revascularizations, as well as slightly more ICA referrals and slightly but not significantly less noninvasive cardiac imaging tests through the same followup period (low strength of evidence).

Detailed Synthesis

A total of three studies were identified in populations with intermediate to high pretest risk of CAD and two (3 publications) included the following comparisons: PET versus SPECT (1 prospective observational)[93,95] and CCTA versus SPECT (1 RCT)[84] (Table 11); one additional noncomparative study reported on the predictive accuracy of stress echocardiography.[112]

Functional Tests Versus Functional Tests

PET Versus SPECT

One large, fair-quality, registry-based observational study with two publications compared PET with SPECT[93,95] (see Appendix E and G for details); no other studies compared different types of functional testing in this population. The study enrolled 1,113 patients at intermediate to high pretest risk presenting with chest pain and/or dyspnea to hospitals and outpatient centers (42 sites) in the United States and Canada.[93,95] The study was funded by grants from the National Heart, Lung, and Blood Institute and Bracco Diagnostics. Exercise stress testing was used alone (65%) or in combination with pharmacological stress (7%) in those undergoing SPECT; all patients evaluated with PET had pharmacological stress testing. Those receiving PET were slightly older (mean age 63 vs. 60 years), more likely to be female (59% vs. 51%) and Caucasian (80% vs. 68%), and with a greater prevalence of diabetes (41% vs. 31%), elevated cholesterol (65% vs. 60%), and hypertension (73% vs. 66%) compared with those who had SPECT. Angina (68% vs. 79%) was less common in those receiving PET and pretest CAD risk was slightly lower (probability of significant CAD 0.45 vs. 0.38 for SPECT) based on the Pryor method.[93] Outcomes were reported through both 3 months[93] and 24 months.[95] Methodological shortcomings included lack of blinded outcomes assessment and significant baseline differences between groups.

Clinical Outcomes

Mortality through 24 months occurred in significantly more PET patients than in those tested with SPECT (5.5% vs. 1.6%, unadjusted RR 3.4, 95% CI 1.6 to 7.2), while MI occurrence was

similar between groups (1.1% vs. 1.2%) through the same followup period.[95] Clinical outcomes for test-positive versus test-negative patients were not reported.

Clinical Management

ICA referral rates were higher following PET compared with SPECT at both 90 days (11% vs. 4%, adjusted OR 5.03, 95% CI 1.04 to 24.43) and 24 months (15.0% vs. 6.7%, unadjusted RR 2.2, 95% CI 1.5 to 3.2, p<0.0001); however, there were fewer patients with false positives (i.e., no obstructive CAD) according to ICA results following PET (32.8% vs. 45.8%).[95] The proportions of those who did not have obstructive disease at ICA who had a positive imaging study were 28.3 percent and 39.1 percent for PET and SPECT;[93] differences did not reach statistical significance (p=NR). Overall, more PET patients received revascularization through both 90 days (7% vs. 1.4%, RR 3.5, 95% CI 1.7 to 7.0) and 24 months (8% vs. 2.4%, RR 3.3, 95% CI 1.8 to 6.1). PCI was performed more frequently following PET through 90 days (4.6% vs. 1.4%, RR 3.2, 95% CI 1.5 to 7.1, p=0.0020) and 24 months (5.7% vs. 1.8%, RR 2.9, 95% CI 1.5 to 5.7, p=0.0012); similarly, PET was associated with slightly more CABG procedures than SPECT at the index visit (1.6% vs. 0.4%, RR, 4.6, 95% CI 1.007 to 21.4, p=0.0299) and through 24 months (2.0% vs. 0.4%, RR 5.7, 95% CI 1.3 to 25.5, p=0.0103). Of those who had ICA (n=120), PCI frequency was similar for PET (30%) and SPECT (29%), but CABG was more common following PET versus SPECT (13% vs. 2.6%).[95] At 90 days, post-test changes in use of aspirin (OR 1.14, 95% CI 0.79 to1.66), beta-blocker (OR 0.86, 95% CI 0.52 to 1.41), or lipid-lowering agents (OR 1.02, 95% CI 0.71 to 1.47) were similar in both groups after adjustment for baseline characteristics.

Harms of Index Test and Consequences of Testing

PET was associated with significantly lower exposure to radiation at the index visit compared with SPECT (mean 4.0 vs. 11.0 mSv, p<0.0001).[95]

Harms of Additional Testing

Compared with SPECT, the mean total radiation exposure over the 24-month study period was significantly lower following PET (6.0 vs. 11.6 mSv, p<0.0001).[95] However, during followup, radiation exposure was higher in the group initially tested with PET than with SPECT (2.0 vs. 0.6 mSv, p <0.0001).[95]

Differential Effectiveness or Safety in Subgroups

No analyses related to differential effectiveness or safety of PET versus SPECT with regard to patient characteristics or other factors were provided.

Anatomic Tests Versus Functional Tests

CCTA Versus SPECT

One poor-quality trial compared CCTA with SPECT in 180 patients at intermediate to high pretest risk presenting with stable chest pain and suspected CAD at one of two outpatient cardiology clinics in the United States (see Appendix E and G for details);[84] no other studies compared anatomical and functional testing in this population. The trial was funded by grants from GE Healthcare and Vital Images. Outcomes for 98.3 percent of patients were reported at a mean of 1.8 ± 1.1 months. CCTA scans were obtained with a 64-detector row CT scanner and iodinated contrast. Rest-stress SPECT employed exercise or pharmacological stress, though the

percentage of patients who received each type of stress was not reported. No patients had a history of MI, known CAD, or prior revascularization as per inclusion requirements. CCTA patients were slightly younger (mean age 56 vs. 59), more likely to be male (58% vs. 43%), and have typical angina (32% vs. 23%) than SPECT patients. The percentage of patients with atypical or noncardiac angina were similar across groups. CCTA patients were more likely to be at high pretest risk (33% vs. 24%), though there were no differences between groups in intermediate (63% vs. 67%) or low (4% vs. 9%) risk. Pretest Framingham risk estimates were similar between CCTA and SPECT groups (mean score 18.3 vs. 19.2). Methodological shortcomings included unclear methods for randomization and unclear allocation concealment, lack of blinded outcomes assessment, and significant baseline differences between groups. It was not clear whether both groups had similar length of followup.

Clinical Outcomes

All outcomes were reported at the mean followup of 1.8 ± 1.1 months, which correlates to approximately 1 to 3 months.[84] No patient died or had an MI in either group. The frequency of CAD-related hospitalization was similar between the CCTA and SPECT groups (12% vs. 11%). Test results were positive (abnormal) in 30 percent of CCTA and 36 percent of SPECT patients; the remaining patients tested negative. There were no differences between groups in the mean change from baseline of any subscale of the Seattle Angina Questionnaire, including quality of life/disease perception, physical limitation, angina stability, angina frequency, and treatment satisfaction subscales. Clinical outcomes for test-positive versus test-negative patients were not reported.

Clinical Management

ICA referral rates were higher following CCTA versus SPECT (13% vs. 8%, RD 5, 95% CI -4 to 14 per 100 people) through a mean of 1.8 ± 1.1 months, though the difference did not reach statistical significance.[84] Fewer CCTA patients had any additional noninvasive cardiac imaging test during the followup period but the result was not significant (3% vs. 10%, RD -7, 95% CI -14 to 0.4 per 100 people). However, CCTA patients were more likely to undergo subsequent revascularization (CABG or PCI) (8% vs. 1%, RD 6.6, 95% CI 0.7 to 12.5 per 100 people) during followup. Compared with baseline use, more CCTA patients used aspirin (within-person change from baseline: 22% vs. 8%, p=0.04) and statin (within-person change from baseline: 7% vs. -3.5%, p=0.03) during followup than SPECT patients, however there was no difference between groups in the within-person change in other medications (nonstatin lipid-lowering medications, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, or calcium channel blockers). Overall, initial testing with CCTA is more likely to result in coronary revascularization and more aggressive medical therapy than initial testing with SPECT.

Harms of Index Test and Consequences of Testing

CCTA was associated with significantly lower exposure to radiation at the index visit compared with SPECT (median IQR] 6.5 [5.1 to 13.3] vs. 13.3 [13.1 to 38.0] mSv, p<0.0001).

Harms of Additional Testing

Compared with SPECT, the median total radiation exposure over the 1.8-month followup period was significantly lower following CCTA (7.3 [IQR 5.1 to 13.7] vs. 13.3 [IQR 13.1 to

38.0] mSv, p<0.0001); however, during followup, radiation exposure was higher in the group initially tested with CCTA than with SPECT (0.8 vs. 0 mSv).

Differential Effectiveness or Safety in Subgroups

No analyses related to differential effectiveness or safety of CCTA versus SPECT with regard to patient characteristics or other factors were provided.[84]

Noncomparative Studies: Functional

No noncomparative studies of anatomical testing in patients at intermediate to high risk met the inclusion criteria that reported outcomes of interest. For functional testing in this population, only studies of stress echocardiography were identified.

Stress Echocardiography

One noncomparative study of stress echocardiography in patients at low to intermediate pretest risk reported on predictive accuracy.[112] This study enrolled 244 women with a mean age of 60 ± 10 years, and employed either exercise or pharmacological (70% dipyridamole; 30% dobutamine) stress in an outpatient setting. Atypical as opposed to typical angina was more common (63% vs. 36%). The frequency of any cardiac event over a mean of 36 months was substantially higher in those who had a positive compared with a negative result on stress echocardiography (33 vs. 2 per 100 people) (see Appendix F for details).

Table 11. Summary of findings and strength of evidence: Intermediate to high pretest risk

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	PET vs. SPECT	1 observational study (N=1113)	Hospital and outpatient centers	Through 24 months, mortality was more common in PET than SPECT patients (5.5% vs. 1.6%, unadjusted RR 3.4, 95% CI 1.6 to 7.2). Definitive conclusions are not possible†	Insufficient
	CCTA vs. SPECT	1 RCT (N=180)	Outpatient	There were no deaths in either group through a mean of 55 days followup. Definitive conclusions are not possible†	Insufficient
Myocardial Infarction	PET vs. SPECT	1 observational study (N=1113)	Hospital and outpatient centers	The frequency of MI was similar between groups: 1.1% (PET) vs. 1.2% (SPECT). Definitive conclusions are not possible†	Insufficient
	CCTA vs. SPECT	1 RCT (N=180)	Outpatient	There were no MIs in either group through a mean of 55 days followup. Definitive conclusions are not possible†	Insufficient
Invasive Coronary Angiography Referral	PET vs. SPECT	1 observational study (N=1113)	Hospital and outpatient centers	PET was associated with significantly more ICA referrals through 90 days (11% vs. 4%, adjusted OR 5.03, 95% CI 1.04 to 24.43) and 24 months (15.0% vs. 6.7%, unadjusted RR 2.2, 95% CI 1.5 to 3.2, p<0.0001). Definitive conclusions are not possible†	Insufficient
	CCTA vs. SPECT	1 RCT (N=180)	Outpatient	Strength of evidence is low that difference in ICA referral was not found: CCTA vs. SPECT (13% vs. 8%, RD 5, 95% CI -4 to 14 per 100 people, p=NS) through a mean of 1.8 months	Low
Revascularization	PET vs. SPECT	1 observational study (N=1113)	Hospital and outpatient centers	Revascularization was performed more frequently following PET at both 90 days (7% vs. 1.4%, RR 3.5, 95% CI 1.7 to 7.0) and 24 months (8% vs. 2.4%, RR 3.3, 95% CI 1.8 to 6.1). Definitive conclusions are not possible†	Insufficient
	CCTA vs. SPECT	1 RCT (N=180)	Outpatient	CCTA was associated with more revascularizations than SPECT (8% vs. 1%, RD 6.6%, 95% CI 0.7%–12.5%) through a mean of 1.8 months.	Low
Percutaneous Coronary Intervention	PET vs. SPECT	1 observational study (N=1113)	Hospital and outpatient centers	PCI was performed more frequently following PET through 90 days (4.6% vs. 1.4%, RR 3.2, 95% CI 1.5 to 7.1) and 24 months (5.7% vs. 1.8%, RR 2.9, 95% CI 1.5 to 5.7). Definitive conclusions are not possible†	Insufficient
Coronary Artery Bypass Graft	PET vs. SPECT	1 observational study (N=1113)	Hospital and outpatient centers	CABG was performed slightly more frequently following PET at the index visit (1.6% vs. 0.4%, RR, 4.6, 95% CI 1.007 to 21.4) and through 24 months (2.0% vs. 0.4%, RR 5.7, 95% CI 1.3 to 25.5). Definitive conclusions are not possible†	Insufficient

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Additional Testing	CCTA vs. SPECT	1 RCT (N=180)	Outpatient	There is low-strength evidence that a difference in use of additional testing was not found. Fewer CCTA patients had additional noninvasive cardiac imaging test through a mean of 1.8 ± 1.1 months though the result was not significant (3% vs. 10%, RD -7, 95% CI -14 to 0.4 per 100 people).	Low
Hospitalization (Cardiac related)	CCTA vs. SPECT	1 RCT (N=180)	Outpatient	CAD-related hospitalization was similar between the CCTA and SPECT groups (12% vs. 11%) through a mean of 1.8 months	Low

CABG = coronary artery bypass graft; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ICA = invasive coronary angiography; NS = not statistically significant; PCI = percutaneous coronary intervention; PET = positron emission tomography; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SPECT = single-photon emission computed tomography

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Definitive conclusions are not possible because of study limitations and/or imprecision in observational studies or lack of data in RCTs.

High Pretest Risk of Coronary Artery Disease

Key Points

Given the focus of the report on evaluation of testing based on pretest risk, results for the high pretest risk groups are presented here even though evidence from these groups was rated as insufficient.

SPECT Versus Exercise ECG

- In a small subgroup of high-risk outpatients, there was insufficient evidence that ICA referral was less common in SPECT compared with the exercise ECG group; data also suggest that additional noninvasive imaging following SPECT may be less common, though the sample size was too small to reach statistical significance (insufficient evidence).

Detailed Synthesis

One RCT was identified in a population with high pretest risk of CAD and compared SPECT versus exercise ECG (Table 12).[85]

Functional Tests Versus Functional Tests

SPECT Versus Exercise ECG

One fair-quality trial compared SPECT with exercise ECG in high-risk patients (see Appendix E and G for details). No other studies compared different types of functional testing in this population.[85] The trial included 457 patients referred for stable chest pain to a single outpatient center in the United Kingdom. Grants were received from Bristol-Myers Squibb and Northwick Park Cardiac Research as well as from an individual. Results were stratified based on pretest risk; 106 patients had high pretest likelihood of CAD. Patients underwent either SPECT (n=45) or exercise ECG (n=61). Treadmill exercise was employed in both groups and pharmacological stress was employed in some patients receiving SPECT. Groups were similar overall in age (mean age 59 years), sex (43.5% female), and cardiac risk factors but were not compared within the high-risk group. Baseline risk scores were not reported. Outcomes were reported for 96.9 percent of patients over a mean of 22 months. Methodological shortcomings included lack of allocation concealment and lack of blinded outcome assessment.

Clinical Outcomes

Not reported for high-risk patients.

Clinical Management

ICA referral through 22 months occurred in significantly fewer SPECT than exercise ECG patients (44% vs. 85%, RD -41, 95% CI -58 to -24 per 100 people). This trial used Bayesian methods to model post-test risk and reported that 77 percent of those with high pretest risk finished with high post-test risk (SPECT 56% vs. ECG 93%) and that those with a normal or low-risk test in either arm did not receive ICA. Additional noninvasive imaging was performed somewhat less frequently in patients who underwent SPECT compared with exercise ECG (0% vs. 5%, RD -5, 95% CI -10 to 1 per 100 people), but the difference was not statistically

significant. Medication therapy was prescribed significantly more often in the SPECT group based on initial test results (56% vs. 10%, RD 46, 95% CI 29 to 62 per 100 people).

Harms of Index Test and Consequences of Index and Additional Testing; Differential Effectiveness or Safety in Subgroups

Not reported for high-risk patients.

Noncomparative Studies

No noncomparative studies of anatomical or functional noninvasive tests were identified that reported on predictive accuracy in high pretest risk patients in our specific population.

Table 12. Summary of findings and strength of evidence: High pretest risk

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	CCTA vs. usual care†	1 RCT (n=56 in high-risk subgroup)	ED	No deaths through 1 month in either group. Definitive conclusions are not possible.‡	Insufficient
Invasive Coronary Angiography Referral	CCTA vs. usual care†	1 RCT (n=56 in high-risk subgroup)	ED	At the index visit, fewer CCTA patients underwent ICA (75% vs. 93%, RD -18, 95% CI -37 to 0.8, p=0.0714). Definitive conclusions are not possible.‡	Insufficient
	SPECT vs. exercise ECG	1 RCT (n=106 in high-risk subgroup)	Outpatient	ICA was less common following SPECT vs. exercise ECG through a mean of 22 months (44% vs. 85%, RD -41, 95% CI -58 to -24 per 100 people). Definitive conclusions are not possible.‡	Insufficient
Revascularization	CCTA vs. usual care†	1 RCT (n=56 in high-risk subgroup)	ED	Revascularization frequencies at the index visit were: CCTA (43%) vs. usual care(50%) (RD -7, 95% CI -33 to 19 per 100 people, p=NS). Definitive conclusions are not possible.‡	Insufficient
Additional Testing	SPECT vs. exercise ECG	1 RCT (n=106 in high-risk subgroup)	Outpatient	Additional testing through a mean of 22 months was: SPECT (0%) vs. ECG (5%), RD -5, 95% CI -10 to 1 per 100 people, p=NS). Definitive conclusions are not possible.‡	Insufficient
Hospitalization (Cardiac related)	CCTA vs. usual care†	1 RCT (n=56 in high-risk subgroup)	ED	Hospitalization for acute coronary syndrome at the ED index visit were: CCTA (57%) vs. usual care (64%) (RD -07, 95% CI -33 to 18 per 100 people, p=NS). Definitive conclusions are not possible.‡	Insufficient

CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ED = emergency department; ICA = invasive coronary angiography; NS = not statistically significant; RCT = randomized controlled trial; RD = risk difference; SPECT = single-photon emission computed tomography

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Usual care consisted of a conventional diagnostic strategy using serial ECGs and cardiac biomarkers.

‡Definitive conclusions are not possible because of lack of data from subgroup analyses in RCTs.

Mixed Population*:* Pretest Risk Not Reported or Results Not Stratified by Risk

Key Points

Evidence for all primary outcomes and comparators not listed was insufficient to draw conclusions because of study limitations and/or imprecision in the observational study or because of lack of evidence.

CCTA Versus Usual Care

- In a population presenting to the ED and not stratified by risk (1 fair-quality trial), there was low-strength evidence that a difference between groups was not found in 1-month MI or contrast-induced nephropathy.

SPECT Versus Exercise ECG

- In outpatients not stratified by risk, there was low-strength evidence from one trial that a difference was not found between groups in all-cause mortality or MI through a mean of 22 months, while SPECT was associated with fewer revascularizations than exercise ECG.

Exercise ECG Versus Nuclear MPI

- Low-strength evidence from a large administrative database of mixed risk-level Medicare outpatients suggested that 6-month mortality was similar between groups. Patients who underwent exercise ECG were less likely to undergo ICA through 6 months than those who were tested with MPI; revascularization (including CABG and PCI evaluated separately) was performed similarly between groups (low strength of evidence for both).

Stress Echocardiography Versus Nuclear MPI

- Low-strength evidence from a large administrative database of mixed risk-level Medicare outpatients suggested that 6-month mortality was similar between groups. Through 6 months, ICA referral was statistically less frequent in the stress echocardiography group, while additional noninvasive testing was slightly more common in this group (low strength of evidence). There were no apparent clinical differences between groups in referral for revascularization (including CABG and PCI evaluated separately) (low strength of evidence).

CCTA Versus Exercise ECG

- One fair-quality trial of ED patients at various pretest risk levels with 12 months followup found low-strength evidence that a difference between groups was not found in all-cause mortality or MI, while there was moderate-strength evidence that cardiac-related hospitalizations were less common in the CCTA group. CCTA was associated with more ICAs and more revascularizations (including PCI), though CABG was utilized similarly between groups (low strength of evidence).

CCTA Versus Nuclear MPI

- One large fair-quality database study of mixed-risk level Medicare outpatients provided low-strength evidence that all-cause mortality was similar through 6 months. CCTA patients were more likely to undergo ICA, additional noninvasive testing, and revascularization (including PCI and CABG evaluated separately) through 6 months (low strength of evidence).
- One fair-quality registry study provided low-strength evidence that revascularization was more common following CCTA through a median of 1.42 years; the setting was not reported.

Detailed Synthesis

A total of 18 studies were identified in populations with mixed pretest risk of CAD or for whom risk was not reported. Nine studies included the following comparisons (1 administrative database study reported outcomes for 6 different test comparisons): CCTA versus usual care (1 RCT),[75] exercise ECG (1 RCT,[82] 1 administrative database[102]), SPECT (1 prospective registry,[104] 1 administrative database[97]), nuclear MPI (1 prospective observational,[105] 1 administrative database[102]), and stress echocardiography (1 administrative database);[102] SPECT versus exercise ECG (1 RCT,[85] 1 administrative database[102]); and stress echocardiography versus exercise ECG (1 RCT,[86] 1 prospective observational,[96] 1 administrative database[102]) and SPECT (1 administrative database[102]) (Tables 13–15). Four additional noncomparative studies (1 study reported data for 2 separate tests) reported on the predictive accuracy of stress echocardiography (2 studies),[117,121] stress ECG (2 studies),[115,117] and calcium scoring (1 study);[124] and five studies were included for safety only following CT (2 prospective observational)[98,99] and stress echocardiography (2 prospective,[91,101] 1 retrospective observational[103]).

Anatomic Tests Versus Standard of Care

CCTA Versus Standard of Care

One fair-quality RCT compared CCTA with usual care in patients combined across three pretest risk levels (low 37%, intermediate 42%, high 21%) (see Appendix E and G for details). Only those results not stratified by pretest risk level (which are reported in the appropriate sections) are reported here. The trial enrolled 266 patients presenting with chest pain to a single ED in South Korea.[75] Study funding was not reported. CCTA was performed with 64-slice scanning (n=133) and usual care consisted of a conventional diagnostic strategy (e.g., serial ECGs and cardiac biomarkers) (n=133). Subsequent diagnostic tests were done at the discretion of the treating physician. Overall, groups were similar in age (mean 57.5 years), sex (38.7% female), and cardiac risk factors. Baseline risk scores were not reported. Outcomes were reported at the index visit and at 1-month followup. Methodological shortcomings included unclear randomization method, allocation concealment, and blinding of outcomes assessment.

Clinical Outcomes

Through 1-month followup, no patients in the CCTA group and one patient in the usual care group experienced a nonfatal MI (0% vs. 0.8%, p=0.32).[75]

Clinical Management

Ten percent of CCTA patients underwent additional noninvasive stress testing after the index visit and through 30 days. In the usual care group, noninvasive testing was done at the discretion of the physician in 50 percent of patients at the index visit. Because this is a first test in the usual care patients, it is not considered "additional" noninvasive testing.[75]

Harms of Index Test and Consequences of Testing

No incidence of contrast-induced nephropathy was reported in either group. Following imaging with CCTA, two patients (1.5%) developed a diffusing, irritating skin rash which resolved spontaneously; radiation exposure averaged 12.5 ± 2.0 mSv in this group (not reported for the usual care group).[75]

Harms of Additional Testing, Differential Effectiveness or Safety in Subgroups

Not reported for this population.

Table 13. Summary of findings and strength of evidence: Mixed pretest risk—anatomical testing versus standard of care

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Myocardial infarction	CCTA vs. usual care†	1 RCT (N=266)	ED	There was low-strength evidence a difference in MI was not found. Through 30 days, no patient in the CCTA group had a myocardial infarction vs. one in the usual care group (0% vs. 0.8%).	Low
Harms of the Index Test	CCTA vs. usual care†	1 RCT (N=266)	ED	There were no cases of contrast-induced nephropathy between groups.	Low

CCTA = coronary computed tomography angiography; ED = emergency department; RCT = randomized controlled trial.
*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.
†Usual Care consisted of a conventional diagnostic strategy using serial ECGs and cardiac biomarkers.

Functional Tests Versus Functional Tests

SPECT Versus Exercise ECG

One fair-quality RCT compared SPECT with exercise ECG and enrolled patients at various pretest risk levels (low 16%, intermediate 61%, high 23%) presenting with stable chest pain at a single outpatient center in the United Kingdom (see Appendix E and G for details).[85] Only those results not stratified by pretest risk level (which are reported in the appropriate sections) are reported here. This trial was funded by unrestricted grants from Bristol-Myers Squibb Medical Imaging, Northwick Park Cardiac Research Fund, and from an individual. A symptom limited Bruce or modified Bruce exercise protocol was used in 62 percent of patients undergoing SPECT (n=250) and 100 percent of patients undergoing ECG testing (n=207); the remaining SPECT patients received dipyridamole infusion unless there was a contraindication in which case dobutamine stress was performed. The two groups were similar with regard to mean age (59 years) and sex (44% female), but more patients in the SPECT group were Caucasian (56% vs. 47%) and were more likely to have hypertension (53% vs. 46%) and diabetes (19% vs. 14%). The pretest likelihood of CAD differed substantially in subjects undergoing SPECT versus exercise ECG: low (11% vs. 21%), intermediate (71% vs. 49%), and high (18% vs. 29%). Baseline risk scores were not reported. Outcomes were reported for 96.9 percent of patients over

a mean of 22 months. Methodological concerns included lack of concealed allocation and uncertainty regarding blinded assessment of outcomes.

Clinical Outcomes

Overall mortality was very low in both SPECT and exercise ECG groups through a mean of 22 months followup (0.8% vs. 0.9%). MI through the same followup occurred in no SPECT patients and one exercise ECG patient (0% vs. 0.5%); this event was fatal.[85]

Clinical Management

ICA referral was significantly less following SPECT (16% vs. 47%; RD -30.9, 95% CI -39.2 to -22.7) and results showed false positives (i.e., no obstructive disease) in fewer SPECT patients (17.1% vs. 36.7%). Fewer patients who had SPECT as the index test underwent revascularization compared with those who had an exercise ECG as their index test (10.8% vs. 17.9%, RD -7.1, 95% CI -13.6 to -0.6 per 100 people).[85]

Harms of Index Test and Consequences of Testing, Harms of Additional Testing, Differential Effectiveness or Safety in Subgroups

Not reported in this population.

Exercise ECG Versus Nuclear MPI

One large, fair-quality administrative database study was conducted using a 20 percent random sample of Medicare claim records from 2006 to 2008 (N=282,830);[102] patients could receive one of four tests including exercise ECG (n=61,063) and MPI (n=132,343) (see Appendix E and G for details). Included claims were limited to those in an outpatient setting for patients aged 66 years or older; no patient had a history of known CAD (within the previous 9 months) or prior MI or revascularization (within the previous 12 months). This study was designed to evaluate CCTA, but the data provided allowed some comparisons across the other tests. Current Procedural Terminology (CPT) codes that included both and stress (exercise and pharmacological) ECG and stress SPECT and PET were provided; test details that included information regarding how a test was chosen for a given patient were not reported. Pretest CAD risk and other baseline risk scores were also not reported. Exercise ECG patients were slightly younger than MPI patients (mean age 73.1 vs. 75.7 years), slightly less likely to be female (49.0% vs. 54.5%), and had significantly fewer risk factors and comorbidities. Outcomes were reported at 6 months and adjusted for confounding baseline variables. This study was funded by the American Heart Association. Methodological limitations included lack of blinded outcomes assessment and significant baseline differences between groups, although these differences were controlled for with the adjusted risk estimates.

Clinical Outcomes

The 6-month risk of death from any cause was similar between exercise ECG and MPI (0.78% vs. 1.28%, adjusted OR 0.93, 95% CI 0.83 to 1.04), as was the risk of hospitalization for acute MI (0.32% vs. 0.43%, adjusted OR 0.86, 95% CI 0.72 to 1.03).[102] Clinical outcomes for test-positive versus test-negative patients were not reported.

Clinical Management

Lower 6-month ICA referral rates were reported following exercise ECG compared with MPI (9.04% vs. 12.13%, adjusted OR 0.72, 95% CI 0.70 to 0.75). Any additional noninvasive testing

through 6 months was significantly more common in ECG versus MPI patients (19.34% vs. 3.22%, adjusted OR 7.46, 95% CI 7.16 to 7.77); this difference was statistically significant for all types of noninvasive tests employed (e.g., MPI, stress echocardiography, and exercise ECG) except CCTA. The need for any revascularization through 6 months was similar between groups although the difference was statistically meaningful (4.31% vs. 4.59%, respectively; adjusted OR 0.90, 95% CI 0.85 to 0.94); this trend held true for both PCI (2.57% vs. 3.37%, adjusted OR 0.72, 95% CI 0.68 to 0.77) and CABG (1.82% vs. 1.29%, adjusted OR 1.37, 95% CI 1.26 to 1.49). Although fewer patients underwent ICA in the exercise ECG group, they were significantly more likely to receive revascularization following ICA than MPI patients (46.49% vs. 37.53%, adjusted OR 1.30, 95% CI 1.21 to 1.40).

Harms of Index Test and Consequences of Testing and Harms of Additional Testing

No harms related to either the index or additional testing were reported.

Differential Effectiveness or Safety in Subgroups

No analyses related to differential effectiveness or safety of nuclear MPI and exercise ECG with regard to patient characteristics or other factors were provided, however the database study focused on Medicare beneficiaries (age ≥ 66 years).[102]

Stress Echocardiography Versus Exercise ECG

One poor-quality RCT[86] and two observational studies, one fair quality[102] and one poor quality,[96] were identified that compared stress echocardiography to exercise ECG (see Appendix E and G for details).

The RCT compared dobutamine (n=47) and exercise stress echocardiography (n=57), and exercise ECG (n=54) in women with chest pain who had no history of cardiac disease but who had at least two cardiac risk factors.[86] Patients were recruited from family medicine, EDs, and inpatient cardiology (number of sites and locations not reported) and 90.3 percent were followed for a mean of 28.1 ±14.2 months. Ages were similar across groups (mean 54.5 years) as was the proportion of Caucasians (97.5%). Patients in the stress echocardiography groups were more likely to have hypertension than those in the exercise ECG group (53.8% vs. 38.9%); all other relevant cardiac risk factors were similar. Pretest CAD risk and other baseline risk scores were not reported. This trial was funded in part by a clinical research grant from the American Society of Echocardiography. Methodological shortcomings included lack of information on random sequence generation and allocation concealment, lack of information on patients who withdrew after consent, potentially clinically significant baseline differences between groups, and failure to control for possible confounding.

One poor-quality prospective observational study compared exercise stress echocardiography with exercise ECG in patients with suspected or known CAD.[96] Results were stratified according to history of CAD; therefore, only data for the 5,894 (77.0%) patients without known CAD are included in this report. However, demographics, risk factors, and test details were not reported separately for this subgroup. The study was conducted in the United States at a single large cardiac referral center; choice of test was made according to physician preference and institutional practice. Funding was received from the American Society of Echocardiography and the National Heart Foundation of Australia. Complete followup data were available for all patients for a mean of 33.6 months; however, followup periods differed between the echocardiography and ECG groups (mean 38.4 ± 24 vs. 30 ± 24 months, respectively). Overall,

groups were similar in mean age (62 years) and sex (41% female) and there were no statistically significantly differences between groups in clinical risk factors. Twelve percent of the patients were considered low risk, 59 percent intermediate, and 29 percent high risk when pretest clinical risk was defined as predicted annualized risk of death or MI. Methodological shortcomings included lack of information regarding blinded outcome assessment and whether baseline risks were similar in the subset of patients with no history of CAD, and unclear reporting of loss-to-followup.

A large, fair-quality administrative database study was conducted using a 20 percent random sample of Medicare claim records from 2006 to 2008 (N=282,830).[102] Patients could receive one of four tests, including stress echocardiography (n=80,604) and exercise ECG (n=61,063), and the followup period was 6 months. Pretest CAD risk and other baseline risk scores were not reported. Included claims were limited to an outpatient setting for patients aged 66 years or older; no patient had a history of known CAD (within the previous 9 months) or prior MI or revascularization (within the previous 12 months). This study was designed to evaluate CCTA, but the data provided allowed some comparisons across the other tests. No test details were reported to include information regarding how a test was chosen for a given patient; only CPT codes that included both stress echocardiography and exercise and pharmacological stress ECG were provided. Both groups were similar in regards to mean age (73.5 years), the proportion of Caucasian patients (88.3%), and relevant cardiac risk factors; however, the stress echocardiography group included more women (57.5% vs. 49.0%). This study was funded by the American Heart Association. Methodological limitations included lack of blinded outcomes assessment and lack of adjustment for differences in age.

Clinical Outcomes

The RCT reported that cardiac outcomes (defined as a composite including cardiac death, MI, unstable angina, or coronary angiography demonstrating 50% or more luminal narrowing) occurred at a similar rate following stress echocardiography and exercise ECG (7.7% vs. 7.4%).[86] When stratified by the result of the test, patients with positive result stress echocardiography results were slightly more likely to have a cardiac outcome than patients with a positive stress ECG (44% [7/16] vs. 38% [3/8]), however the sample size was small. Patients with a negative stress echocardiography result were slightly less likely to have a noncardiac outcome (defined as no cardiac event and/or diagnosis of a noncardiac source of the original pain) than patients with a negative exercise ECG (86% [74/86] vs. 91% [30/33]). Ten of 21 patients with a positive test result had a cardiac outcome (positive predictive value 47.6 per 100 people). The proportion of cases with definitive and accurate results was statistically higher for exercise stress echocardiography than exercise ECG (84% vs. 67%, RD 17, 95% CI 3 to 31). The poorer performance of the exercise ECG was driven by the number of inconclusive tests rather than inaccurate results.

The prospective observational study reported adjusted cardiac death and a composite of death or MI split according to three categories of post-test risk, namely low, intermediate, and high.[96] Through a mean of 34 months followup, adjusted rates stratified by low, intermediate, and high post-test risk were consistently and statistically lower in the exercise echocardiography group versus the exercise ECG group for both cardiac death (0.4% vs. 0.9%; 1.3% vs. 1.4%; 2.5% vs. 2.9%) and for the composite of death or MI (1.6% vs. 1.8%; 2.2% vs. 3.4%; 4.6% vs. 5.5%) ($p<0.006$).

The database study of Medicare claims reported that the 6-month risk of death from any cause was somewhat higher following stress echocardiography than exercise ECG (0.95% vs.

0.78%, unadjusted RR 1.21, 95% CI 1.08 to 1.35).[102] Hospitalization for acute MI was the same (0.32%) for both groups.

Clinical Management

The RCT reported that additional pharmacological stress echocardiography was performed because indeterminate test results were seen in significantly fewer exercise echocardiography patients than exercise ECG patients (4% vs. 24%, RD -21, 95% CI -33 to -8 per 100 people).[86] This is not reported for the patients randomized to pharmacologic stress echocardiography as the initial test, as this test was considered definitive and no patients in this group were referred for additional testing per protocol. All of the second tests were negative; no other information was provided on followup treatment or testing.

The prospective study found that through a mean of 34 months, ICA was performed in a similar percentage of stress echocardiography patients at low (6% vs. 8%) and intermediate post-test risk (12% vs. 14%); however ICA was more common following stress echocardiography in those considered to be at high post-test risk (40% vs. 28%, $p<0.0001$).[96] The pattern was the same for revascularization (low post-test risk 5% vs. 7%; intermediate 8% vs. 9%; high 29% vs. 20%), including PCI (low post-test risk 4% vs. 6%; intermediate 5% vs. 6%; high 22% vs. 12%). However, the pattern was different in terms of referral for CABG, with similar results following stress echocardiography between all post-test risk groups: (low post-test risk 1% vs. 2%; intermediate 3% in both groups; high 6% vs. 8%).

In the database study on Medicare claims, there was no difference between groups in referral for ICA (9.50% vs. 9.04%, unadjusted RR 1.05, 95% CI 1.02 to 1.09), although the result was statistically significant.[102] In the patients referred for ICA, fewer stress echocardiography patients received revascularization (43.65% vs. 46.49%, unadjusted RR 0.94, 95% CI 0.90 to 0.98). Referral for any additional noninvasive cardiac test was done in fewer stress echocardiography than exercise ECG patients in the 6 months following initial testing (5.57% vs. 19.34%, unadjusted RR 0.29, 95% CI 0.28 to 0.30). The need for any revascularization in the same time period was similar between groups (4.22% vs. 4.31%); this was also true for PCI (2.61% vs. 2.57%) and CABG (1.69% vs. 1.82%).

Harms of Index Test and Consequences of Testing

No information on harms was provided by the previously-described studies. However, three additional studies were identified in the population of interest comparing stress echocardiography with exercise ECG that reported complications. There were no incidences of major periprocedural side effects or complications in either group (all patients had both tests), as reported by two large studies (N=429 and 244 women).[101,112] Two studies reported side effects for the echocardiography group only; all patients underwent dipyridamole stress. One study[91] reported chest pain (37%), flushing (22%), headache (30%), dyspnea (11%), hypotension (6.4%), nausea (5.5%), dizziness (4.5%), and ST segment depression (49.5%) in 109 of 130 patients and the other reported low incidences of excessive tachycardia with palpitations (0.2%) and hypotension and symptomatic bradycardia (0.5%) in their population (N=429).[101]

Harms or Consequences of Additional Testing

None of the three studies reported harms or consequences of additional testing.

Differential Effectiveness or Safety in Subgroups

No analyses related to differential effectiveness or safety of stress echocardiography and exercise ECG with regard to patient characteristics or other factors were provided, however the trial enrolled only women[86] and one focused on Medicare beneficiaries.[102]

Stress Echocardiography Versus Nuclear MPI

Only one fair-quality study compared stress echocardiography to nuclear MPI; pretest risk was not reported (see Appendix E and G for details). Shreibati et al. conducted a large administrative database study using a 20 percent random sample of Medicare claim records from 2006 to 2008 (N=282,830); patients could receive one of four tests including stress echocardiography (n=80,604) and MPI (n=132,343).[102] Pretest CAD risk and other baseline risk scores were not reported. Claims were limited to those in an outpatient setting for patients ages 66 years or older; no patient had a history of known CAD (within the previous 9 months) or prior MI or revascularization (within the previous 12 months). This study was designed to evaluate CCTA, but the data provided allowed some comparisons across the other tests. No test details were reported to include information regarding how a test was chosen for a given patient; only CPT codes that included both stress echocardiography and stress SPECT and PET were provided. Patients in the stress echocardiography and MPI groups were similar, respectively, in terms of mean age (73.8 vs. 75.7 years), sex (57.5% vs. 54.5% female), and race (89.1% vs. 89.3% Caucasian). However, those who underwent stress echocardiography had significantly fewer reported cardiac risk factors (i.e., diabetes 20.8% vs. 31.6%; hyperlipidemia 64.6% vs. 74.8%; hypertension 60.2% vs. 74.9%). Outcomes were reported at 6 months and adjusted for confounding baseline variables. This study was funded by the American Heart Association. Methodological limitations included lack of blinded outcomes assessment and significant baseline differences between groups.

Clinical Outcomes

In this study of Medicare claims, the 6-month risk of death from all causes was similar for stress echocardiography and MPI (0.95% vs. 1.28%, adjusted OR 1.00, 95% CI 0.90 to 1.10), as was the rate of hospitalization for acute MI (0.32% vs. 0.43%, adjusted OR 0.83, 95% CI 0.70 to 0.98), although the results were statistically significant.[102]

Clinical Management

Through 6-month followup, referral for ICA was significantly less frequent following stress echocardiography (9.50% vs. 12.13%; adjusted OR 0.78, 95% CI 0.76 to 0.81). The need for any revascularization in the same time period was similar between groups (4.22% vs. 4.59%, adjusted OR 0.93, 95% CI 0.88 to 0.98); this was true for both PCI (2.61% vs. 3.37%, adjusted OR 0.76, 95% CI 0.72 to 0.81) and CABG (1.69% vs. 1.29%, adjusted OR 1.40, 95% CI 1.29 to 1.52). In the patients referred for ICA, more stress echocardiography patients received revascularization (43.65% vs. 37.53%, adjusted OR 1.23, 95% CI 1.15 to 1.32). Referral for any additional noninvasive cardiac test was somewhat more frequent in stress echocardiography patients (5.57% vs. 3.22%; adjusted OR 1.92, 95% CI 1.83 to 2.0).[102]

Harms of Index Test and Consequences of Testing

No information on harms was provided by the previously-described study. However, one additional study was identified in the population of interest that compared dobutamine stress echocardiography with SPECT and reported complications for the echocardiography arm only

(n=70).[103] Overall, there were no serious side effects including sustained arrhythmia, severe hypotension, or MI. Reported complications included: chest pain requiring test termination (11%), extracardiac side effects (e.g., dyspnea, nausea) (5.7%), increased blood pressure (2.9%), and multiple ventricular ectopy (1.4%).

Harms of Additional Testing

Not reported.

Differential Effectiveness or Safety in Subgroups

No analyses related to differential effectiveness or safety of stress echocardiography and MPI with regard to patient characteristics or other factors were provided, however the database study included only Medicare patients.

Table 14. Summary of findings and strength of evidence: Mixed pretest risk—functional versus functional testing

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	SPECT vs. exercise ECG	1 RCT (N=457)	Outpatient	There was low-strength evidence a difference in mortality was not found; frequency by 22 months was 0.8% vs. 0.9% for SPECT and exercise ECG, respectively.	Low
	Exercise ECG vs. nuclear MPI	1 observational study (N=193,406 Medicare)	Outpatient	Frequency of mortality was similar between groups through 6 months (0.78% vs. 1.28%, adjusted OR 0.93, 95% CI 0.83 to 1.04).	Low
	Stress echocardiography vs. exercise ECG	1 observational study (n=5894 with no known CAD)	Outpatient	Through a mean of 34 months followup, adjusted rates stratified by low, intermediate, and high post-test risk were consistently and statistically lower in the exercise echocardiography group vs. the exercise ECG group for cardiac death (0.4% vs. 0.9%; 1.3% vs. 1.4%; 2.5% vs. 2.9%, p<0.006). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. exercise ECG	1 observational study (N=141,667 Medicare)	Outpatient	6-month mortality was similar between groups although the difference was statistically significant (0.95% vs. 0.78%; unadjusted RR 1.2, 95% CI 1.1 to 1.4). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. nuclear MPI	1 observational study (N=212,947 Medicare)	Outpatient	All-cause mortality was similar for stress echocardiography and MPI through 6 months (0.95% vs. 1.28%, adjusted OR 1.00, 95% CI 0.90 to 1.10).	Low
Myocardial Infarction	SPECT vs. exercise ECG	1 RCT (N=457)	Outpatient	There was low-strength evidence a difference in MI was not found through a mean of 22 months followup (0% vs. 0.5%).	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Invasive Coronary Angiography Referral	Exercise ECG vs. nuclear MPI	1 observational study (N=193,406 Medicare)	Outpatient	By 6 months, referral for ICA was less frequent following exercise ECG (9.04% vs. 12.13%, adjusted OR 0.72, 95% CI 0.70 to 0.75).	Low
	Stress echocardiography vs. exercise ECG	1 observational study (n=5894 with no known CAD)	Outpatient	Through a mean of 34 months, ICA referral was similar in patients at low (6% vs. 8%) and intermediate post-test risk (12% vs. 14%) but more frequency in stress echocardiography patients considered to be at high post-test risk (40% vs. 28%, p<0.0001). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. exercise ECG	1 observational study (N=141,667 Medicare)	Outpatient	Through 6 months, ICA referral was similar although the difference was statistically significant (9.50% vs. 9.04%, unadjusted RR 1.05, 95% CI 1.02 to 1.09). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. nuclear MPI	1 observational study (N=212,947 Medicare)	Outpatient	By 6 months, referral for ICA was less frequent following stress echocardiography (9.50% vs. 12.13%; adjusted OR 0.78, 95% CI 0.76 to 0.81).	Low
Revascularization	SPECT vs. exercise ECG	1 RCT (N=457)	Outpatient	SPECT was associated with fewer revascularizations that exercise ECG (10.8% vs. 17.9%, RD -7.1, 95% CI -13.6 to -0.6 per 100 people).	Low
	Exercise ECG vs. nuclear MPI	1 observational study (N=193,406 Medicare)	Outpatient	Revascularization through 6 months was similar between groups although the difference was statistically significant (4.31% vs. 4.59%, respectively; adjusted OR 0.90, 95% CI 0.85 to 0.94).	Low
	Stress echocardiography vs. exercise ECG	1 observational study (n=5894 with no known CAD)	Outpatient	Through a mean of 34 months, revascularization was performed in a similar percentage of stress echocardiography patients at low (5% vs. 7%) and intermediate post-test risk (8% vs. 9%) but in more stress echocardiography patients considered to be at high post-test risk (29% vs. 20%). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. exercise ECG	1 observational study (N=141,667 Medicare)	Outpatient	Through 6 months, the frequency of revascularization was similar between groups (4.22% vs. 4.31%). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. nuclear MPI	1 observational study (N=212,947 Medicare)	Outpatient	Revascularization through 6 months was similar between groups although the difference was statistically significant (4.22% vs. 4.59%, adjusted OR 0.93, 95% CI 0.88 to 0.98).	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Percutaneous Coronary Intervention	Exercise ECG vs. nuclear MPI	1 observational study (N=193,406 Medicare)	Outpatient	Through 6 months, PCI was similar between groups although the difference was statistically meaningful (2.57% vs. 3.37%, adjusted OR 0.72, 95% CI 0.68 to 0.77).	Low
	Stress echocardiography vs. exercise ECG	1 observational study (n=5894 with no known CAD)	Outpatient	Through a mean of 34 months, PCI was performed in a similar percentage of stress echocardiography patients at low (4% vs. 6%) and intermediate post-test risk (5% vs. 6%) but in more stress echocardiography patients considered to be at high post-test risk (22% vs. 12%). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. exercise ECG	1 observational study (N=141,667 Medicare)	Outpatient	Through 6 months, there was a similar frequency of PCI between groups (2.61% vs. 2.57%). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. nuclear MPI	1 observational study (N=212,947 Medicare)	Outpatient	Through 6 months, PCI referral occurred at a similar rate between groups although the difference was statistically significant (2.61% vs. 3.37%, adjusted OR 0.76, 95% CI 0.72 to 0.81).	Low
Coronary Artery Bypass Graft	Exercise ECG vs. nuclear MPI	1 observational study (N=193,406 Medicare)	Outpatient	Through 6 months, CABG was done similarly between groups although the difference was statistically significant (1.82% vs. 1.29%, adjusted OR 1.37, 95% CI 1.26 to 1.49).	Low
	Stress echocardiography vs. exercise ECG	1 observational study (n=5894 with no known CAD)	Outpatient	Through a mean of 34 months, CABG was performed in a similar percentage of stress echocardiography patients at low (1% vs. 2%) and intermediate post-test risk (3% in both groups) but in fewer stress echocardiography patients considered to be at high post-test risk (6% vs. 18%). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. exercise ECG	1 observational study (N=141,667 Medicare)	Outpatient	CABG was performed similarly between groups through 6 months (1.69% vs. 1.82%). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. nuclear MPI	1 observational study (N=212,947 Medicare)	Outpatient	Through 6 months, CABG referral occurred at a similar rate between groups although the difference was statistically significant (1.69% vs. 1.29%, adjusted OR 1.40, 95% CI 1.29 to 1.52).	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Additional Testing	Exercise ECG vs. nuclear MPI	1 observational study (N=193,406 Medicare)	Outpatient	Referral for additional testing was significantly more frequent for exercise ECG than MPI in the 6 months after initial testing (19.34% vs. 3.22%, adjusted OR 7.46, 95% CI 7.16 to 7.77).	Low
	Exercise echocardiography vs. exercise ECG	1 RCT (N=111)	Various	Stress echocardiography was associated with significantly less additional testing compared with exercise ECG (3.5% vs. 24.1%; RD=22, 95% CI -34 to -10). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. exercise ECG	1 observational study (N=141,667 Medicare)	Outpatient	Additional noninvasive testing through 6 months was more common following stress (5.57% vs. 19.34%, unadjusted RR 0.29, 95% CI 0.28 to 0.30); this was driven by significantly fewer referrals for MPI (4.03% vs. 16.47%; unadjusted RR 0.24, 95% CI 0.24 to 0.25). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. nuclear MPI	1 observational study (N=212,947 Medicare)	Outpatient	Referral for additional testing was somewhat more frequent for stress echocardiography than MPI in the 6 months after initial testing (5.57% vs. 3.22%; adjusted OR 1.92, 95% CI 1.83 to 2.0).	Low
Hospitalization (Cardiac related)	Exercise ECG vs. nuclear MPI	1 observational study (N=193,406 Medicare)	Outpatient	Similar very low frequency of hospitalization for acute MI through 6 months (0.32% vs. 0.43%). Definitive conclusions are not possible.†	Insufficient
	Stress echo vs. exercise ECG	1 observational study (N=141,667 Medicare)	Outpatient	Similar very low frequency of hospitalization for acute MI through 6 months (0.32% in both groups). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. nuclear MPI	1 observational study (N=212,947 Medicare)	Outpatient	Hospitalization for acute MI through 6 months was similar between groups although the difference was statistically significant (0.32% vs. 0.43%, adjusted OR 0.83, 95% CI 0.70 to 0.98). Definitive conclusions are not possible.†	Insufficient

CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; ECG = electrocardiography; ICA = invasive coronary angiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; NS = not statistically significant; OR = odds ratio; PCI = percutaneous intervention; RCT = randomized controlled trial; RD = risk difference; SPECT = single-photon emission computed tomography

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Definitive conclusions are not possible because of study limitations and/or imprecision in observational studies or lack of data in RCTs.

Anatomic Tests Versus Functional Tests

CCTA Versus Exercise ECG

Two fair-quality studies, one RCT[82] and one retrospective database study,[102] compared CCTA with exercise ECG in patients with mixed pretest risk (see Appendix E and G for details).

In the trial, patients with low (43%), intermediate (23%), and high (34%) pretest risk (defined as <30%, 30%–60%, and >60% according to Diamond and Forrester) presented with stable chest pain to two EDs in Northern Ireland.[82] Patients were randomized to either 64-slice CCTA with contrast (n=243) or exercise ECG testing using the Bruce protocol (n=245). Both groups were similar in terms of mean age (58 years), presenting symptoms, and all patients reported cardiac risk factors. However, more women received CCTA compared with exercise ECG (47% vs. 39%). Outcomes were reported at 3 and 12 months and 97.6 percent of patients completed final followup. This trial received funding from the South Eastern Health and Social Care Trust and the Northern Ireland Cardiovascular Network. Methodological shortcoming included no statement of concealed allocation and lack of clear blinding of outcome assessors.

A large administrative database study was conducted using a 20 percent random sample of Medicare claim records from 2006 to 2008 (N=282,830). Patients could receive one of four tests including CCTA (n=8820) and exercise ECG (n=61,063) and the followup period was 6 months.[102] Pretest CAD risk and other baseline risk scores were not reported. Included claims were limited to those in an outpatient setting for patients aged 66 years or older; no patient had a history of known CAD (within the previous 9 months) or prior MI or revascularization (within the previous 12 months). This study was designed to evaluate CCTA, but the data provided allowed some comparisons across the other tests. No test details were reported. Only CPT codes that included both CCTA and stress (exercise and pharmacological) ECG were provided regarding how a test was chosen for a given patient. Mean age was similar in both groups (73 years) and a higher percentage of women had undergone CCTA (55.8% vs. 49.0%). Cardiac risk factors were more prevalent in the CCTA compared with the ECG group: hypertension (65.5% vs. 57.5%), hyperlipidemia (72.1% vs. 65.1%), and diabetes (30.0% vs. 25.0%). This study was funded by the American Heart Association. Methodological limitations included lack of blinded outcomes assessment and significant baseline differences between groups.

Clinical Outcomes

In the trial, no difference was found in all-cause mortality between groups through 12 months (0.4% vs. 0.4%) and no patients died of cardiac-related events.[82] Similarly, there was no difference in the incidence of MI (0.41% vs. 0.82%, RD -0.4, 94% CI -1.8 to 1.0 per 100 people) or acute coronary syndrome (0.41% vs. 1.2%, RD -0.8, 95% CI -2 to 0.8 per 100 people). Hospitalization for cardiac causes occurred significantly less frequently in the CCTA group (0.8% vs. 6.9%, RD -6.1, 95% CI -9.5 to -2.7 per 100 people) through 12 months. In the Medicare claims study, 6-month all-cause mortality was similar between groups, although the results were statistically significant (1.05% vs. 0.78%; RR 1.3, 95% CI 1.08 to 1.68). Risk of hospitalization for MI was reduced in the CCTA group compared with the exercise ECG group (0.19% vs. 0.32%, unadjusted RR 0.60, 95% CI 0.37 to 0.99).[102]

In the RCT, using the Seattle Angina Questionnaire, quality of life improved slightly more from baseline in the CCTA group versus the exercise ECG group at 3 (difference between groups: -5.7, p=0.014) and 12 months (difference between groups: -4.8; p=0.041). Using the same tool, patient assessment of angina stability was also improved more in the CCTA group at

3 (difference between groups: -11.1; p=0.001) and 12 months (difference between groups: -6.8; p=0.028). Frequencies of angina symptoms were similar between groups at both timepoints.[82]

Clinical Management

The trial of ED patients reported that through 12 months, CCTA was associated with a greater frequency of ICA referral compared with exercise ECG (27.2% vs. 20.8%, RD 6.3, 95% CI -1.2 to 13.9 per 100 people, p=0.1011), though the result did not achieve statistical significance.[82] During this period, more patients underwent revascularization following testing with CCTA compared with exercise ECG (15.2% vs. 7.7%, RD 7.5, 95% CI 1.9 to 13.0 per 100 people), including PCI (12% vs. 5%, RD 7, 95% CI 2 to 12 per 100 people), and referral for CABG was similar between groups (3.3% vs. 2.9%, RD 0.00, 95% CI -0.03 to 0.04 per 100 people). CCTA resulted in significantly fewer additional noninvasive cardiac tests through 12 months (2.4% vs. 31.3%, RD -29, 95% CI -37 to -23 per 100 people). More patients assigned to CCTA received medical therapy (40.7% vs. 14.3%, RD 26, 95% CI 19 to 34 per 100 people) and fewer received no intervention (44% vs. 78%; RD -0.37, 95% CI -0.45 to -0.29) compared with the exercise ECG group. However, the CCTA group had fewer revisits for chest pain (3.3% vs.13.1%; RD -0.10, 95% CI -0.15 to -0.05) and fewer days in the hospital for chest pain (mean 7 vs. 56 days) than exercise ECG.

The database study of Medicare outpatients found that CCTA was associated with higher referral rates for ICA through 6 months (22.9% vs. 9.0%, unadjusted RR 2.5, 95% CI 2.4 to 2.7) as well as higher rates of revascularization (11% vs. 4.3%, unadjusted RR 2.65, 95% CI 2.47 to 2.84). Similarly, the study found increased referral for PCI with CCTA compared with exercise ECG through 6 months (7.9% vs. 2.6%, unadjusted RR 3.05, 95% CI 2.80 to 3.33) but there was only a small difference between groups in the risk for CABG (3.7% vs. 1.8%, unadjusted RR 2.04, 95% CI 1.80 to 2.30). There was less additional noninvasive testing in CCTA patients through 6 months (5% vs. 19%; unadjusted RR 0.26, 95% CI 0.23 to 0.28), driven by a significantly lower referral rate for MPI (2.7% vs. 16.5%, unadjusted RR 0.17, 95% CI 0.15 to 0.19, respectively).[102]

Harms of Index Test and Consequences of Testing

In the RCT of mixed risk-level patients comparing CCTA and exercise ECG testing, there was only a statement of no complications associated with any investigation.[82]

Harms of Additional Testing

Not reported by either study.

Differential Effectiveness or Safety in Subgroups

No analyses related to differential effectiveness or safety of CCTA versus exercise ECG with regard to patient characteristics or other factors were provided in either study, however the database study included only Medicare patients.

CCTA Versus SPECT

Two observational studies, one fair quality[97] and one poor quality,[104] compared CCTA to SPECT but did not report or stratify results by pretest risk of CAD (see Appendix E and G for details).[97,104] Min et al. 2008 compared CCTA (n=1,938) to SPECT (n=7,752) in an administrative database study using records dated January through March 2006 from a large private United States claims database where SPECT patients were matched to CCTA patients.[97]

Pretest CAD risk and other baseline risk scores were not reported. Outcomes were reported at 9 months. Tandon et al. 2012 reported 6-month results from a prospective registry study of 2,442 patients (University of Ottawa Heart Institute Cardiac CT Registry); 1,221 consecutive CCTA patients were enrolled between 2006 and 2009 and matched to 1,221 SPECT patients from the same time period.[104] Overall, the median pretest CAD risk in this population was 12.3 (scale not reported) and the Morise score was a mean 10.7 ± 3.0. The number of sites and the setting was not reported in either study, and the database study was conducted in the United States and the registry study in Canada. Funding for the database study came from a GE Healthcare grant; the registry study received support from the Ontario Research Fund and the Canada Foundation for Innovation. The database study did not report any test details.[97] The registry study used 64-slice CCTA with contrast and rest-stress SPECT employed exercise or pharmacological stress (percentage of each not reported).[104] The database study considered patients with no history of CAD recorded in the 9 months prior to testing and the registry study enrolled patients with no history of CAD or revascularization. Except slightly more CCTA patients having baseline dyslipidemia (47.4% vs. 38.7%) in the registry study,[97] CCTA and SPECT groups were comparable in all baseline characteristics reported; this is likely a consequence of the patient-matching process during enrollment. Methodological limitations included lack of blinded outcomes assessment, unclear attrition, and lack of controlling for confounding of baseline differences between groups in dyslipidemia in the registry study.

Clinical Outcomes

In the registry study, 0.2 percent of CCTA patients died of cardiac causes during the followup period, but mortality rates in the SPECT group were not reported.[104] The database study reported similar 9-month risk of MI in both CCTA and SPECT groups (0.4% vs. 0.6%),[97] and the registry study reported MI in 0.5 percent of CCTA patients during 6-month followup, but again did not report data for the SPECT group.[104] The database study found the 9-month risk of hospitalization for cardiovascular causes was similar in the CCTA and SPECT patients (4.2% vs. 4.1%), although the length of stay was significantly shorter in the CCTA group (4.5 ± 4.1 vs. 7.4 ± 13.3 days, mean difference -2.9, 95% CI -3.5 to 2.3).[97] The database study also found no difference between groups in the risk of new-onset angina through 9 months (3.0% vs. 3.5%).[97]

Clinical Management

The database study reported that fewer CCTA patients underwent ICA within the 9-month followup period compared with SPECT patients (6.2% vs. 9.5%, OR 1.61, 95% CI 1.32 to 1.97),[97] while the registry found no difference between groups (10.6% vs. 10.2%) through 6 months.[104] In the latter study, however, ICA results showed significantly fewer false positives (i.e., no obstructive CAD) in patients that received CCTA as the index test (9.7% vs. 25.8%). Although there was no difference between CCTA and SPECT groups in the database study in the 9-month risk of additional CCTA testing (0.8% vs. 0.7%), CCTA patients were more likely to undergo additional SPECT (7.5% vs. 1.4%, OR 0.17, 95% CI 0.13 to 0.22).[97] The registry did not report additional noninvasive testing.[104] Both studies found no difference between CCTA and SPECT groups in the need for subsequent revascularization, including PCI and CABG, during the followup periods.[97,104] The database study reported similar CAD-specific medication use between groups; there was also no difference in the percentage of patients who attended cardiovascular outpatient visits during the 9-month followup period.[97]

Harms of Index Test and Consequences of Testing

Radiation exposure was significantly greater following index CCTA compared with SPECT in one registry study (median, IQR 14.9 [13.1 to 17.1] vs. 10.5 [10.1 to 11.4] mSv, p<0.001).[104]

Harms of Additional Testing

Radiation exposure from subsequent invasive coronary angiography was also significantly greater in patients who underwent CCTA versus SPECT in one registry study (median, IQR 15.2 [12.7 to 17.1] [n=129] vs. 10.8 [10.2 to 11.7] [n=125] mSv, p<0.001).[104]

Differential Effectiveness or Safety in Subgroups

No analyses related to differential effectiveness or safety of CCTA versus SPECT with regard to patient characteristics or other factors were provided in either study.[97,104]

CCTA Versus Nuclear MPI

Two fair-quality observational studies compared CCTA to MPI (SPECT or PET) (see Appendix E and G for details).[102,105] Shreibati et al. conducted a large administrative database study using a 20 percent random sample of Medicare claim records from 2006 to 2008 (N=282,830). Patients could receive one of four tests including CCTA (n=8820) and MPI (n=132,343).[102] The database study was limited to claims in an outpatient setting for patients ages 66 years or older and patients did not have a history of known CAD (within the previous 9 months) or prior MI or revascularization (within the previous 12 months). Yamauchi et al. reported data from a prospective observational study conducted across 81 centers in Japan in which patients could receive CCTA (n=635), MPI (n=1221), or ICA (not included in this report). The setting was not reported.[105] The database study reported 6-month outcomes,[102] while the prospective study reported outcomes for 96.6 percent of patients at a median followup of 17.0 ± 5.9 months.[105] In general, no test details were reported in either study. Both studies employed MPI and Shrebati et al. specified a number of CPT codes that included both SPECT and PET.[102] Yamauchi et al. did not indicate which types of imaging constituted MPI[105] and an assumption was made by the authors of this report that both SPECT and PET were likely to have been used. No information was provided regarding how a test was chosen for a given patient in the database study;[102] in the prospective nonrandomized study the test was selected at the discretion of the physician.[105] In the database study, CCTA patients were slightly younger than MPI patients (mean age 73.56 vs. 75.71 years, p<0.001), had fewer risk factors and comorbidities, and outcomes were adjusted for confounding baseline variables. Females comprised 54.6 percent of the population, and pretest CAD risk (or other baseline risk score) was not reported.[102] Those in the prospective nonrandomized study population had a mean age of 66 years, and 44.5 percent were female. Patients tested with CCTA group were less likely than those who received MPI to have milder symptoms (New York Heart Association class I [80.6% vs. 91.9%]; and Canadian Cardiovascular Society class I [61.8% vs. 77.9%]).[105] The database study was funded by the American Heart Association and the prospective observational study did not report its source of funding. Methodological limitations included lack of blinded outcomes assessment and significant baseline differences between groups.

Clinical Outcomes

In the database study, the 6-month risk of death from any cause was similar between CCTA and MPI groups (1.05% vs. 1.28%, adjusted OR 1.11, 95% CI 0.88 to 1.38). The same study reported a slightly lower 6-month risk of acute MI hospitalization in the CCTA group (0.19% vs.

0.43%, adjusted OR 0.60, 95% CI 0.37 to 0.98).[102] The prospective observational study found no difference between CCTA and MPI groups in the median 17-month risk of the composite major adverse cardiac event (e.g., death, acute MI, major cardiac event, or late [>3 months] revascularization) (2.1% vs. 2.6%, crude RR 0.81, 95% CI 0.43 to 1.53).[105] Clinical outcomes for test-positive versus test-negative patients were not reported.

Clinical Management

While the database study reported higher 6-month ICA referral rates following CCTA compared with MPI (22.94% vs. 12.13%, adjusted OR 2.19, 95% CI 2.08 to 2.32 [MPI as reference group]),[102] the prospective observational study found no difference between the two groups through a median of 17 months of followup (31% vs. 33%).[105] In the database study, any additional noninvasive testing through 6 months was more common in CCTA than MPI patients (4.98% vs. 3.22%, adjusted OR 1.52, 95% CI 1.37 to 1.69, MPI as reference group); this difference was statistically significant for all types of noninvasive tests employed (MPI, stress echocardiography, exercise ECG) except CCTA.[102] The prospective observational study reported similar trends, with any additional test (including ICA) being performed in more CCTA than MPI patients (40% vs. 35%, crude RR 1.14, 95% CI 1.01 to 1.29) through a median of 17 months of followup.[105] The database study found that the need for any revascularization was higher in CCTA patients (11.41% vs. 4.59%, adjusted OR 2.76, 95% CI 2.56 to 2.98 [MPI as reference group]) through 6 months; this trend held true for both PCI (7.85% vs. 3.37%, adjusted OR 2.49, 95% CI 2.28 to 2.72) and CABG (3.71% vs. 1.29%, adjusted OR 3.00, 95% CI 2.63 to 3.42 [MPI as reference group]).[102] In the database study, not only did more CCTA patients undergo ICA, they were more likely to receive revascularization following ICA than MPI patients (48.79% vs. 37.53%, adjusted OR 1.56, 95% CI 1.41 to 1.73 [MPI as reference group], $p<0.001$).[102] The prospective observational study similarly reported a higher risk of any revascularization in the CCTA group (percentages not reported, adjusted OR 1.62, 95% CI 1.20 to 2.18) through a median of 17 months of followup.[105]

Harms of Index Test

There was no difference in the risk of adverse events during the test between CCTA and MPI patients (0.5% vs. 0.9%), as reported by one observational study.[105] No additional details were provided.

Harms of Additional Testing

No harms of additional testing were reported in either of the two studies.

Differential Effectiveness or Safety in Subgroups

Although no formal test for interaction was performed, the database study[102] found that the unadjusted 6-month risk of catheterization and revascularization (evaluated separately) were significantly higher in CCTA patients than MPI patients across all subgroups tested, including age (stratified into four groups: 66-69 years, 70-74 years, 75-79 years, and 80-84 years), sex, race (African-American, Caucasian), hypertension, hyperlipidemia, diabetes, tobacco use, Medicaid, year of index test, and referral region.

CCTA Versus Stress Echocardiography

One large, fair-quality administrative database study was identified (see Appendix E and G for details). This study analyzed a 20 percent random sample of Medicare claim records from

2006 to 2008 (N=282,830) and patients could receive one of four tests including CCTA (n=8820) and stress echocardiography (n=80,604). The followup period was 6 months.[102] Pretest CAD risk and other baseline risk scores were not reported. Included claims were limited to those in an outpatient setting for patients ages 66 years or older. No patient had a history of known CAD (within the previous 9 months) or prior MI or revascularization (within the previous 12 months). No test details were reported to include information regarding how a test was chosen for a given patient; only CPT codes that included both CCTA and stress echocardiography were provided. Mean age was similar in both groups (74 years) as was sex (CCTA 56% vs. echocardiography 58% female). Cardiac risk factors were more prevalent in the CCTA compared with the echocardiography group: hypertension (65.5% vs. 60.2%), hyperlipidemia (72.1% vs. 64.6%), and diabetes (29.9% vs. 26.4%). This study was funded by the American Heart Association. Methodological limitations included lack of blinded outcomes assessment and significant baseline differences between groups.

Clinical Outcomes

The 6-month risk of death from any cause was similar between CCTA and stress echocardiography (1.05% vs. 0.95%, unadjusted RR 1.11, 95% CI 0.90 to 1.38), as was the risk of hospitalization for acute MI (0.19% vs. 0.32%, unadjusted RR 0.61, 95% CI 0.37 to 1.00). Clinical outcomes for test-positive versus test-negative patients were not reported.

Clinical Management

Significantly higher 6-month ICA referral rates were reported following CCTA compared with stress echocardiography (22.94% vs. 9.50%, unadjusted RR 2.41, 95% CI 2.31 to 2.52). Any additional noninvasive testing through 6 months was similar between groups, respectively (4.98% vs. 5.57%, unadjusted RR 0.89, 95% CI 0.81 to 0.98), but statistically meaningful; this held true for all types of noninvasive tests employed (e.g., CCTA, MPI, stress echocardiography, and exercise ECG). The need for any revascularization through 6 months was significantly greater following CCTA compared with echocardiography (11.41% vs. 4.22%, respectively; unadjusted RR 2.70, 95% CI 2.53 to 2.89); this trend held true for both PCI (7.85% vs. 2.61%, unadjusted RR 3.01, 95% CI 2.77 to 3.27) and CABG (3.71% vs. 1.69%, unadjusted RR 2.19, 95% CI 1.94 to 2.47). Not only were patients who received CCTA significantly more likely to undergo ICA, they also slightly more likely to receive revascularization following ICA compared with exercise ECG patients (48.79% vs. 43.65%, unadjusted RR 1.12, 95% CI 1.06 to 1.18).

Harms of Index Test and Consequences of Testing and Harms of Additional Testing

No harms related to either the index or additional testing were reported.

Differential Effectiveness or Safety in Subgroups

No analyses related to differential effectiveness or safety of nuclear MPI and exercise ECG with regard to patient characteristics or other factors were provided, however the database study focused on Medicare beneficiaries (age ≥ 66 years).

Noncomparative Studies: Anatomical

Calcium Scoring

One noncomparative study of calcium scoring in patients with an unclear pretest risk reported on predictive accuracy.[124] Calcium scoring was performed via nonenhanced electron beam computed tomography; a score of ≥1.4 was considered a positive test result and a score of <1.4 was considered a negative test result. A total of 255 patients were analyzed with a mean age of 58 ± 11 years; the proportion of males and females and relevant cardiac risk factors were not reported. Over a mean followup period of 42 months, the frequency of major adverse cardiac events was significantly higher in those who had a positive compared with a negative result: 20 versus 2 per 100 people (see Appendix F for details).

Two additional studies were identified in our patient population that reported incidental findings at the time of index testing. One study reported incidental findings in 80 (7.8%) of the 1,031 patients who underwent calcium scoring via multidetector CT at the time of SPECT in a single ED.[98] Findings included pulmonary nodules or mediastinal/hilar calcifications (n=11), pleural effusions or pulmonary infiltrates (n=7), dilated aorta (n=28), pericardial thickening or effusion (n=16), hiatal hernia (n=7), liver cysts (n=2), valvular calcifications (n=8), and abnormal venous anatomy (n=1). No information was provided about subsequent treatment. In the second study, major noncardiac abnormal findings on CCTA (plus calcium scoring) included pulmonary embolism (n=86), acute aortic syndromes (n=13), malignancy (n=6), pneumonia (n=35), advanced emphysema (n=1), and large pericardial (n=15) or pleural (n=22) effusion; these patients were subsequently excluded from analysis because of concerns regarding the effect on immediate patient care or short- or long-term prognosis.[99] Nonacute findings (e.g. lung nodules <8 mm, subsegmental atelectasis, bronchial wall thickening, or hiatal hernia) did not preclude exclusion in the study, however the authors did not report if or how many of these findings were present in their population (N=458).

Noncomparative Studies: Functional

Stress Echocardiography

Two noncomparative studies of stress echocardiography in patients with unknown pretest risk reported on predictive accuracy. Both studies were conducted in an outpatient setting and employed treadmill exercise stress. One study enrolled a high number of patients with known CAD but only the outcomes for the subgroup of patients without known CAD are presented here (n=211).[121] The second study enrolled only women and 18 percent of the population had known CAD (N=405).[117] Mean ages were 62 and 56 years. Cardiac risk factors were reported variably across studies. In the study conducted in women only, the frequency of any cardiac events was 31 versus 4 per 100 people over a mean of 41 months (OR 9.8, 95% CI 4.4 to 21.9; and for cardiac death: OR 13.6, 95% CI 4.5 to 42). In the second study, the frequency of any cardiac event and MI at 12 months was 32 versus 7 per 100 people and 9 versus 1 per 100 people, respectively; there were no deaths reported in either group (see Appendix F for details).

Stress ECG

Two noncomparative studies of stress ECG in patients with unknown pretest risk reported on predictive accuracy. One study (N=132) was conducted in elderly patients (mean age 71 years) hospitalized for cardiac events associated with suspected CAD, and utilized bicycle exercise or

dipyridamole stress.[115] The second study was conducted in an outpatient setting, enrolled women only (mean age 56 years), and employed treadmill exercise (N=405).[117] The latter study also excluded patients with early revascularization to control for test-driven events. In the study that enrolled women only, a positive test, compared with a negative test, was associated with a significantly greater risk of any cardiac event over a mean 41 months of followup (15 vs. 5 per 100 people; OR 3.1, 95% CI 1.2 to 7.9) but not with the risk of cardiac-related death (OR 1.6, 95% CI 0.3 to 8.8). In the study enrolling only elderly patients, the frequency of any cardiac event was higher in test-positive compared with test-negative patients (40 vs. 22 per 100 people); the rate in the positive group was driven by a high occurrence of hospitalization for revascularization. Conversely, the frequency of reported MI was less in those with positive results (3 vs. 14 per 100 people) and frequency of mortality was the same between groups (7 per 100 people) (see Appendix F for details).

Table 15. Summary of findings and strength of evidence: Mixed pretest risk—anatomical versus functional testing

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	CCTA vs. exercise ECG	1 RCT (N=500)	ED	There is low-strength evidence that no difference was found in all-cause mortality between groups through 12 months (0.4% in both groups).	Low
	CCTA vs. exercise ECG	1 observational study (N=69,883 Medicare)	Outpatient	Through 6 months, mortality was similar between groups although the results were statistically significant (1.05% vs. 0.78%, unadjusted RR 1.3, 95% CI 1.08 to 1.68). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. SPECT	1 observational study (N=9690)	NR	The 9-month risk of MI was similar in both groups (0.4% vs. 0.6%). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. nuclear MPI	1 observational study (N=141,163 Medicare)	Outpatient	No difference between groups through 6 months (1.05% vs. 1.28%, adjusted OR 1.11, 95% CI 0.88 to 1.38).	Low
	CCTA vs. stress echocardiography	1 observational study (N=89,424 Medicare)	Outpatient	6-month mortality was similar between groups (0.95% vs. 1.05%, unadjusted RR 1.1 95% CI 0.9 to 1.4). Definitive conclusions are not possible.†	Insufficient
Myocardial Infarction	CCTA vs. exercise ECG	1 RCT (N=500)	ED	There is low-strength evidence that no difference was found through 12 months in the incidence of MI between groups (0.41% vs. 0.82%, RD -0.4, 94% CI -1.8 to 1.0 per 100 people).	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Invasive Coronary Angiography Referral	CCTA vs. exercise ECG	1 RCT (N=500)	ED	CCTA was associated with higher referral rates for ICA through 12 months, though the difference was not statistically significant (27.2% vs. 20.8%; RD 6.3, 95% CI -1.2 to 13.9 per 100 people, p=0.1011).	Low
	CCTA vs. exercise ECG	1 observational study (N=69,883 Medicare)	Outpatient	CCTA was associated with higher referral rates for ICA through 6 months (22.9% vs. 9.0%, unadjusted RR 2.5, 95% CI 2.4 to 2.7). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. SPECT	2 observational studies (N=12,132)	NR	Results were inconsistent between studies, with one reporting that ICA was less common in CCTA patients through 9 months (6.2% vs. 9.5%, OR 1.61, 95% CI 1.32 to 1.97), while the other study found no difference between groups (10.6% vs. 10.2%) through 6 months. Definitive conclusions are not possible.†	Insufficient
	CCTA vs. nuclear MPI	1 observational study (N=1856)	NR	Groups were similar regarding ICA referral through a median of 1.42 years followup (31% vs. 33%). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. nuclear MPI	1 observational study (N=141,163 Medicare)	Outpatient	Higher 6-month ICA referral following CCTA compared with MPI was reported (22.94% vs. 12.13%, adjusted OR 2.19, 95% CI 2.08 to 2.32).	Low
	CCTA vs. stress echocardiography	1 observational study (N=89,424 Medicare)	Outpatient	ICA was more common following CCTA through 6 months (22.9% vs. 9.5%, unadjusted RR 2.4, 95% CI 2.3 to 2.5). Definitive conclusions are not possible.†	Insufficient

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Revascularization	CCTA vs. exercise ECG	1 RCT (N=500)	ED	Through 12 months there was greater risk of revascularization with CCTA compared with exercise ECG (15.2% vs. 7.7%, RD 7.5, 95% CI 1.9 to 13.0 per 100 people).	Low
	CCTA vs. exercise ECG	1 observational study (N=69,883 Medicare)	Outpatient	CCTA was associated with more revascularization procedures through 6 months (11% vs. 4.3%, unadjusted RR 2.65, 95% CI 2.47 to 2.84). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. SPECT	2 observational studies (N=12,132)	NR	CCTA and SPECT groups were similar regarding subsequent revascularization (2.1%–6.2% vs. 1.6%–5.9%) during 6 to 9 months followup. Definitive conclusions are not possible.†	Insufficient
	CCTA vs. nuclear MPI	1 observational study (N=1856)	NR	Revascularization was more common following CCTA than SPECT through a median of 1.42 years (% NR, adjusted OR 1.62, 95% CI 1.20 to 2.18).	Low
	CCTA vs. nuclear MPI	1 observational (N=141,163 Medicare)	Outpatient	Revascularization was higher in CCTA than MPI at 6 months (11.41% vs. 4.59%, adjusted OR 2.76, 95% CI 2.56 to 2.98).	Low
	CCTA vs. stress echocardiography	1 observational study (N=89,424 Medicare)	Outpatient	Revascularization was more common in the 6 months following CCTA compared with stress echocardiography (11.4% vs. 4.2%, unadjusted RR 2.7, 95% CI 2.5 to 2.9). Definitive conclusions are not possible.†	Insufficient

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Percutaneous Coronary Intervention	CCTA vs. exercise ECG	1 RCT (N=500)	ED	CCTA was associated with a significantly higher risk of PCI through 12 months (11.9% vs. 4.9%, RD 7, 95% CI 2 to 12 per 100 people).	Low
	CCTA vs. exercise ECG	1 observational study (N=69,883 Medicare)	Outpatient	Through 6 months, CCTA patients had more PCI procedures (7.9% vs. 2.6%, unadjusted RR 3.05, 95% CI 2.80 to 3.33). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. SPECT	2 observational studies (N=12,132)	NR	Both studies found no difference between CCTA and SPECT groups in the frequency of PCI (0.1%–3.9% vs. 0.1%–4.0%) during 6 to 9 months followup. Definitive conclusions are not possible.†	Insufficient
	CCTA vs. nuclear MPI	1 observational study (N=141,163 Medicare)	Outpatient	PCI rates were higher in CCTA patients through 6 months followup (7.85% vs. 3.37%, adjusted OR 2.49, 95% CI 2.28 to 2.72).	Low
	CCTA vs. stress echocardiography	1 observational study (N=89,424 Medicare)	Outpatient	By 6 months, PCI was more common in the CCTA group (7.85% vs. 2.61%, unadjusted RR 3.01 95% CI 95% CI 2.77 to 3.27). Definitive conclusions are not possible.†	Insufficient
Coronary Artery Bypass Graft	CCTA vs. exercise ECG	1 RCT (N=500)	ED	Through 12 months, there was no difference between groups in CABG (3.3% vs. 2.9%, RD 0.00, 95% CI -0.03 to 0.04 per 100 people).	Low
	CCTA vs. exercise ECG	1 observational study (N=69,883 Medicare)	Outpatient	There was only a small difference between groups in the risk for CABG through 6 months (3.7% vs. 1.8%; unadjusted RR 2.04 95% CI 1.80 to 2.30). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. SPECT	2 observational studies (N=12,132)	NR	Both studies found no difference between CCTA and SPECT groups in the need for CABG (0.7%–2.3% vs. 0.5%–1.9%) during 6 to 9 months followup. Definitive conclusions are not possible.†	Insufficient
	CCTA vs. nuclear MPI	1 observational study (N=141,163 Medicare)	Outpatient	CABG was more common in CCTA patients through 6 months followup (3.71% vs. 1.29%, adjusted OR 3.00, 95% CI 2.63 to 3.42).	Low
	CCTA vs. stress echocardiography	1 observational study (N=89,424 Medicare)	Outpatient	By 6 months, CABG had been performed somewhat more frequently in the CCTA group (3.71% vs. 1.69%, unadjusted RR 2.19, 95% CI 1.94 to 2.47). Definitive conclusions are not possible.†	Insufficient

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Additional Testing	CCTA vs. exercise ECG	1 RCT (N=500)	ED	CCTA resulted in fewer additional noninvasive cardiac tests through 12 months (2.4% vs. 31.3%, RD -29, 95% CI -37 to -23 per 100 people).	Moderate
	CCTA vs. exercise ECG	1 observational study (N=69,883 Medicare)	Outpatient	There was less additional noninvasive testing in CCTA patients through 6 months (5% vs. 19%; unadjusted RR 0.26, 95% CI 0.23 to 0.28). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. SPECT	2 observational studies (N=12,132)	NR	Results were inconsistent between studies, with one study showing no difference between groups in the 9-month risk of additional testing (0.8% vs. 0.7%), and the other study showing that CCTA patients were more likely to undergo additional testing through 6 months (7.5% vs. 1.4%, OR 0.17, 95% CI 0.13 to 0.22). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. nuclear MPI	1 observational study (N=141,163 Medicare)	Outpatient	Any additional noninvasive testing through 6 months was more common in CCTA than MPI patients (4.98% vs. 3.22%, adjusted OR 1.52, 95% CI 1.37 to 1.69).	Low
	CCTA vs. stress echocardiography	1 observational study (N=89,424 Medicare)	Outpatient	Additional noninvasive testing through 6 months was similar between groups, although the difference was statistically significant (4.98% vs. 5.57%, unadjusted RR 0.89, 95% CI 0.81 to 0.98). Definitive conclusions are not possible.†	Insufficient

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Hospitalization (Cardiac related)	CCTA vs. exercise ECG	1 RCT (N=500)	ED	Hospitalization for cardiac causes occurred less frequently in the CCTA group (0.8% vs. 6.9%, RD -6.1, 95% CI -9.5 to -2.7 per 100 people) through 12 months.	Moderate
	CCTA vs. exercise ECG	1 observational study (N=69,883 Medicare)	Outpatient	Through 6 months, hospitalization for acute MI occurred at a similar rate across groups although the results were statistically significant (0.19% vs. 0.32%, unadjusted RR 0.60, 95% CI 0.37 to 0.99). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. SPECT	1 observational study (N=9690)	NR	The 9-month rate of hospitalization for cardiovascular causes was similar in the CCTA and SPECT patients (4.2% vs. 4.1%). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. nuclear MPI	1 observational study (N=141,163 Medicare)	Outpatient	Hospitalization for acute MI through 6 months was similar between groups, though the results were statistically significant (0.19% vs. 0.43%, adjusted OR 0.60, 95% CI 0.37 to 0.98). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. stress echocardiography	1 observational study (N=89,424 Medicare)	Outpatient	Through 6 months, hospitalization for acute MI slightly was similar between groups (0.19% vs. 0.32%, unadjusted RR 0.61, 95% CI 0.37 to 1.0). Definitive conclusions are not possible.†	Insufficient
Harms of Index Test	CCTA vs. exercise ECG	1 RCT (N=500)	ED	There were no complications associated with either test (specifics not reported). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. nuclear MPI	1 observational study (N=1856)	NR	There was no difference in the risk of adverse events during the test between CCTA and MPI patients (0.5% vs. 0.9%); no other details were reported. Definitive conclusions are not possible.†	Insufficient

CABG = coronary artery bypass graft; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ED = emergency department; ICA = invasive coronary angiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; NS = not statistically significant; OR = odds ratio; PCI = percutaneous intervention; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SPECT = single-photon emission computed tomography

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Definitive conclusions are not possible because of study limitations and/or imprecision in observational studies or lack of data in RCTs.

Discussion

Key Findings and Strength of Evidence

Evidence to determine the comparative effectiveness and safety of different noninvasive testing strategies for coronary artery disease (CAD) is limited. While there is a robust body of literature on the diagnostic performance of these tests based on traditional measures of test accuracy (e.g., sensitivity, specificity), only a small number of studies were identified that evaluated the impact of noninvasive testing on clinical outcomes measures in the population of interest for this report. The key findings and strength of evidence for the outcomes identified as being most clinically important are summarized in Tables 8–15 in the Results section; factors used to determine the overall strength of evidence are summarized in Appendix J.

A total of 24 comparative studies that evaluated the impact of noninvasive testing on clinical outcomes and/or clinical management outcomes in the population of interest for this report formed the basis of this review: 14 randomized controlled trials (RCTs) (2 good quality, 9 fair quality, and 3 poor quality)[75-88] and 10 comparative observational studies (7 fair quality and 3 poor quality).[90,92-97,100,102,104-107] Common methodological shortcomings in the RCTs include unclear description of randomization sequence and/or test allocation and lack of blinded outcomes assessment. In the observational studies, lack of controlling for confounding and/or blinding of outcomes assessment were common methodological shortcomings. The comparative studies served as the basis of the report and were stratified based on pretest risk, test type (anatomic or functional), and setting. For most outcomes reported in trials, the strength of evidence was rated as low (meaning that our confidence in the estimates of effect is low) based on concerns related to precision and study limitations. However, for some outcomes reported by trials, the strength of evidence was found to be moderate or high. For the majority of outcomes reported by comparative observational studies, the strength of evidence was found to be insufficient because of study limitations, although some outcomes were graded as low strength of evidence when the estimates were considered to be at low risk for imprecision and confounding was controlled. Eight RCTs and one observational study were conducted in emergency department (ED) settings or specialized chest pain clinics[82] and compared coronary computed tomography (CCTA) with functional testing[77-79,82] or usual care.[75,80,81,83,92,94] In these studies, most of the available data were reported for the index ED visit, and with the exception of two trials reporting 12-month followup, the maximum followup in ED studies was 6 months. The remaining 5 trials[76,84-87] and 13 comparative observational studies were conducted in outpatient, various, or unspecified settings; in general, these studies had longer followup periods, which ranged from a mean of 55 days to 30 months. Pretest risk could not be standardized across studies and was variably determined and defined across studies. Thus, categories of pretest risk used here are based on how the study authors defined risk.

Clinical Outcomes

There was no clear difference in myocardial infarction (MI) or in all-cause mortality between different testing strategies across settings and pretest risk groups that included patients with intermediate pretest risk based on low- to moderate-strength evidence from eight trials. The definition of intermediate pretest risk was broad. The frequency of all-cause mortality was low across studies in all settings. In trials enrolling outpatients, the frequency of all-cause mortality ranged from 0 to 1.5 percent for a variety of noninvasive testing strategies and the frequency in

trials in the ED setting past the initial index visit ranged from 0 to 1.08 percent, across a variety of noninvasive testing or usual-care strategies, with no statistical difference between any groups. Similarly, the frequency of MI was low, ranging from 0 to 0.8 percent (up to median of 25 months) in outpatient settings and 0 to 3 percent (up to 12 months) in ED settings, with no statistical differences between groups. The strongest evidence came from three trials: one that compared CCTA with functional testing in an outpatient setting[76] and two that compared CCTA with single photon emission computed tomography (SPECT) in an ED setting.[77,78] For the trial of CCTA versus functional testing, which was also the largest trial (N=10,003), there were no differences in all-cause mortality between groups through 12 months (0.42% vs. 0.64%) or at a median of 25 months followup (1.48% vs. 1.50%) or in nonfatal MI at 12 months (0.36% vs. 0.54%, risk difference [RD] -0.18, 95% confidence interval [CI] -0.44 to 0.08 per 100 people) or at a median of 25 months followup (0.60% vs. 0.80%, RD -0.20, 95% CI -0.53 to 0.13 per 100 people)[76] (moderate strength of evidence for both outcomes). Across the two trials comparing CCTA with SPECT in an ED setting, there was low-strength evidence that no difference was found between tests for mortality or MI; there were no deaths or MIs reported through a mean of 6 months past the initial ED visit.[77,78] Across the remaining trials, no difference was found between tests because of lack of precision and study limitations (low strength of evidence). Higher-quality observational studies (i.e., those that controlled for confounding) supported these findings. No conclusions can be drawn regarding the impact of testing on clinical outcomes for patients at low risk or high risk (without ECG changes or troponin elevation or other characteristics of acute coronary syndrome [ACS]), as only subanalyses of fewer than 100 patients were available.

Several factors may have contributed to finding no statistical differences between tests on clinical outcomes. Given the low incidence of mortality and MI in the studies previously noted, sample sizes in even the largest trials may have been too small to detect differences between tests. The low incidence of mortality and MI suggests that study populations may generally have been at the lower end of the intermediate pretest risk range. Improvements in medical therapy in the past few decades, including use of statins, may have contributed to the low incidence of these outcomes. An additional consideration is the possibility that differences between tests in true sensitivity to detect treatable CAD or ability to identify high-risk disease are not large. Small differences in sensitivity may have little impact on the probability of disease when the pretest probability is low. Even if two tests do not have the same sensitivity, the lack of difference in the occurrence of outcome events in most studies between people who were assigned to receive different tests could result from either the lack of efficacy of treatments administered to test-positive people or the lack of difference in the receipt of effective treatments between test-positive and test-negative people. Given that included studies did not present data on treatments administered to individual study participants (or how testing directed those decisions), we could not distinguish between these alternatives. Furthermore, information on post-test risk stratification or treatment based on such stratification was not reported in most studies. Information on clinical decisions and outcomes based on whether tests were positive, negative, or indeterminate was not given in most comparative studies. It is possible that over- or undertreatment may have contributed to similarity in clinical findings. Length of followup may have also impacted the findings of no difference in clinical outcomes. Two larger trials in outpatient settings (SPECT vs. stress electrocardiography [ECG][87] and CCTA vs. functional testing[76]) followed patients for 2 or more years. Most studies in the ED setting did not provide data beyond 6 months of the ED visit; testing was only able to affect clinical events after the

index visit, and consequently there was insufficient evidence to draw conclusions regarding longer-term clinical outcomes.

Referral for Invasive Coronary Angiography

There was some variability in conclusions regarding invasive coronary angiography (ICA) referral following noninvasive testing. In most studies, ICA was more common following CCTA than following various functional tests. The strongest evidence came from one good-quality trial that compared CCTA with functional testing in outpatients. The trial found that ICA was significantly more common in the CCTA group than the functional testing group by 90 days (12.19% vs. 8.11%, RD 4.08, 95% CI 2.90 to 5.26 per 100 people) (high strength of evidence). Interestingly, fewer catheterizations in the CCTA group showed no obstructive CAD (3.4% vs. 4.3%),[76] perhaps because of to a lower false positive rate with CCTA. The strength of the quality of evidence regarding ICA referral was low across the remaining trials. Two fair-quality trials comparing CCTA with exercise ECG suggested that ICA referral is more common following CCTA up to 12 months following an initial ED visit in one trial of low- to intermediate-risk patients (RD 4.8, 95% CI 0.8 to 8.9 per 100 people) and in the other trial of mixed-risk patients (RD 6.3, 95% CI -1.2 to 13.9 per 100 people); statistical significance was not reached and strength of evidence was low because of study limitations and lack of precision.

A large administrative data study in Medicare patients found that ICA was significantly more common following CCTA compared with nuclear myocardial perfusion imaging (MPI) (22.94% vs. 12.13%, adjusted odds ratio [OR] 2.19, 95% CI 2.08 to 2.32) (low strength of evidence).[102] In contrast, across studies comparing CCTA with usual care there were no statistical differences between testing strategies in any of the trials regardless of pretest risk or setting, however in the small high-risk group from one trial, fewer CCTA patients had ICA at the index visit (RD -18, 95% CI -37 to 0.8, p=0.0714) (low strength of evidence). Evidence from observational studies for comparisons of CCTA with other tests was considered insufficient because of study limitations and lack of precision. Regarding comparisons of functional tests, two RCTs[85,87] and one large administrative database study[102] provided low-strength evidence on ICA referral in outpatient settings. One trial comparing SPECT with exercise ECG in intermediate-risk women reported a 6 percent referral for ICA in each test group by 24 months. However, the other trial making this comparison reported a significantly lower frequency of ICA referral by 22 months following SPECT in a subgroup of patients with intermediate pretest risk (RD -32, 95% CI -43 to -22 per 100 people) as well as in a subgroup of high-risk patients (RD -41, 95% CI -58 to -24 per 100 people).[85] This same trial used Bayesian methods to model post-test risk and reported that 86 percent of those with low pretest risk finished with low post-test risk. Patients in either arm whose tests were normal or indicated low risk test did not receive ICA; 3 percent and 38 percent in the intermediate and high post-test risk groups had ICA following SPECT compared with 13 percent and 85 percent in the intermediate and high post-test groups following exercise ECG. This type of modeling is not a standard approach to post-test risk assessment, so the generalizability of these results is not clear. The administrative database study of Medicare patients reported that, compared with nuclear MPI, ICA referral was lower following exercise ECG (OR 0.72, 95% CI 0.70 to 0.75) and stress echocardiography (OR 0.78, 95% CI 0 .76 to 0.81)[102] (low strength of evidence). Evidence from the remaining observational studies was considered insufficient.

None of the studies provided analysis or explicit information regarding unnecessary treatment or testing.

Revascularization

Findings were inconsistent across diagnostic strategies with regard to revascularization referral. There was high-strength evidence from one large trial that any revascularization within 90 days was more common following CCTA compared with functional testing (RD 3.07, 95% CI 2.24 to 3.90 per 100 patients); the same was true for percutaneous coronary intervention (PCI) specifically (RD 2.4, 95% CI 1.7 to 3.1 per 100 patients)[76] (high strength of evidence). Revascularization was also more common 6 to 12 months following CCTA compared with exercise ECG across two studies (1 RCT, 1 observational study)[82,102] of mixed risk ED patients (low strength of evidence), as well as across two observational studies comparing CCTA with nuclear MPI[102,105] in an outpatient setting up to 1.4 years (low strength of evidence). In contrast, the frequency of revascularization was similar for CCTA and SPECT (pooled RD 2 per 100 patients, 95% CI 0 to 4 per 100 patients) at the index ED visit and at 6 months (pooled RD 0, 95% CI 0 to 1 per 100 patients) across two trials (moderate strength of evidence).[77,78] PCI and coronary artery bypass graft (CABG) frequencies in these trials were also similar between tests (moderate strength of evidence). Further, there was low-strength evidence of no statistical differences in revascularization frequency between CCTA and usual care at the index visit or at 1 to 3 months followup based on data from four trials.[75,80,81,83] Evidence comparing functional tests was inconsistent, with one small trial reporting fewer revascularizations following SPECT than exercise ECG (RD -7.1, 95% CI -13.6 to -0.6 per 100 patients)[85] (low strength of evidence), and one large Medicare administrative database study reporting a similar frequency of revascularization, including PCI and CABG, for exercise ECG (4.31%, vs. 4.59%) and stress echocardiography (4.22% vs. 4.59%) as for nuclear MPI (low strength of evidence). For the latter study, although the differences between groups were statistically significant for both comparators, they may not be clinically significant. Studies did not describe post-test reclassification of risk or decisionmaking for treatment.

Additional Noninvasive Testing

Additional noninvasive testing, which impacts the cost and efficiency of care, was common in most studies. In the ED setting, there was high-strength evidence from two trials of patients with low to intermediate risk that additional noninvasive testing was significantly more common following CCTA than SPECT at the index visit (RD for largest trial 9.4, 95% CI 6.1 to 12.7 per 100 patients).[77,78] In the same setting, there was moderately strong evidence that CCTA was associated with less frequent noninvasive testing compared with usual care at the index visit in one trial[81] and compared with exercise ECG through 12 months past the index ED visit[82] in another trial. In intermediate-risk patients, the frequency of additional testing following CCTA was similar to the frequency following usual care up to 1 month past the ED visit in one trial (low strength of evidence), possibly because many in the usual-care group also received noninvasive imaging.[80] In outpatient settings, the strength of evidence was moderate that SPECT was associated with significantly less additional noninvasive testing compared with exercise ECG through 22 months based on one large trial of intermediate-risk women (RD -9, 95% CI -14 to -4 per 100 patents)[87] as well as a from a subgroup of intermediate-risk patients in another trial (RD -38, 95% CI -48 to -29 per 100 patients).[85] These results likely indicate greater clinician confidence when stress testing is paired with imaging based on general understanding from accuracy studies that positive and negative predictive values are better for SPECT than for stress testing. In the Medicare administrative database study, both CCTA and stress echocardiography

were associated with a significantly higher frequency of additional noninvasive testing compared with nuclear MPI (OR 1.52, 95% CI, 1.37 to 1.69 and OR 1.92, 95% CI 1.83 to 2.0, respectively), but strength of evidence was low. Studies generally did not describe post-test reclassification of risk or decisionmaking for related further testing.

Hospitalization

Cardiovascular-related hospitalizations varied somewhat among pretest risk groups across studies. There was moderate-strength evidence from one large trial of ED patients with low to intermediate risk that the CCTA group was significantly less likely than the usual-care group to be hospitalized or admitted for observation at the index visit (RD -26.8, 95% CI -31.9 to -21.8 per 100 patients), but that after this visit through 1 month, there was no difference (3% for CCTA vs. 2% for usual care).81 Low-strength evidence from a large trial of intermediate-risk ED patients suggested that there were fewer hospitalizations following CCTA compared with usual care at the index visit (RD -33, 95% CI -39 to -28 per 100 patients).80 These data imply clinician confidence in the negative predictive value of the anatomic test, yet there is a predisposition of patients to return with unexplained symptoms that can be from a variety of other causes of chest pain, including vasospasm and microvascular dysfunction. In contrast, no statistical differences between CCTA and usual care were identified for ACS hospitalization at the index visit based on subgroups of low- or high-risk patients in one trial,75 but strength of evidence was low. There was moderate-strength evidence that there was no difference in cardiovascular hospitalizations between CCTA and functional testing groups in low- to intermediate-risk ED patients within 6 months (0% in both groups) based on one trial,77 and through 30 months based on one observational study90 that compared CCTA with SPECT. In another trial of mixed pretest risk patients presenting to specialized chest pain clinics, moderate-strength evidence suggested that hospitalization for cardiac causes occurred less frequently in the CCTA group compared with the exercise ECG group (RD -6.1, 95% CI -9.5 to -2.7 per 100 people) through 12 months.82 Two trials conducted in outpatient settings reported no differences in cardiac-related hospitalizations between groups. The strongest evidence came from the large trial comparing CCTA with functional testing, which reported no differences at a median of 25 months (RD -0.30, 95% CI -0.10 to 0.71 per 100 people)76 (moderate strength of evidence). The trial of SPECT versus exercise ECG in women also found no difference between groups (low strength of evidence).[87]

Special Populations

With regard to evaluation of special populations, one good-quality trial comparing CCTA with functional testing reported that none of the prespecified subgroups modified the primary composite outcome (all-cause death, nonfatal MI, hospitalization for unstable angina or a major procedural complication such as stroke, major bleeding, anaphylaxis, and renal failure requiring dialysis). Results across subgroups were consistent with those for the entire study population. Subgroups examined included age, sex, race, pretest risk assessment, CAD equivalence, and pretest probability of CAD.[76] None of the other studies identified evaluated differential effectiveness or safety for the primary clinical outcomes (e.g., mortality and MI). As previously noted, one fair-quality trial of exercise SPECT compared with exercise ECG in women found no differences between tests for mortality, ICA referral, revascularization, or hospitalization, but the trial reported a significantly lower use of additional noninvasive testing following SPECT.[87] The strength of evidence was moderate for additional testing and low for other outcomes. An

additional small poor-quality RCT in women compared stress echocardiography with exercise ECG; this trial reported similar frequency of a composite outcome which included cardiac death, MI, unstable angina, or coronary angiography, demonstrating 50 percent or more luminal narrowing (7.7% vs. 7.4%).[86] However, the strength of evidence was insufficient because of high risk of bias, lack of precision, and unknown consistency. Also as noted earlier, a large, fair-quality administrative data study in the Medicare population was identified.[102] Consistent with findings in other studies, this study found no differences in adjusted effect estimates for all-cause mortality for the comparisons of nuclear MPI with stress echocardiography, exercise ECG, or CCTA. CCTA was significantly associated with increased referral for ICA and revascularization (particularly PCI) and use of additional noninvasive testing compared with nuclear MPI (strength of evidence was low for these outcomes and comparisons).

Harms and Consequences of Testing

Harms of testing were rarely reported and details on comparisons of harms for tests were sparse with many studies stating only that no harms were observed and not providing further detail; 16 of the 27 comparative studies made no mention of evaluation of harms. There were no compelling safety outcomes data that can be used to recommend one approach versus another (low or insufficient strength of evidence). No differences in major procedural complications were identified in the trial comparing CCTA with functional imaging although mild contrast reactions were significantly more common in the CCTA group than in the functional testing group (moderate strength of evidence).[76] No differences were reported between CCTA and usual care in bradyarrhythmia in one trial[81] or periprocedural complications in another[80] (low strength of evidence for both). A third trial reported that there was no clinical or laboratory evidence of contrast-induced nephropathy in either the CCTA or the usual care group.[75] One observational study reported incidental findings requiring further investigation in 7.1 percent of those receiving CCTA (insufficient evidence).[90] Evidence from observational studies regarding test-related harms and impact of incidental findings following CCTA was insufficient to draw conclusions.

An important patient safety concern related to noninvasive testing is exposure to low to moderate levels of ionizing radiation, which add to cumulative lifetime radiation exposure. To the extent that noninvasive tests for CAD reduce the need for conventional angiography, cumulative exposure might be reduced. To the extent that they result in the need for additional testing, it may be increased. The true attributable risk from radiation-based diagnostic tests cannot be determined. Some experts consider the potential for harm from radiation exposure (based on either deterministic or stochastic modeling) to be clinically significant, particularly since patients may be likely to have additional tests using radiation over many years. Estimates of radiation exposure from included studies are provided in Appendix G (Table G4); the introduction provides contextual information on radiation exposure ranges for testing. Radiation exposure from included studies for initial testing strategies ranged from 3.8 to 17 mSv for CCTA and 10.5 to 38 for SPECT. One study reported a mean of 4.0 mSv for positron emission tomography (PET)[95] and another study[80] reported a mean of 4.7 mSv for usual care. Consideration of cumulative radiation exposure related to downstream testing and intervention is important when discussing with patients the benefits and consequences of the different noninvasive tests and their contribution to lifetime radiation exposure. Higher mean cumulative radiation accounting for additional testing was seen in single trials following CCTA compared with usual care (14.3 ± 10.9 vs. 5.3 ± 9.6 mSv)[80] and functional testing (12.0 ± 8.5 vs. 10.1 ± 9.0 mSv).[76] One study reported higher cumulative exposure following CCTA than following SPECT

in patients referred for ICA (medians 15.2 mSv, interquartile range 12.7 to 17.1 vs. median 10.8 mSv, interquartile range 10.2 to 11.7).[104] By contrast, another trial reported lower cumulative exposure for additional testing following CCTA versus SPECT (median 7.3 mSv, interquartile range 5.1 to 13.7 vs. median 13.3 mSv, interquartile range13.1 to 38.0).[84] One observational study of CCTA and exercise ECG reported higher exposure to index and downstream testing for CCTA for patients whose tests were negative, positive, or inconclusive. However, among those who tested positive and had revascularization, mean cumulative exposure was slightly higher in the ECG group (28 vs. 32 mSv).[100] Consideration of patient preferences with regard to the impact of radiation exposure should be part of shared decisionmaking around noninvasive testing.

Findings in Relationship to What Is Already Known

Few prior reviews have evaluated the impact of noninvasive testing on clinical and management outcomes. Systematic reviews and studies on noninvasive testing for CAD identified from our search focused on traditional measures of test performance (e.g., sensitivity, specificity) compared with ICA. They generally did not directly compare the effectiveness and safety of different modalities with regard to impact on clinical outcomes specifically in the population of interest in this report. Consistent with this review, prior systematic reviews[126,127] have reported few or no comparative studies evaluating the impact of noninvasive tests on clinical outcomes, decisionmaking, or use of additional testing, and they note that harms are rarely reported. Relevant studies from these reports were included in this systematic review. The recent Agency for Healthcare Research and Quality (AHRQ) report on noninvasive testing for CAD in women reported that there was insufficient evidence from three studies that treatment decisionmaking and clinical outcomes were impacted by noninvasive testing;[128] consistent with our report, there were no differences in clinical events or hospitalization in studies comparing noninvasive tests. The authors also concluded that studies were underpowered to detect clinical outcomes.

Applicability

A number of factors that impact the applicability of this report's findings are discussed in this section.

Patients

Eight of the 13 trials identified were in patients presenting to the ED with CAD symptoms; however, the largest trial was in an outpatient setting. Patients presenting to the ED represent a broad spectrum of pretest risk probabilities, including those at low or intermediate risk as well as those at high risk for CAD. The severity, newness, and duration of symptoms may differ from those seen in outpatient settings, in which patients generally present with more mild to moderate symptoms. Definitions of pretest risk varied across included studies, and some did not report or stratify by pretest risk, making it difficult to fully evaluate results based on pretest risk across settings. It is likely that the patients enrolled in the included studies are representative of those in the broad range of clinical practice regardless of setting.

Interventions and Comparators

The evidence may be skewed toward newer testing modalities, and studies of established tests may not reflect current technology and diagnostic performance. CCTA was the noninvasive test most often assessed, accounting for 48 percent of included studies. The high proportion of studies dealing with CCTA may be because it is a newer modality and thus is compared with established tests such as stress echocardiography and MPI. Few studies comparing different types of functional testing, particularly established functional tests such as stress echocardiography, exercise ECG, and nuclear stress testing, were identified. A recent systematic review suggested that over the past 2 decades, there has been substantial decline in investigations related to echocardiography and nuclear cardiology, compared with a marked increase in cardiac CT imaging studies.[129] Input from clinical team members and the Technical Expert Panel suggested that there is substantial variation in clinical practice with regard to which test may be ordered as an initial test based on patient presentation, testing availability, and clinical perspective. The applicability of this report may be impacted by lack of clarity on the extent to which CCTA may or may not be the initial noninvasive test for first-line evaluation of symptomatic patients without known CAD after a resting ECG. None of the included studies included a no testing arm. To the extent that clinical decisionmaking is based on clinical evaluation and judgment without testing, findings in this report may be less applicable to settings in which testing is not routinely done.

Outcomes

Findings related to rare outcomes of death, MI, or hospitalization may not be fully applicable to broader clinical populations in part because of small study sizes and inability to fully characterize such outcomes, particularly over the longer term. Moreover, the impact of a negative test or the treatment downstream from a positive test may extend beyond traditional major adverse coronary events to quality of life, reduction in symptoms, and level of activity. These outcomes were not examined in the majority of included studies. The majority of trials reported outcomes at the time of an index ED visit. The clinical management objectives are somewhat different in an ED setting than in an outpatient setting.

Settings

Most RCTs were conducted in the ED, where test data help determine immediate disposition for discharge or the need for additional evaluation and/or hospitalization. The initial goal is to make a diagnosis for the cause of chest pain in order to inform appropriate treatment and next steps at the index visit. Thus, MI reported at the index visit may reflect a test's ability to make the diagnosis for immediate decisionmaking but not the test's ability to impact future clinical outcomes. Testing is able to affect events only after the index visit, and long-term followup from ED studies was limited. Thus the applicability of findings from ED studies to general outpatient settings over the long term is likely limited. Six RCTs evaluating CCTA were multi-center studies and five were in single-center sites. It is possible that results from single-center trials may be different and less generalizable than results from multicenter trials. Assessing discernible patterns between the multi-center and single-center site studies in this report was a challenge given the heterogeneity across studies with regard to pretest risk and how comparators such as usual care are defined.

Implications for Clinical and Policy Decisionmaking

The 2012 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guideline states that diagnostic testing is most valuable when the pretest probability of ischemic heart diseases is intermediate (10%–90%) and provides a range of options for which test may be used in a given scenario.[8] However, the effectiveness of different modalities with regard to impact on clinical outcomes is not compared. Currently, a variety of tests as the initial (and additional) diagnostic tests for patients at intermediate pretest risk of CAD are employed, and there is uncertainty regarding which tests, if any, may be most suitable and beneficial in patients who present with symptoms suggestive of CAD but have no prior history of it. Although several ACCF/AHA Appropriate Use Criteria are available, including the 2013 multi-modality imaging Appropriate Use Criteria,[130] they do not explicitly compare multiple noninvasive testing modalities nor do they make specific recommendations for the timing and sequencing of tests or for repeat testing based on pretest risk group.

Low- to moderate-strength evidence from nine trials suggested that there is no clear difference in MI or in all-cause mortality between different testing strategies across settings and pretest risk grouping that included those at intermediate risk. Possible contributors to this finding, including lack of power to detect a difference, were previously described. Information from two studies that provided data on groups with low and high pretest risk (without ACS) do not provide insight into best testing strategies in those groups and the strength of evidence was insufficient for the few outcomes reported and no conclusion can be drawn. Across studies that enrolled intermediate-risk groups, no clear benefits of one testing strategy versus another were seen and no clear picture of harms for various tests was available from included studies. One apparent trend uncovered by the review is that tests that evaluate coronary anatomy such as CT result in a greater likelihood of referral for ICA and subsequent intervention than functional tests do; however, the strength of evidence varied from high to low depending on the comparator and the impact on clinical outcomes is not known as most studies did not present data on treatments administered to individual study participants. Thus, it is not clear if the increased referrals were helpful or not with regard to influencing clinical outcomes. In addition, potential harm from use of invasive treatments (which carry specific risks) if clinical benefit is not clear was not described. Only two studies provided limited information on the overall impact of testing and resulting treatment strategies on patient symptoms and quality of life. No studies that compared testing with an arm that received no testing were identified, so the impact of any of the noninvasive testing pathways on clinical evaluation is not known.

As defined in the ACCF/AHA Guideline, the intermediate pretest group is broad and heterogeneous (10%–90%), and in the absence of information on post-test risk, the value of the various tests for influencing important management decisions at each end of the spectrum was not clear. The ACCF/AHA Guideline and various Appropriate Use Criteria[20,131-133] provide general recommendations for testing and treatment.

In general, next steps following a positive result from an initial noninvasive test is in part based on the post-test annual predicted rate of cardiac mortality as described in the 2012 ACCF/AHA Guideline: low risk (<1% per year), intermediate risk (1%–3% per year), or high risk for cardiac mortality (>3% per year).[8] Clinical presentation and test results are both considered in this determination. In general, indications for revascularization are based on the clinical presentation (ACS or stable angina), the severity of the angina (based on Canadian Cardiovascular Society Classification), the extent of ischemia on noninvasive testing, and the presence or absence of other prognostic factors including congestive heart failure, depressed left

ventricular function, diabetes, the extent of medical therapy, and the extent of anatomic disease.[134,135]

Thus, post-test disease probability is an important factor in determining next steps for testing and treatment. From the included studies, however, it is not clear how post-test risk was assessed, which clinical pathways were followed after the initial test, which test(s) may lead to the most appropriate treatment give the post-test risk, or whether the treatments impacted outcomes. While the ACCF/AHA Guidelines and various Appropriate Use Criteria provide a range of options for which test may be used in a given scenario and treatment initiated, the effectiveness of different testing modalities leading to appropriate treatment are not compared with regard to impact on clinical outcomes.

In the absence of high-strength evidence regarding testing options, including the possibility of not testing, decisions must necessarily be made on the basis of other factors related to the initial test and potential followup. The ability of a test to accurately diagnose treatable CAD is important; so too are the costs and consequences beyond the initial test, such as followup of false negative results (e.g., tests with high false-positive rates in a population with low pretest risk) and the costs and consequences of missing significant disease (e.g., dismissal from the ED of patients with CAD needing treatment). The costs and consequences depend to some extent on the role a test plays in the diagnostic work-up pathway as well as the availability and convenience of a test. Patient pretest probability of disease and consideration of the likelihood ratios with regard to goals of ruling in or ruling out CAD should be a part of the decisionmaking process. Consequences of testing that need to be considered include those related to patient anxiety and patient quality of life and those related to radiation exposure of the index test, as well as potential downstream exposure from additional testing resulting from the initial test and future testing and/or treatment. Consideration of patients' preferences based on their understanding the range of consequences of initial and downstream testing is an important part of shared decisionmaking for initiating noninvasive testing.

Limitations of the Systematic Review Process

This review has some potential limitations. Stratifying by pretest risk, which was in keeping with the intent of Key Questions, may have resulted in fewer studies to pool and left single studies for most comparisons. This, combined with substantial heterogeneity in how pretest risk was defined, the time frames over which outcomes were evaluated, and clinical heterogeneity between the tests evaluated, resulted in too few studies for head-to-head meta-analysis for most outcomes and network meta-analysis was not feasible.

Variable reporting on patient symptoms and characteristics related to CAD risk precluded application of a standardized method for calculating or assigning pretest risk across studies. In light of this, test comparisons were evaluated according to pretest risk as specified by authors to discern patterns within and across pretest risk levels and setting, and qualitatively synthesize outcomes in which pooling was not possible. This approach resulted in limited ability to truly examine the evidence by pretest risk.

Inclusion was restricted to studies published in English; however, this is not likely to have impacted the evidence base, as few potential non-English-language studies were seen in the searches. Given the paucity of RCTs, comparative observational studies were included. Despite a focus on outcomes where authors controlled for confounding, there was a possibility that residual confounding influenced reported results, lowering confidence in effect estimates. The comparative studies included may not have adequately captured harms safety issues in the

population of interest. The focused criteria on inclusion of studies comparing established first-line test (beyond a resting ECG) narrowed the review scope substantially, but this focus was intended to provide a clearer approach to addressing the areas of uncertainty. It is possible that older historical studies outside of our population of interest could provide more detailed information about the safety of various tests, particularly more established tests.

There were too few studies of any given comparison to meaningfully evaluate reporting and publication bias. Where available, protocols of trials were reviewed to consider the extent to which outcomes were reported selectively and information from Scientific Information Packets requested from stakeholders was evaluated; while overt publication bias was not detected, there is always the possibility it may be present. This review provides a snapshot of currently available evidence on the questions posed. Included studies may not reflect technological advances that have been made in the various testing modalities.

Limitations of the Evidence Base

Important limitations of the evidence base include the paucity of studies that compared the impact of different noninvasive tests on hard clinical outcomes such as mortality and MI, and few RCTs were available, in particular for comparisons of established functional tests in the population of interest. No trials that included a no testing arm were identified. Methods for assessing pretest risk, defining cardiovascular outcomes, and defining usual care were poorly reported and not standardized. The variable methods for determination and classification of pretest risk across studies and inability to implement a standardized method for assessing pretest risk across studies precluded detailed evaluation of testing strategies by pretest risk level to determine the comparative values of tests for a given pretest risk. The intermediate risk range was broad (10%–90%). Studies did not provide information on the impact of test results on post-test risk stratification or clinical decisionmaking for treatment or further testing precluding evaluation of the impact of testing in this group. Some studies reported composite cardiovascular outcomes, which can be misleading depending on the effects on the individual components.[136] Studies did not evaluate aspects of unnecessary testing. Reporting of harms was suboptimal; 16 of the 27 comparative studies made no mention of evaluation of harms and another 3 merely stated that there were no adverse events. With the exception of one study, authors reported few details about harms. As mentioned previously, study sample sizes and short-term followup may preclude evaluation of rare events. Studies did not describe the impact of testing on treatment choices. Few studies on PET, CACS, and established tests such as stress echocardiography were identified.

Research Gaps and Recommendations

The gaps in the available evidence are many. Two primary issues relate to the need to improve reporting and standardization of pretest CAD risk and to enhance the evidence linking testing strategies and clinical pathways with clinical outcomes. Use of standardized risk models that refine and narrow the currently broad “intermediate-risk” group is needed. For example, because of health care trends to streamline and reduce the cost of care, newer risk models such as the Duke Clinical Score have narrowed the intermediate range and tend to reclassify many of those classified as “intermediate risk” in the Diamond and Forrester model to “low risk”.[137] Documentation of post-test risk stratification and its impact on clinical management (treatment and referral for additional testing) is needed to determine optimal testing strategies and roles of tests in different pretest risk groups. This may facilitate comparison of tests to effectively parse

out patients at the highest risk end and those at the lower risk end, as well as evaluation of the impact of management decisions in these groups, as they likely will differ. Documentation of management of those who test positive compared with those who test negative and followup of these groups for sufficient time to evaluate clinical outcomes are needed. Prospective cohort studies that address selection bias and confounding by indication have the potential to enhance the evidence base and may be more feasible than RCTs for some settings. Studies comparing testing versus clinical evaluation without testing would provide valuable information for assessing the need for testing, possible overuse of testing, and impact of testing in general. Comparative studies (RCTs, pragmatic trials, or prospective cohorts) of functional tests that reflect technological advances as applied to symptomatic patients without known CAD would update the evidence base. Meta-analysis of patient-level data from existing trials may allow for more specific stratification by pretest probability or specific risk factors. Important insights into the overall impact of testing on long-term outcomes could come from studies that (1) document how test results specifically influence decisionmaking regarding further testing and treatment strategies and (2) follow patients to evaluate the impact of the testing pathway. Future research also needs to incorporate evaluation of patient-centered outcomes, such as quality of life, symptom status, and the impact of testing.

Primary gaps and considerations for future research are summarized in Table 16.

Table 16. Overview of research gaps and recommendations

Research Components	Evidence Gap	Future Research Recommendations
Study Design Methods and Reporting	Gaps include lack of a standardized approach to determining and reporting pretest risk across studies; variable definitions of pretest risk, which precluded effective stratification by pretest risk; the large range of pretest likelihoods for “intermediate” risk patients (10%–90%), which precluded detailed evaluation of the impact of testing for patients at the lowest and highest ends of the range.	A standardized approach for determination of pretest risk that can be applied across study designs is needed. Future research should use risk models that further refine the range of pretest probability for those at intermediate risk (e.g., the Duke Clinical Score) to delineate the impact of testing on clinical decisionmaking at the lower and higher ends of the range. Tools that refine the range may also be clinically useful.
	Studies describing outcomes at the index ED visit do not allow conclusions regarding the impact of testing on clinical outcomes over the longer term.	Longer followup (>12 months) and documentation of the impact of testing on treatment decisions and hard clinical outcomes are needed. RCTs, pragmatic trials, or prospective cohort studies that address selection bias and confounding by indication could be employed.
	None of the included studies evaluated issues of unnecessary testing or treatment in patients without known CAD.	As a first step, a priori definitions for necessary vs. unnecessary testing or treatment are needed and they should be evidence-based. Given the variability of clinical practice and medico-legal concerns, this may be challenging. Evaluation of Appropriate Use Criteria and examination of evidence on the clinical outcomes based on application of such criteria may help further define necessary vs. unnecessary.

Research Components	Evidence Gap	Future Research Recommendations
Patient Populations	There is a paucity of studies on patients with low or very low pretest probability of CAD and the value of testing is not clear for this population.	Studies (RCTs, pragmatic trials or methodologically rigorous comparative cohort studies) that compare a testing strategy (and related clinical management) with a strategy of no testing (and related clinical management) are needed. Sufficient sample size may be a challenge given the low prevalence of CAD that is likely in this group.
	Few active trials listed in ClinicalTrials.gov pertain to symptomatic patients *without* known CAD, yet this group of patients commonly presents for evaluation and testing, particularly in outpatient settings. (See Appendix K).	Future studies focused on those without known/prior CAD history or studies that analyze outcomes for this group of patients separately from those with known CAD are needed.
	There is a paucity of high-quality studies comparing various testing strategies in outpatient clinic populations.	Studies of patients who typically present in outpatient settings are needed. Greater integration of cardiologists into hospital settings may facilitate the conduct of studies of outpatients and enhance opportunities for followup of patients initially presenting to the ED.
	Studies do not generally report the extent to which clinical decisionmaking and clinical outcomes may be modified by patient characteristics, sociodemographic factors (e.g., age, sex, race, ethnicity, education, socioeconomic status) or provider characteristics.	RCTs or pragmatic trials with sufficient sample size to compare differential effectiveness and safety of testing strategies based on prespecified analyses are needed.
Interventions and Comparators	There is a lack of studies comparing outcomes following testing and resulting treatment strategies vs. a strategy of clinical evaluation without testing and resultant treatment strategies.	Studies (RCTs, pragmatic trials or methodologically rigorous comparative cohort studies) that compare a testing strategy (and related clinical management) with a strategy of no testing (and related clinical management) are needed.
	Older studies of established tests (particularly functional tests) may not be as applicable in light of advances in technology. There was a paucity of studies comparing functional tests with each other.	Studies (RCTs, pragmatic trials or methodologically rigorous comparative cohort studies) that compare functional tests using more state of the art technology and methods with each other and with anatomic tests are needed. New studies should focus on the impact each test makes on clinical decisionmaking and hard clinical outcomes.

Research Components	Evidence Gap	Future Research Recommendations
Outcome Measures	Studies comparing of the impact of noninvasive testing on hard clinical outcomes in those without known CAD are few compared with studies of test accuracy.	Additional sufficiently powered studies examining the impact of testing on hard clinical outcomes (death, MI) at longer-term followup (>12 months) are needed.
	There is limited high-quality comparative evidence linking established tests with clinical decisionmaking and subsequent outcomes in the population of interest by pretest risk, particularly in nonemergent settings and over the longer term. Further, there is limited evidence on the impact of tests on post-test risk stratification and the best testing strategy(ies) for post-test risk stratification to identify patients who may be at highest risk and may benefit most from various treatment strategies. It is not clear whether the individuals who would most benefit from given treatment strategies were referred to those strategies and whether the strategies were effective.	Studies that document and compare tests with regard to their impact on prespecified clinical decisionmaking components (e.g., referral for additional testing, initiation or change in medication), particularly in outpatient settings, are needed. Such documentation should also include: post-test risk stratification and factors that influenced its determination, what decisions were made based on the test results (positive, negative or inconclusive results) and impact on hard clinical outcomes (death, MI) over time.
	There is limited evidence on the impact of testing strategies (including consequences of downstream testing and treatment) on patient-related outcomes such as quality of life and symptom status.	Future studies should incorporate standardized, validated measures for patient reported outcomes and document the impact of testing, including downstream testing, on patient psychological status (particularly with false positive results), health status and resource use.
	Adverse events and consequences of testing are poorly reported.	Future study protocols should delineate, a priori, possible adverse events and consequences (including those related to psychological aspects of testing, radiation exposure, resource use) and report their occurrence per the protocol.
Analysis	The lack of a standardized approach to determining and reporting pretest risk across studies and variable definitions of pretest risk used in included studies precluded ability to effectively stratify by pretest risk or pool data.	Individual patient data meta-analysis of RCTs may provide opportunities to use a standardized approach for pretest risk stratification and may facilitate evaluation of modification by patient characteristics and other factors.
	A number of studies did not provide details for pretest risk or report results stratified by pretest risk.	Studies should stratify by pretest risk of CAD using a standard method and report outcomes based on pretest risk strata.

CAD = coronary artery disease; ED = emergency department; MI = myocardial infarction; RCT = randomized controlled trial

Conclusion

A review of current studies found no clear differences between testing strategies across settings with regard to clinical or management outcomes that would allow recommendation of one strategy over another for any given pretest risk group that included patients with intermediate pretest risk. No conclusions regarding low-risk patients or those without acute coronary syndrome at high risk were possible. Limited evidence from randomized controlled trials (RCTs) found no clear differences between coronary computed tomography angiography (CCTA) versus other strategies in clinical outcomes across risk groups, although anatomic testing may result in a higher frequency of referral for invasive coronary angiography (ICA) and revascularization. The frequency of all-cause mortality and myocardial infarction (MI) was low across studies in all settings. The absence of information on post-test risk stratification and subsequent decisionmaking precluded evaluation of the impact of testing on patient management or outcomes of management. Testing strategies vary in radiation exposure; there is inadequate comparative evidence to make judgments regarding exposure for the initial test or downstream testing. Assessment of harms was limited. Future research using more refined, evidence-based definitions of pretest risk, coupled with information on post-test risk stratification, its impact on clinical management (treatment and referral for additional testing) and longer-term followup to assess clinical outcomes, is needed to determine optimal testing strategies and roles of tests in different pretest risk groups.

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Abbreviations and Acronyms

ACCF	American College of Cardiology Foundation
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
BMIPP	Beta-methyl iodophenyl pentadecanoic acid
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CER	Comparative Effectiveness Review
CMR	Cardiac magnetic resonance
CT	Computed tomography
EBCT	Electron beam computed tomography
ECG	Electrocardiography
FDG-PET	Fludeoxyglucose (18F) positron emission tomography
FDA	Food and Drug Administration
FFR	Fractional flow reserve
F/U	Followup
HIV	Human immunodeficiency virus
ICA	Invasive coronary angiography
IQR	Interquartile range
KQ	Key Question
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
MDCT	Multidetector computed tomography
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition scan
N/A	Not applicable
NR	Not reported
NS	Not statistically significant
NSTE-ACS	Non-ST elevation acute coronary syndromes
NSTEMI	Non-ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomized controlled trial
RD	Risk difference
RR	Relative risk
SD	Standard deviation
SPECT	Single photon emission computed tomography
STEMI	ST-segment elevation myocardial infarction
TEE	Transesophageal echocardiography
TEP	Technical Expert Panel
TIMI	Thrombolysis in Myocardial Infarction Risk Score

Appendix A. Search Strategy

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to July Week 3 2015>

Search Strategy:

1	exp Coronary Disease/di, pa, ra, ri, us [Diagnosis, Pathology, Radiography, Radionuclide Imaging, Ultrasonography]
2	exp Coronary Circulation/
3	1 or 2
4	exp Exercise Test/
5	exp Electrocardiography/
6	exp Echocardiography/
7	5 or 6
8	4 and 7
9	3 and 8
10	exp Tomography, Emission-Computed, Single-Photon/
11	exp Positron-Emission Tomography/
12	3 and 10
13	3 and 11
14	(radionuclid$ adj5 scintigra$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
15	3 and 14
16	exp Vasodilator Agents/
17	exp Dobutamine/
18	16 or 17
19	exp Magnetic Resonance Imaging/
20	3 and 18 and 19
21	exp Tomography, X-Ray Computed/
22	22 3 and 21
23	exp Image Interpretation, Computer-Assisted/
24	exp Calcium/
25	exp Calcium Compounds/
26	exp Calcium Metabolism Disorders/
27	24 or 25 or 26
28	23 and 27
29	exp Heart Diseases/
30	exp Heart/
31	exp Cardiovascular Physiological Phenomena/
32	29 or 30 or 31
33	28 and 32
34	exp Cardiac Imaging Techniques/
35	21 and 34
36	3 and 35
37	exp Magnetic Resonance Imaging/
38	3 and 37
39	9 or 12 or 13 or 15 or 20 or 22 or 33 or 36 or 38
40	limit 39 to english language

41	limit 39 to abstracts
42	40 or 41

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 2015>

Search Strategy:

1	(coronary adj5 (diseas$ or occlus$ or occlud$ or block$ or stenos$ or stenotic$ or arterioscler$ or atheroscler$ or vasospas$ or aneurysm$)).mp. [mp=title, abstract, full text, keywords, caption text]
2	(coronary adj5 (circulat$ or ((blood adj3 flow$) or supply$ or supplie$))).mp.
3	((stable adj2 angina$) or (chest adj2 pain$)).mp. [mp=title, abstract, full text, keywords, caption text]
4	1 or 2 or 3
5	((Exercis$ or treadmill$ or bicycl$ or step or steps or stress$) adj3 (echocardiogra$ or electrocardiogra$ or ekg or ecg)).mp.
6	6 ((Exercis$ or treadmill$ or bicycl$ or step or steps or stress$) adj3 Test$).mp.
7	(Electrocardiogra$ or ekg or ecg).mp.
8	Echocardiogra$.mp.
9	7 or 8
10	6 and 9
11	5 or 10
12	4 and 11
13	(spect or (single adj3 photon$ adj5 (emit$ or emission$) adj7 tomogra$)).mp.
14	4 and 13
15	15 ((pet adj2 scan$) or (Positron$ adj3 (emit$ or emission$) adj7 tomogra$)).mp.
16	4 and 15
17	(radionuclid$ adj5 scintigra$).mp.
18	4 and 17
19	vasodilator$.mp.
20	dobutamine.mp.
21	19 or 20
22	(mri or (magnet$ adj3 resonan$ adj3 imag$)).mp.
23	4 and 21 and 22
24	cine ct.mp.
25	25 ((x-ray$ or spiral$ or multidetector$ or cone beam$ or electron beam$) adj5 (comput$ adj3 tomogra$)).mp.
26	((x-ray$ or spiral$ or multidetector$ or cone beam$ or electron beam$) adj5 ((cat or ct) adj scan$)).mp.
27	24 or 25 or 26
28	4 and 27
29	29 (comput$ adj5 assist$ adj7 (imag$ adj5 process$)).mp. [mp=title, abstract, full text, keywords, caption text]
30	(calcium or ca++ or ca ion$ ca2+ or ca+2).mp. [mp=title, abstract, full text, keywords, caption text]
31	29 and 30
32	4 and 31
33	(heart$ or cardia$ or cardio$ or myocard$ or coronar$).mp. [mp=title, abstract, full text, keywords, caption text]
34	32 and 33

35	(non-invasiv$ adj5 (imag$ or procedur$ or interven$ or scan$ or test$ or diagno$ or radiogra$ or x-ray$)).mp. [mp=title, abstract, full text, keywords, caption text]
36	("not " adj invasiv$ adj5 (imag$ or procedur$ or interven$ or scan$ or test$ or diagno$ or radiogra$ or x-ray$)).mp.
37	35 or 36
38	4 and 37
39	12 or 14 or 16 or 18 or 23 or 28 or 34 or 38

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <July 2015>

Search Strategy:

1	(coronary adj5 (diseas$ or occlus$ or occlud$ or block$ or stenos$ or stenotic$ or arterioscler$ or atheroscler$ or vasospas$ or aneurysm$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2	(coronary adj5 (circulat$ or ((blood adj3 flow$) or supply$ or supplie$))).mp.
3	((stable adj2 angina$) or (chest adj2 pain$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4	1 or 2 or 3
5	((Exercis$ or treadmill$ or bicycl$ or step or steps or stress$) adj3 (echocardiogra$ or electrocardiogra$ or ekg or ecg)).mp.
6	((Exercis$ or treadmill$ or bicycl$ or step or steps or stress$) adj3 Test$).mp.
7	(Electrocardiogra$ or ekg or ecg).mp.
8	Echocardiogra$.mp.
9	7 or 8
10	6 and 9
11	11 5 or 10
12	4 and 11
13	(spect or (single adj3 photon$ adj5 (emit$ or emission$) adj7 tomogra$)).mp.
14	4 and 13
15	((pet adj2 scan$) or (Positron$ adj3 (emit$ or emission$) adj7 tomogra$)).mp.
16	4 and 15
17	(radionuclid$ adj5 scintigra$).mp.
18	4 and 17
19	vasodilator$.mp.
20	dobutamine.mp.
21	19 or 20
22	22 (mri or (magnet$ adj3 resonan$ adj3 imag$)).mp.
23	4 and 21 and 22
24	cine ct.mp.
25	((x-ray$ or spiral$ or multidetector$ or cone beam$ or electron beam$) adj5 (comput$ adj3 tomogra$)).mp.
26	((x-ray$ or spiral$ or multidetector$ or cone beam$ or electron beam$) adj5 ((cat or ct) adj scan$)).mp.
27	24 or 25 or 26
28	4 and 27
29	(comput$ adj5 assist$ adj7 (imag$ adj5 process$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

30	(calcium or ca++ or ca ion$ ca2+ or ca+2).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
31	29 and 30
32	4 and 31
33	(heart$ or cardia$ or cardio$ or myocard$ or coronar$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
34	32 and 33
35	(non-invasiv$ adj5 (imag$ or procedur$ or interven$ or scan$ or test$ or diagno$ or radiogra$ or x-ray$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
36	("not " adj invasiv$ adj5 (imag$ or procedur$ or interven$ or scan$ or test$ or diagno$ or radiogra$ or x-ray$)).mp.
37	37 35 or 36
38	4 and 37
39	12 or 14 or 16 or 18 or 23 or 28 or 34 or 38

Database: EBM Reviews - Health Technology Assessment <2nd Quarter 2015>

Search Strategy:

1	(coronary adj5 (diseas$ or occlus$ or occlud$ or block$ or stenos$ or stenotic$ or arterioscler$ or atheroscler$ or vasospas$ or aneurysm$)).mp. [mp=title, text, subject heading word]
2	(coronary adj5 (circulat$ or ((blood adj3 flow$) or supply$ or supplie$))).mp.
3	((stable adj2 angina$) or (chest adj2 pain$)).mp. [mp=title, text, subject heading word]
4	1 or 2 or 3
5	((Exercis$ or treadmill$ or bicycl$ or step or steps or stress$) adj3 (echocardiogra$ or electrocardiogra$ or ekg or ecg)).mp.
6	((Exercis$ or treadmill$ or bicycl$ or step or steps or stress$) adj3 Test$).mp.
7	(Electrocardiogra$ or ekg or ecg).mp.
8	Echocardiogra$.mp.
9	7 or 8
10	6 and 9
11	5 or 10
12	4 and 11
13	(spect or (single adj3 photon$ adj5 (emit$ or emission$) adj7 tomogra$)).mp.
14	4 and 13
15	((pet adj2 scan$) or (Positron$ adj3 (emit$ or emission$) adj7 tomogra$)).mp.
16	4 and 15
17	(radionuclid$ adj5 scintigra$).mp.
18	4 and 17
19	vasodilator$.mp.
20	dobutamine.mp.
21	19 or 20
22	(mri or (magnet$ adj3 resonan$ adj3 imag$)).mp.
23	4 and 21 and 22
24	cine ct.mp.
25	((x-ray$ or spiral$ or multidetector$ or cone beam$ or electron beam$) adj5 (comput$ adj3 tomogra$)).mp.
26	((x-ray$ or spiral$ or multidetector$ or cone beam$ or electron beam$) adj5 ((cat or ct) adj

	scan$)).mp.
27	24 or 25 or 26
28	4 and 27
29	(comput$ adj5 assist$ adj7 (imag$ adj5 process$)).mp. [mp=title, text, subject heading word]
30	(calcium or ca++ or ca ion$ ca2+ or ca+2).mp. [mp=title, text, subject heading word]
31	29 and 30
32	4 and 31
33	(heart$ or cardia$ or cardio$ or myocard$ or coronar$).mp. [mp=title, text, subject heading word] (1374)
34	32 and 33
35	(non-invasiv$ adj5 (imag$ or procedur$ or interven$ or scan$ or test$ or diagno$ or radiogra$ or x-ray$)).mp. [mp=title, text, subject heading word]
36	("not " adj invasiv$ adj5 (imag$ or procedur$ or interven$ or scan$ or test$ or diagno$ or radiogra$ or x-ray$)).mp.
37	35 or 36
38	4 and 37
39	12 or 14 or 16 or 18 or 23 or 28 or 34 or 38

Appendix B. List of Included Studies

1. Buchsbaum M, Marshall E, Levine B, et al. Emergency department evaluation of chest pain using exercise stress echocardiography. Acad Emerg Med. 2001 Feb;8(2):196-9. PMID: 11157301.
2. Chang SA, Choi SI, Choi EK, et al. Usefulness of 64-slice multidetector computed tomography as an initial diagnostic approach in patients with acute chest pain. Am Heart J. 2008 Aug;156(2):375-83. PMID: 18657674.
3. Cheezum MK, Hulten EA, Taylor AJ, et al. Cardiac CT angiography compared with myocardial perfusion stress testing on downstream resource utilization. J Cardiovasc Comput Tomogr. 2011 Mar-Apr;5(2):101-9. PMID: 21256102.
4. Cho I, Shim J, Chang HJ, et al. Prognostic value of multidetector coronary computed tomography angiography in relation to exercise electrocardiogram in patients with suspected coronary artery disease. J Am Coll Cardiol. 2012 Nov 20;60(21):2205-15. PMID: 23103039.
5. Colon PJ, 3rd, Guarisco JS, Murgo J, et al. Utility of stress echocardiography in the triage of patients with atypical chest pain from the emergency department. Am J Cardiol. 1998 Nov 15;82(10):1282-4, A10. PMID: 9832109.
6. Dedic A, Genders TS, Ferket BS, et al. Stable angina pectoris: head-to-head comparison of prognostic value of cardiac CT and exercise testing. Radiology. 2011 Nov;261(2):428-36. PMID: 21873254.
7. Dodi C, Cortigiani L, Masini M, et al. The incremental prognostic value of pharmacological stress echo over exercise electrocardiography in women with chest pain of unknown origin. Eur Heart J. 2001 Jan;22(2):145-52. PMID: 11161916.
8. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. New Engl J Med. 2015 Mar 14PMID: 25773919.
9. Elhendy A, Shub C, McCully RB, et al. Exercise echocardiography for the prognostic stratification of patients with low pretest probability of coronary artery disease. Am J Med. 2001 Jul;111(1):18-23. PMID: 11448656.
10. Ferrara N, Leosco D, Abete P, et al. Dipyridamole echocardiography as a useful and safe test in the assessment of coronary artery disease in the elderly. J Am Geriatr Soc. 1991 Oct;39(10):993-9. PMID: 1918787.
11. Fine NM, Pellikka PA, Scott CG, et al. Characteristics and outcomes of patients who achieve high workload (>10 metabolic equivalents) during treadmill exercise echocardiography. Mayo Clin Proc. 2013 Dec;88(12):1408-19. PMID: 24290114.
12. Gentile R, Vitarelli A, Schillaci O, et al. Diagnostic accuracy and prognostic implications of stress testing for coronary artery disease in the elderly. Ital Heart J. 2001 Jul;2(7):539-45. PMID: 11501963.
13. Goldstein JA, Chinnaiyan KM, Abidov A, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. J Am Coll Cardiol. 2011 Sep 27;58(14):1414-22. PMID: 21939822.
14. Goldstein JA, Gallagher MJ, O'Neill WW, et al. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. J Am Coll Cardiol. 2007 Feb 27;49(8):863-71. PMID: 17320744.
15. Gruettner J, Fink C, Walter T, et al. Coronary computed tomography and triple rule out CT in patients with acute chest pain and an intermediate cardiac risk profile. Part 1: impact on patient management. Eur J Radiol. 2013 Jan;82(1):100-5. PMID: 22749769.
16. Hachamovitch R, Berman DS, Kiat H, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. Circulation. 1996 Mar 1;93(5):905-14. PMID: 8598081.

17. Hachamovitch R, Nutter B, Hlatky MA, et al. Patient management after noninvasive cardiac imaging results from SPARC (Study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease). J Am Coll Cardiol. 2012 Jan 31;59(5):462-74. PMID: 22281249.

18. Hamilton-Craig C, Fifoot A, Hansen M, et al. Diagnostic performance and cost of CT angiography versus stress ECG--a randomized prospective study of suspected acute coronary syndrome chest pain in the emergency department (CT-COMPARE). Int J Cardiol. 2014 Dec 20;177(3):867-73. PMID: 25466568.

19. Henzler T, Gruettner J, Meyer M, et al. Coronary computed tomography and triple rule out CT in patients with acute chest pain and an intermediate cardiac risk for acute coronary syndrome: part 2: economic aspects. Eur J Radiol. 2013 Jan;82(1):106-11. PMID: 22835878.

20. Heupler S, Mehta R, Lobo A, et al. Prognostic implications of exercise echocardiography in women with known or suspected coronary artery disease. J Am Coll Cardiol. 1997 Aug;30(2):414-20. PMID: 9247513.

21. Hlatky MA, Shilane D, Hachamovitch R, et al. Economic outcomes in the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease registry: the SPARC Study. J Am Coll Cardiol. 2014 Mar 18;63(10):1002-8. PMID: 24636556.

22. Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. New Engl J Med. 2012 Jul 26;367(4):299-308. PMID: 22830462.

23. Innocenti F, Cerabona P, Donnini C, et al. Long-term prognostic value of stress echocardiography in patients presenting to the ED with spontaneous chest pain. Am J Emerg Med. 2014 Jul;32(7):731-6. PMID: 24768667.

24. Innocenti F, Lazzeretti D, Conti A, et al. Stress echocardiography in the ED: diagnostic performance in high-risk subgroups. Am J Emerg Med. 2013 Sep;31(9):1309-14. PMID: 23827088.

25. Kim YJ, Hur J, Lee HJ, et al. Meaning of zero coronary calcium score in symptomatic patients referred for coronary computed tomographic angiography. Eur Heart J Cardiovasc Imaging. 2012 Sep;13(9):776-85. PMID: 22461571.

26. Krivokapich J, Child JS, Gerber RS, et al. Prognostic usefulness of positive or negative exercise stress echocardiography for predicting coronary events in ensuing twelve months. Am J Cardiol. 1993 Mar 15;71(8):646-51. PMID: 8447259.

27. Laudon DA, Behrenbeck TR, Wood CM, et al. Computed tomographic coronary artery calcium assessment for evaluating chest pain in the emergency department: long-term outcome of a prospective blind study. Mayo Clin Proc. 2010 Apr;85(4):314-22. PMID: 20360291.

28. Levsky JM, Spevack DM, Travin MI, et al. Coronary computed tomography angiography versus radionuclide myocardial perfusion imaging in patients with chest pain admitted to telemetry: a randomized trial. Ann Intern Med. Aug 163(3):174-83. PMID: 26052677.

29. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. New Engl J Med. 2012 Apr 12;366(15):1393-403. PMID: 22449295.

30. Marwick TH, Shaw L, Case C, et al. Clinical and economic impact of exercise electrocardiography and exercise echocardiography in clinical practice. Eur Heart J. 2003 Jun;24(12):1153-63. PMID: 12804930.

31. McKavanagh P, Lusk L, Ball PA, et al. A comparison of cardiac computerized tomography and exercise stress electrocardiogram test for the investigation of stable chest pain: the clinical results of the CAPP randomized prospective trial. Eur Heart J Cardiovasc Imaging. 2014 Dec 3. PMID: 25473041.

32. Miller AH, Pepe PE, Peshock R, et al. Is coronary computed tomography angiography a resource sparing strategy in the risk stratification and evaluation of acute chest pain? Results of a randomized controlled trial. Acad Emerg Med. 2011 May;18(5):458-67. PMID: 21569165.

33. Min JK, Koduru S, Dunning AM, et al. Coronary CT angiography versus myocardial perfusion imaging for near-term quality of life, cost and radiation exposure: a prospective multicenter randomized pilot trial. J Cardiovasc Comput Tomogr. 2012 Jul-Aug;6(4):274-83. PMID: 22732201.

34. Min JK, Shaw LJ, Berman DS, et al. Costs and clinical outcomes in individuals without known coronary artery disease undergoing coronary computed tomographic angiography from an analysis of Medicare category III transaction codes. Am J Cardiol. 2008 Sep 15;102(6):672-8. PMID: 18773986.

35. Nabi F, Chang SM, Pratt CM, et al. Coronary artery calcium scoring in the emergency department: identifying which patients with chest pain can be safely discharged home. Ann Emerg Med. 2010 Sep;56(3):220-9. PMID: 20138399.

36. Nance JW, Jr., Schlett CL, Schoepf UJ, et al. Incremental prognostic value of different components of coronary atherosclerotic plaque at cardiac CT angiography beyond coronary calcification in patients with acute chest pain. Radiology. 2012 Sep;264(3):679-90. PMID: 22820732.

37. Nielsen LH, Markenvard J, Jensen JM, et al. Frontline diagnostic evaluation of patients suspected of angina by coronary computed tomography reduces downstream resource utilization when compared to conventional ischemia testing. Int J Cardiovasc Imaging. 2011 Jul;27(6):813-23. PMID: 21042860.

38. Nielsen LH, Olsen J, Markenvard J et al. Effects on costs of frontline diagnostic evaluation in patients suspected of angina: coronary computed tomography angiography vs. conventional ischaemia testing. Eur Heart J Cardiovasc Imaging. 2013 May;14(5):449-55:449-455. PMID: 22922828.

39. Petretta M, Daniele S, Acampa W543, et al. Prognostic value of coronary artery calcium score and coronary CT angiography in patients with intermediate risk of coronary artery disease. Int J Cardiovasc Imaging. 2012 Aug;28(6):1547-56. PMID: 21922205.

40. Poon M, Cortegiano M, Abramowicz AJ, et al. Associations between routine coronary computed tomographic angiography and reduced unnecessary hospital admissions, length of stay, recidivism rates, and invasive coronary angiography in the emergency department triage of chest pain. J Am Coll Cardiol 2013 Aug 6;62(6):543-52. PMID: 23684682.

41. Sabharwal NK, Stoykova B, Taneja AK, et al. A randomized trial of exercise treadmill ECG versus stress SPECT myocardial perfusion imaging as an initial diagnostic strategy in stable patients with chest pain and suspected CAD: cost analysis.[Erratum appears in J Nucl Cardiol. 2007 May-Jun;14(3):414]. J Nucl Cardiol. 2007 Apr;14(2):174-86. PMID: 17386379.

42. Sanfilippo AJ, Abdollah H, Knott TC, et al. Stress echocardiography in the evaluation of women presenting with chest pain syndrome: a randomized, prospective comparison with electrocardiographic stress testing. Can J Cardiol. 2005 Apr;21(5):405-12. PMID: 15861257.

43. Schmermund A, Stang A, Mohlenkamp S, et al. Prognostic value of electron-beam computed tomography-derived coronary calcium scores compared with clinical parameters in patients evaluated for coronary artery disease. Prognostic value of EBCT in symptomatic patients. Z Kardiol. 2004 Sep;93(9):696-705. PMID: 15365737.

44. Severi S, Picano E, Michelassi C, et al. Diagnostic and prognostic value of dipyridamole echocardiography in patients with suspected coronary artery disease. Comparison with exercise electrocardiography. Circulation. 1994 Mar;89(3):1160-73. PMID: 8124803.

45. 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 Sep 13;124(11):1239-49. PMID: 21844080.

46. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. JAMA. 2011 Nov 16;306(19):2128-36. PMID: 22089720.

47. Takeuchi M, Sonoda S, Miura Y, et al. Comparative diagnostic value of dobutamine stress echocardiography and stress thallium-201 single-photon-emission computed tomography for detecting coronary artery disease in women. Coron Artery Dis. 1996 Nov;7(11):831-5. PMID: 8993941.

48. Tandon V, Hall D, Yam Y, et al. Rates of downstream invasive coronary angiography and revascularization: computed tomographic coronary angiography vs. Tc-99m single photon emission computed tomography. Eur Heart J. 2012 Mar;33(6):776-82. PMID: 21893487.

49. Truong QA, Hayden D, Woodard PK, et al. Sex differences in the effectiveness of early coronary computed tomographic angiography compared with standard emergency department evaluation for acute chest pain: the rule-out myocardial infarction with Computer-Assisted Tomography (ROMICAT)-II Trial. Circulation 2013 Jun 25;127(25):2494-502. PMID: 23685743.

50. Villines TC, Hulten EA, Shaw LJ, et al. Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero undergoing coronary computed tomography angiography: results from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry. J Am Coll Cardiol. 2011 Dec 6;58(24):2533-40. PMID: 22079127.

51. Yamauchi T, Tamaki N, Kasanuki H, et al. Optimal initial diagnostic strategies for the evaluation of stable angina patients: a multicenter, prospective study on myocardial perfusion imaging, computed tomographic angiography, and coronary angiography. Circ J. 2012;76(12):2832-9. PMID: 22975716.

Appendix C. List of Excluded Studies With Rationale

1. Abdelmoneim SS, Bernier M, Hagen ME, et al. A multicenter, prospective study to evaluate the use of contrast stress echocardiography in early menopausal women at risk for coronary artery disease: trial design and baseline findings. J Womens Health (Larchmt). 2013 Feb;22(2):173-83. PMID: 23398128. **Wrong population.**
2. Abdelmoneim SS, Dhoble A, Bernier M, et al. Quantitative myocardial contrast echocardiography during pharmacological stress for diagnosis of coronary artery disease: a systematic review and meta-analysis of diagnostic accuracy studies. Eur J Echocardiogr. 2009 Oct;10(7):813-25. PMID: 19549700. **Wrong population, wrong intervention.**
3. Abdulla J, Asferg C, Kofoed KF. Prognostic value of absence or presence of coronary artery disease determined by 64-slice computed tomography coronary angiography a systematic review and meta-analysis. Int J Cardiovasc Imaging. 2011 Mar;27(3):413-20. PMID: 20549366. **Wrong population.**
4. Aggarwal NR, Knickelbine T, Tande A, et al. Noncalcified plaque: relationship between results of multislice computed tomography, risk factors, and late clinical outcome. Catheter Cardiovasc Interv. 2011 Dec 1;78(7):1116-24. PMID: 21542104. **Wrong population.**
5. Amemiya S, Takao H. Computed tomographic coronary angiography for diagnosing stable coronary artery disease: a cost-utility and cost-effectiveness analysis. Circ J. 2009 Jul;73(7):1263-70. PMID: 19436120. **Wrong outcomes.**
6. Arruda AM, Das MK, Roger VL, et al. Prognostic value of exercise echocardiography in 2,632 patients > or = 65 years of age. J Am Coll Cardiol. 2001 Mar 15;37(4):1036-41. PMID: 11263605. **Wrong population.**
7. Arruda-Olson AM, Juracan EM, Mahoney DW, et al. Prognostic value of exercise echocardiography in 5,798 patients: is there a gender difference? J Am Coll Cardiol. 2002 Feb 20;39(4):625-31. PMID: 11849861. **Wrong population.**
8. Ayaram D, Bellolio MF, Murad MH, et al. Triple rule-out computed tomographic angiography for chest pain: a diagnostic systematic review and meta-analysis. Acad Emerg Med. 2013 Sep;20(9):861-71. PMID: 24050793. **Wrong population, wrong intervention.**
9. Bamberg F, Sommer WH, Hoffman V, et al. Meta-analysis and systematic review of the long-term predictive value of assessment of coronary atherosclerosis by contrast-enhanced coronary computed tomography angiography. J Am Coll Cardiol. 2011 Jun 14;57(24):2426-36. PMID: 21658564. **Wrong outcomes.**
10. Banerjee AN, Newman DR, Van den Bruel A, et al. Diagnostic accuracy of exercise stress testing for coronary artery disease: a systematic review and meta-analysis of prospective studies. Int J Clin Pract. 2012 May;66(5):477-92. PMID: 22512607. **Wrong intervention.**
11. Biagini E, Shaw LJ, Poldermans D, et al. Accuracy of non-invasive techniques for diagnosis of coronary artery disease and prediction of cardiac events in patients with left bundle branch block: a meta-analysis. Eur J Nucl Med Mol Imaging. 2006 Dec;33(12):1442-51. PMID: 16847655. **Wrong population, systematic review or meta-analysis, original data used instead.**
12. Bigi R, Desideri A, Cortigiani L, et al. Stress echocardiography for risk stratification of diabetic patients with known or suspected coronary artery disease. Diabetes Care. 2001 Sep;24(9):1596-601. PMID: 11522705. **Wrong population.**
13. Bikiri E, Mereles D, Voss A, et al. Dobutamine stress cardiac magnetic resonance versus echocardiography for the assessment of outcome in patients with suspected or known coronary artery disease. Are the two imaging modalities comparable? Int J Cardiol. 2014 Feb 1;171(2):153-60. PMID: 24342416. **Wrong population.**

14. Bingham SE, Hachamovitch R. Incremental prognostic significance of combined cardiac magnetic resonance imaging, adenosine stress perfusion, delayed enhancement, and left ventricular function over preimaging information for the prediction of adverse events. Circulation. 2011 Apr 12;123(14):1509-18. PMID: 21444886. **Wrong population.**

15. Bobbio M, Pollock BH, Cohen I, et al. Comparative accuracy of clinical tests for diagnosis and prognosis of coronary artery disease. Am J Cardiol. 1988 Nov 1;62(13):896-900. PMID: 3177237. **Wrong intervention.**

16. Bodi V, Sanchis J, Lopez-Lereu MP, et al. Prognostic and therapeutic implications of dipyridamole stress cardiovascular magnetic resonance on the basis of the ischaemic cascade. Heart. 2009 Jan;95(1):49-55. PMID: 18381373. **Wrong population.**

17. Bodi V, Sanchis J, Lopez-Lereu MP, et al. Prognostic value of dipyridamole stress cardiovascular magnetic resonance imaging in patients with known or suspected coronary artery disease. J Am Coll Cardiol. 2007 Sep 18;50(12):1174-9. PMID: 17868810. **Wrong population.**

18. Bouzas-Mosquera A, Peteiro J, Alvarez-Garcia N, et al. Prognostic value of exercise echocardiography in patients with left bundle branch block. JACC Cardiovasc Imaging. 2009 Mar;2(3):251-9. PMID: 19356568. **Wrong population.**

19. Bouzas-Mosquera A, Peteiro J, Broullon FJ, et al. Effect of atrial fibrillation on outcome in patients with known or suspected coronary artery disease referred for exercise stress testing. Am J Cardiol. 2010 May 1;105(9):1207-11. PMID: 20403467. **Wrong population.**

20. Bouzas-Mosquera A, Peteiro J, Broullon FJ, et al. Prognostic value of exercise echocardiography in patients with atrial fibrillation. Eur J Echocardiogr. 2010 May;11(4):346-51. PMID: 20164089. **Wrong population.**

21. Bouzas-Mosquera A, Peteiro J, Broullon FJ, et al. Value of exercise echocardiography for predicting mortality in elderly patients. Eur J Clin Invest. 2010 Dec;40(12):1122-30. PMID: 20718848. **Wrong population.**

22. Brown KA, Boucher CA, Okada RD, et al. Prognostic value of exercise thallium-201 imaging in patients presenting for evaluation of chest pain. J Am Coll Cardiol. 1983 Apr;1(4):994-1001. PMID: 6833659. **Wrong intervention, wrong comparison.**

23. Buckert D, Dewes P, Walcher T, et al. Intermediate-term prognostic value of reversible perfusion deficit diagnosed by adenosine CMR: a prospective follow-up study in a consecutive patient population. JACC Cardiovasc Imaging. 2013 Jan;6(1):56-63. PMID: 23328562. **Wrong population.**

24. Budoff MJ, Liu S, Chow D, et al. Coronary CT angiography versus standard of care strategies to evaluate patients with potential coronary artery disease; effect on long term clinical outcomes. Atherosclerosis. 2014 Dec;237(2):494-8. PMID: 25463080. **Wrong population.**

25. Budoff MJ, Young R, Lopez VA, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2013 Mar 26;61(12):1231-9. PMID: 23500326. **Wrong population.**

26. Bunch AM. A systematic review of the predictive value of a coronary computed tomography angiography as compared with coronary calcium scoring in alternative noninvasive technique in detecting coronary artery disease and evaluating acute coronary syndrome in an acute care setting. Dccn. 2012 Mar-Apr;31(2):73-83. PMID: 22333713. **Systematic review or meta-analysis, using original studies instead.**

27. Cardiac Magnetic Resonance Imaging (MRI) for Patients with Coronary Artery Disease: A Review of Diagnostic Accuracy. Ottawa, ON Canada: Canadian Agency for Drugs and Technologies in Health. Health Technology Inquiry Service (HTIS); February 2009. **Wrong outcomes.**

28. Chang SM, Nabi F, Xu J, et al. Value of CACS Compared With ETT and Myocardial Perfusion Imaging for Predicting Long-Term Cardiac Outcome in Asymptomatic and Symptomatic Patients at Low Risk for Coronary Disease: Clinical Implications in a Multimodality Imaging World. JACC Cardiovasc Imaging. 2015 Feb;8(2):134-44. PMID: 25677886. **Wrong population.**

29. Chatziioannou SN, Moore WH, Ford PV, et al. Prognostic value of myocardial perfusion imaging in patients with high exercise tolerance. Circulation. 1999 Feb 23;99(7):867-72. PMID: 10027807. **Wrong population.**

30. Chen L, Wang X, Bao J, et al. Direct comparison of cardiovascular magnetic resonance and single-photon emission computed tomography for detection of coronary artery disease: a meta-analysis. PLoS One. 2014;9(2):e88402. PMID: 24520382. **Wrong population.**

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Appendix D. Sample Data Extraction Elements

- Author, year
- Study design
    - RCT
    - Prospective cohort
    - Retrospective cohort
    - Administrative database
- Country, number of centers (multicenter / single center), setting (inpatient, outpatient, emergency department, etc.), funding source
- Inclusion criteria
- Exclusion criteria
- Number enrolled, randomized, analyzed, complete followup (%, months)
- Followup time points
    - Note if followup was assessed in-person
    - Note any separate followup studies
- Tests evaluated (number of patients evaluated by each test)
- Test details
    - Type of stressor (specific modality- drug, type of exercise, etc.)
    - Contrast
    - Other pertinent details
- Definition of a positive test (as reported in text)
- Demographics
    - Age (mean)
    - % female
    - Race
    - Note any pertinent subgroups

- Baseline risk for CAD (e.g. very low, low, intermediate to high, high)
    - ACC pre-test likelihood (%)
    - Framingham
    - TIMI score
- Cardiovascular characteristics (%)
    - Chest pain
        - Typical angina
        - Atypical angina
        - Nonspecific chest pain
    - Dyspnea
    - Prior myocardial infarction
    - Prior revascularization
    - Known CAD
    - Chest pain frequency
    - Hypertension
    - Hyperlipidemia
    - Diabetes
- Test results (i.e., normal vs. abnormal) (%)
- Clinical Health Outcomes, % (n/N) for each timepoint (include data if results were stratified by test result)
    - Quality of life
    - Change in angina
    - Myocardial infarction
    - Heart failure
    - Stroke
    - Death
    - Cardiovascular hospitalization for acute coronary syndrome, heart failure or arrhythmias
    - Dysrhythmia

    - Composite outcome (define)
- Adverse events, % (n/N) for each timepoint (include data if results were stratified by test result)
    - Harms of testing (renal failure, allergy, neprogenic systemic fibrosis, contrast-related harms, adverse reaction to medications used for stress testing)
    - Vascular complications
    - Risks and consequences of testing (radiation exposure, psychological consequences of diagnosis, need for additional testing)
- Clinical management outcomes, % (n/N) for each timepoint (include data if results were stratified by test result)
    - Additional testing (including referral for additional testing)
    - Clinical decisionmaking and management based on revised risk stratification (e.g., use of guideline-directed medical therapy including management of lipids, blood pressure and diabetes, counseling related to diet, physical activity, smoking cessation, alcohol use and management of psychological factors; use of additional therapies to reduce risk of MI and death (e.g., antiplatelet therapy)
    - Need for subsequent revascularization (PCI or CABG)
- Harms associated with additional testing
- Differential effectiveness for subgroups: Clinical outcomes
- Differential harms for subgroups
- Differential effectiveness for subgroups: clinical management

Appendix E. Evidence Tables for Comparative Studies

Table E1. Demographics for included RCTs in populations with mixed risk for coronary artery disease

Author (year)		**Chang (2008)[1]**		**Sabharwal (2007)[2]**		**Sanfilippo (2005)[3]**		**McKavanagh (2014)[4]**	
Test Sample size		CCTA (n=133)	Usual Care (n=133)	SPECT (n=250)	Exercise ECG (n=207)	Stress Echo (n=104)	Exercise ECG (n=54)	CCTA (n=250)*	Exercise ECG (n=250)*
Patient demographics	Female, % (n)	39% (52)	38% (51)	44.4% (111)	42.5% (88)	100% (104)	100% (104)	43.2% (105)	46.5% (114)
	Age (years); mean ± SD	57 ± 14	58 ± 14	59.7 ± 12.2	58.9 ± 911.4	54.9†	53.2 ± 10.1	57.8 ± 10.0	58.9 ± 10.2
	Race, % (n)	NR	NR	White: 55.6% (139)	White: 46.9% (97)	97.1% (101)	100% (54)	NR	NR
	Pretest risk, % (n)‡	Low: 37.6% (50) IM: 41.4% (55) High: 21.1% (28)	Low: 36.8% (49)† IM: 42.1% (56) High: 21.1% (28)	Low: 10.8% (27) IM: 71.2% (178) High: 18.0% (45)	Low: 21.3% (44) IM: 49.3% (102) High: 29.5% (61)	Mixed	Mixed	Low: 41.6% (101) IM: 21.8% (53) High: 36.6% (89)	Low: 43.7% (107) IM 25.3% (62) High: 31.0% (76)
	Subgroup	NR	NR	None	None	Women only	Women only	None	None
Cardiac risk factors, % (n)	Chest pain	100% (133)	100% (133)	100% (250)	100% (207)	100% (104)	100% (54)	100% (243)	100% (245)
	Typical angina	NR	NR	NR	NR	NR	NR	34.6% (84)	27.8% (68)
	Atypical angina	NR	NR	NR	NR	NR	NR	6.6% (16)	8.2% (20)
	Unstable angina	NR	NR	NR	NR	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR	NR	NR	NR	NR
	Nonangina	NR	NR	NR	NR	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR	NR	NR
	Prior MI	NR	NR	0% (0)	0% (0)	NR	NR	NR	NR
	Prior revascularization	NR	NR	NR	NR	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR	NR	NR	NR	NR
	Known CAD	12% (16)	17% (23)	0% (0)	0% (0)	NR	NR	0% (0)	0% (0)
	Chest pain frequency	NR	NR	NR	NR	NR	NR	NR	NR
	Hypertension	46% (61)	41% (55)	53.2% (133)	46.3% (96)	53.7% (56)	38.9% (21)†	31.7% (77)	29.8% (73)
	Diabetes	16% (21)	19% (25)	19.2% (48)	14.5% (30)	10.5% (11)	7.4% (4)†	5.8% (14)	4.9% (12)
	Hyperlipidemia	29% (39)	25% (33)	NR	NR	41.3% (43)†	42.6% (23)†	NR	NR
	Current smoker	17% (23)	23% (31)	12.8% (32)	16.4% (34)	18.2% (19)†	25.9% (14)†	18.9% (46)	19.2% (47)

Author (year)		Chang (2008)[1]		Sabharwal (2007)[2]		Sanfilippo (2005)[3]		McKavanagh (2014)[4]	
Test details	CT images (slice)	64	NA	NA	NA	NA	NA	64	NA
	CACS performed	NR	NR	NA	NA	NA	NA	Yes	NA
	Type of stressor	NA	NA	Exercise (treadmill 62%) and/or pharmacologic stress (dipyradimole 38% [or dobutamine if contraindication])	Treadmill (Bruce protocol)	Dobutamine (n=47) or unspecified exercise (n=57)	NR	Opitray (ioversol)	NA
	Contrast (dose)	Lomeprol (80mL lomeron 400; Bracco, Milan, Italy)	NA	Radiotracer: Tc-99m sestamibi	NA	NR	NA	Opitray (ioversol)	NA
Study characteristics	Setting	ED	ED	Outpatient	Outpatient	Outpatient	Outpatient	Rapid Access Chest Pain Clinics	Rapid Access Chest Pain Clinics
	Followup period % completed followup (n)	30 days	30 days	Mean 19.6 months 96.9% (443/457)§	Mean 19.6 months 96.9% (443/457)§	28.1±14.2 months 100 (104)	28.1±14.2 months 100 (54)	12 months 97.2% (243/250)	12 months 98.0% (245/250)
	Study Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Fair	Fair	Poor	Poor	Fair	Fair

CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; Echo = echocardiogram; ED = emergency department; IM = intermediate risk; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography

*Demographics reported only for those who completed followup (n=243 CCTA; n=245 Exercise ECG).

† Back calculated weighted mean.

‡As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.

§ Loss-to-followup not reported by group; 10 patients did not have followup data and there were 2 deaths in each group (SPECT: 2 malignancy; ECG: 1 malignancy and 1 cardiac).

Table E2. Clinical outcomes from randomized controlled trials including populations with mixed risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure, Stroke	Major Adverse Cardiac Events	Unstable Angina	Stability and Frequency of Angina*	Quality of Life*
Chang, 2008[1†]	CCTA (n=133) 30 days	NR	0% (0)	NR	NR	NR	NR	NR
	Usual Care (n=133) 30 days	NR	0.8% (1)	NR	NR	NR	NR	NR
Sabharwal 2007[2†]	SPECT (n=250) Mean 21.7 ± 6.4 months	0.8% (2)	0% (0)	NR	NR	NR	NR	NR
	Exercise ECG (n=207) Mean 21.7 ± 6.4 months	0.9% (2)	0.5% (1)	NR	NR	NR	NR	NR
Sanfillippo 2005[3‡]	Stress echocardiography[§] (n=104) Mean 28.1 ± 14.2 months	NR	NR	NR	7.7% (8)	NR	NR	NR
	Exercise ECG (n=54) Mean 28.1 ± 14.2 months	NR	NR	NR	7.4% (4)	NR	NR	NR
McKavanagh 2014[4]	CCTA (n=243) 12 months	0.41% (1) (noncardiac)	0.41% (1)	NR	NR	0.41% (1)	NR	NR
	Exercise ECG (n=245) 12 months	0.41% (1) (noncardiac)	0.82% (2)	NR	NR	1.2% (3)	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography

*Difference from baseline (95% confidence interval) between CCTA and ECG for the Seattle Angina Questionnaire subscales of "angina stability", "angina frequency", and "disease perception/quality of life outcomes"; the change in the score was significantly improved in the CT arm compared with the EST arm in the angina stability and quality-of-life domains at 3 and 12 months.

†For Chang, myocardial infarction was not reported stratified by risk group; for Sabharwal, mortality and myocardial infarction were not reported stratified by risk group. Thus, these outcomes are reported in the mixed population table.

‡Also reports noncardiac clinical outcomes (no clinical events and either resolution of chest pain or establishment of an alternative cause of chest pain, or negative results on ICA) and Indeterminate clinical outcome (continued presenting chest pain syndrome without clinical confirmatory events ([i.e., symptomatic but stable with unknown cause of chest pain])

§ Includes exercise (n=57) and dobutamine (n=47) stress echocardiography. Results also reported separately by type of stressor.

Table E3. Clinical management and hospitalization outcomes from randomized controlled trials including populations with mixed risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Revascular-ization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Stress Testing With Imaging	Coronary Computed Tomography Angiography	Medical Therapy	Hospitali-zation (chest pain)
Chang, 2008[1*]	CCTA (n=133) 30 days	NR	NR	NR	NR	30 days: 10% (13)	NR	NR	NR	NR
	Usual Care (n=133) 30 days	NR	NR	NR	NR	30 days: NR	NR	NR	NR	NR
Sabharwal 2007[2*]	SPECT (n=250) Mean 21.7 ± 6.4 months	NR	NR	NR	NR	NR	0% (0)†	NR	NR	NR
	Exercise ECG (n=207) Mean 21.7 ± 6.4 months	NR	NR	NR	NR	NR	23% (48)†	NR	NR	NR
Sanfillippo 2005[3]	Stress echocardiography‡ (n=104) Mean 28.1 ± 14.2 months	NR	NR	NR	NR	NR	1.9% (2)†	NR	NR	NR
	Exercise ECG (n=54) Mean 28.1 ± 14.2 months	NR	NR	NR	NR	NR	24.1% (13)†	NR	NR	NR
McKavanagh 2014[4**]	CCTA (n=243) 12 months	27.2% (66)	15.2% (37)	11.9% (29)	3.3% (8)	2.5% (6)	2.5% (6)§	0% (0)	40.7% (99)	0.82% (2)
	Exercise ECG (n=245) 12 months	20.8% (51)	7.8% (19)	4.9% (12)	2.9% (7)	31.4% (77)	24.9% (61)§	6.5% (16)	14.3% (35)	6.9% (17)

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography

*For Chang 2008, additional noninvasive testing was reported at 30 days in the CCTA as a whole, i.e. not stratified by pretest risk; thus this outcomes is included in the mixed population table. For Sabharwal, referral for additional testing was not reported stratified by pretest risk and so is included here.

†Dobutamine stress echocardiography.

‡Includes exercise (n=57) and dobutamine (n=47) stress echocardiography. Results also reported separately by type of stressor.

§Includes myocardial perfusion imaging and dobutamine stress echocardiography. Rates for the CCTA group and ECG group respectively are 2.5% (n=6) and 0% versus 24.5% (n=60) and 0.4% (n=1).

**Also reports proportions of patients with 1 to 3 outpatient cardiology visits Exercise ECG (18.4% [100]) versus CCTA (10.4% [26]).

Table E4. Demographics for observational studies in patients with mixed pretest risk for coronary artery disease comparing functional test versus functional test

Author (year)		**Marwick (2003)[5]**		**Shreibati (2011)[6]**		
Test **Sample size**		Ex Echo (n=3860)	Ex ECG (n=3796)	Stress Echo (n=80604)	Ex ECG (n=61063)	Nuclear MPI (n=132,343)
Patient demographics	Female, % (n)	40% (1544)	42% (1594)	57.5% (46,347)	49.0% (29,913)	54.5% (72,165)
	Age (years); mean ± SD	61.4 ± 12[†]	63.2 ± 12[†]	73.8 ± 5.8	73.1 ± 5.6	75.7 ± 5.9
	Race, % (n)	NR	NR	White: 89.7% (71802) Black: 5.8% (4695) Hispanic: 1.1% (863)	White: 87.2% (53,223) Black: 5.5% (3,346) Hispanic: 1.8% (1067)	White: 89.3% (118,185) Black: 6.7% (8902) Hispanic: 1.5% (1898)
	Pretest risk, % (n)[*]	Low: 11% (425) IM: 58% (2239) High: 31% (1197)	Low: 12% (456) IM: 60% (2278) High: 28% (1063)	Mixed	Mixed	Mixed
	Subgroup	No	No	Medicare population (100%)	Medicare population (100%)	Medicare population (100%)
Cardiac risk factors, % (n)	Chest pain	100% (3860)	100% (3796)	NR	NR	NR
	Typical angina	NR	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR
	Prior MI	NR	NR	0% (0)[§]	0% (0)[§]	0% (0)[§]
	Prior revascularization	NR	NR	0% (0)[§]	0% (0)[§]	0% (0)[§]
	Prior CABG/PCI	NR	NR	0% (0)[§]	0% (0)[§]	0% (0)[§]
	Known CAD	25% (965)[‡]	21% (797)[‡]	0% (0)[**]	0% (0)[**]	0% (0)[**]
	Chest pain frequency	NR	NR	NR	NR	NR
	Hypertension	48% (1853)	50% (1898)	60.2% (48,495)	57.5% (35,091)	57.5% (35,091)
	Diabetes	17% (656)	18% (683)	26.4% (21,242)	25.0% (15,249)	25.0% (15,249)
	Hyperlipidemia	NR	NR	64.6% (52056)	65.1% (39,737)	65.1% (39,737)
	Current smoker	26% (1004)	30% (1139)	2.3% (1896)	2.1% (1268)	2.1% (1268)
Test details	CT images (slice)	NA	NA	NA	NA	NA
	CACS performed	NA	NA	NA	NA	NA
	Type of stressor	Treadmill	Treadmill	NR	Exercise or pharmacologic stress (types NR)	Exercise or pharmacologic stress (types NR)
	Contrast (dose)	NR	NA	NR	NA	NA

Author (year)		Marwick (2003)[5]		Shreibati (2011)[6]		
Study characteristics	Setting	NR	NR	Outpatient	Outpatient	Outpatient
	Followup period % completed followup (n)	38.4 ± 24 months	30 ± 24 months	6 months 100% (80,604)	6 months 100% (61,063)	6 months 100% (61,063)
	Study Design	Retro cohort	Retro cohort	Retro admin database	Retro admin database	Retro admin database
	Study Quality	Poor	Poor	Fair	Fair	Fair

CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; ECG = electrocardiogram; Echo = echocardiogram; Ex = exercise; IM = intermediate risk; MI = myocardial infarction; MPI = myocardial perfusion imaging; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; Retro = retrospective; SPECT = single-photon emission computed tomography

*As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.

†$p<0.05$

‡Results stratified for patients with and without a history of CAD. Demographics were not provided for these subgroups.

§ Within previous 12 months.

** Within previous 9 months.

Table E5. Clinical outcomes from observational studies including populations with mixed risk for coronary artery disease and comparing functional testing with functional testing

Author, Year Study design	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction, Heart Failure, Change in Angina	Major Adverse Cardiac Events	Unstable Angina	Quality of Life*
Marwick, 2003[5]* Prospective cohort	Exercise Echocardiography (n=2895) Mean 3.2 +/- 2.0 years	4.2% (122) (cardiac)	NR	8.4% (243)‡	NR	NR
	Exercise ECG (2999) Mean 2.5 +/- 2.0 years	5.2% (156) (cardiac)	NR	10.7% (321)‡	NR	NR
Shreibati, 2011[6] Administrative database	Stress echocardiography (n=80,604) 6 months	0.95% (765) (all-cause)	NR	NR	NR	NR
	Exercise ECG (n=61,063) 6 months	0.78% (479) (all-cause)	NR	NR	NR	NR
	Nuclear MPI (n=132,343) 6 months	1.28% (1694) (all-cause)	NR	NR	NR	NR

ECG = electrocardiography; MPI = myocardial perfusion imaging; NR = not reported
*Only the subgroups without known CAD included in our analysis.
†Clinical management outcomes include percutaneous coronary intervention, coronary artery bypass graft, medical therapy, outpatient cardiovascular visit.
‡Death or myocardial infarction.

Table E6. Clinical management and hospitalization outcomes from observational studies including populations with mixed risk for coronary artery disease and comparing functional testing with functional testing

Author, Year Study Design	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Revascular-ization	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Any Additional Noninvasive Testing	Hospitalization
Marwick, 2003[5]* Prospective cohort	Exercise Echocardiography (n=2895) Mean 3.2 +/- 2.0 years	58% (NR)	42% (NR)	31% (NR)	10% (NR)	NR	NR
	Exercise ECG (2999) Mean 2.5 +/- 2.0 years	50% (NR)	36% (NR)	24% (NR)	13% (NR)	NR	NR
Shreibati, 2011[6] Administrative database	Stress Echocardiography (n=80,604) 6 months	9.50% (7659)	4.22% (3403)	2.61% (2100)	1.69% (1365)	5.57% (4492)‡	0.32% (255) for acute MI
	Exercise ECG (n=61,063) 6 months	9.04% (5520)	4.31% (2632)	2.57% (1569)	1.82% (1112)	19.34% (11,812)§	0.32% (195) for acute MI
	Nuclear MPI (n=132,343) 6 months	12.13% (16,058)	4.59% (6078)	3.37% (4465)	1.29% (1709)	3.22% (4257)**	0.43% (575) for acute MI

CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; NR = not reported

*Only the subgroups without known CAD included in our analysis. We could not back-calculate the number of patients because the authors only reported risk-adjusted rates based on post-test risk and it is unclear how many patients were included in each category; thus, only percentages are reported.

†Death or myocardial infarction.

‡ Includes: MPI (4.03%, n=3248); CCTA (0.68%, n=551), stress echo (0.74%, n=593), Ex ECG 0.95% (n=762).

§ Includes: MPI (16.47%, n=10,060); CCTA (0.76%, n=465) stress echo (1.75%, n=1067), Ex ECG 2.57% (n=1569)

**Includes: MPI (1.64%, n=2165); CCTA (0.95%, n=1261) stress echo (0.27%, n=356), Ex ECG 0.68% (n=906)

Table E7. Demographics for observational studies in patients with mixed pretest risk for coronary artery disease comparing anatomic test versus functional tests

Author (year)		**Yamauchi (2012)[7‡]**		**Tandon (2012)[8*]**		**Min (2008)[9* †‡]**	
Test **Sample size**		CCTA (n=635)	MPI (n=1221)	CCTA (n=1221)	SPECT (n=1221)	CCTA (n=1938)	SPECT (n=7752)
Patient demographics	Female, % (n)	46.6% (291)	43.8% (528)	49.1% (599)	49.1% (599)	43.2% (837)	43.2% (3349)
	Age (years); mean ± SD	66.0±10.3	66.2±10.6	58.1±10.9	58.1±10.9	52.1±8.7	52.1±8.7
	Race, % (n)	NR	NR	NR	NR	NR	NR
	Pretest risk, % (n)[§]	NR (NYHA class)	NR (NYHA class)	NR	NR	NR	NR
	Subgroup (%)	None	None	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	NR	NR	50.8% (620)	48.8% (596)	NR	NR
	Typical angina	NR	NR	NR	NR	NR	NR
	Atypical angina	0% (0)	0% (0)	NR	NR	NR	NR
	Unstable angina	NR	NR	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR	NR	NR
	Nonangina	NR	NR	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR
	Prior MI	0% (0)	0% (0)	NR	NR	0% (0)	0% (0)
	Prior revascularization	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	Known CAD	NR	NR	0% (0)	0% (0)	0% (0)[††]	0% (0)[††]
	Chest pain frequency	NR	NR	NR	NR	NR	NR
	Hypertension	57.8% (361)	56.4% (679)	47.9% (585)	47.5% (580)	34.8% (674)	34.8% (2698)
	Diabetes	26.6% (166)	28.1% (339)	11.4% (139)	11.9% (145)	8.6% (167)	8.6% (667)
	Hyperlipidemia	49.8% (311)[‡‡]	44.2% (532)[‡‡]	47.4% (579)[‡‡]	38.7% (472)[‡‡]	48.3% (936)	48.3% (3744)
	Smoker (current or past)	21.6% (135)	20.7% (249)	54.1% (661)	47.9% (585)	NR	NR
Test details	CT images (slice)	NR	NA	64	NA	NR	NA
	CACS performed	NR	NA	No	NA	NR	NA
	Type of stressor	NA	NR	NA	Exercise (type NR) or pharmacologic (dipyridamole)	NA	NR
	Contrast/radioisotope	NR	NR	Visapaque or Omnipaque	Tc-99m sestamibi	NR	NR
Study characteristics	Setting	NR	NR	NR	NR	NR	NR
	Followup period % completed followup (n)	Median 1.4±0.5 years; 98.4% (625/635)	Median 1.4±0.5 years; 98.7% (1205/1221)	6 months (%NR)	6 months (%NR)	9 months (%NR)	9 months (%NR)
	Study Design	Pro cohort	Pro cohort	Pro registry	Pro registry	Retro admin database	Retro admin database
	Study Quality	Fair	Fair	Poor	Poor	Fair	Fair

Admin = administrative; CACS = coronary artery calcium scoring; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; NA = not applicable; NR = not reported; Pro = prospective; Retro = retrospective; SPECT = single-photon emission computed tomography
*One group of patients were selected through patient matching: CCTA (Cheezum), SPECT (Tandon; Min).
† It was not clear that all patients who met the inclusion criteria and underwent CCTA were included.
‡Patient numbers per group were only reported for those patients who underwent examination and testing. Coronary angiography was also examined as a comparator for initial diagnostic test (n=950) but is excluded for the purpose of this report.
§As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.
**Within the previous 12 months.
††Within the previous 9 months.
‡‡p<0.05.

Table E7. Continued.

Author (year)		**Shreibati (2011)[6]**			
Test **Sample size**		CCTA (n=8820)	Stress Echo (n=80604)	Ex ECG (n=61063)	Nuclear MPI (n=132,343)
Patient demographics	Female, % (n)	55.8% (4919)	57.5% (46,347)	49.0% (29,913)	54.5% (72,165)
	Age (years); mean ± SD	73.6 ± 5.8	73.8 ± 5.8	73.1 ± 5.6	75.7 ± 5.9
	Race, % (n)	White: 90.7% (8001) Black: 5.0% (444) Hispanic: 1.1% (97)	White: 89.7% (71802) Black: 5.8% (4695) Hispanic: 1.1% (863)	White: 87.2% (53,223) Black: 5.5% (3,346) Hispanic: 1.8% (1067)	White: 89.3% (118,185) Black: 6.7% (8902) Hispanic: 1.5% (1898)
	Pretest risk, % (n)*	Mixed	Mixed	Mixed	Mixed
	Subgroup	Medicare population (100%)	Medicare population (100%)	Medicare population (100%)	Medicare population (100%)
Cardiac risk factors, % (n)	Chest pain	NR	NR	NR	NR
	Typical angina	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR
	Prior MI	0% (0)†	0% (0)†	0% (0)†	0% (0)†
	Prior revascularization	0% (0)†	0% (0)†	0% (0)†	0% (0)†
	Prior CABG/PCI	0% (0)†	0% (0)†	0% (0)†	0% (0)†
	Known CAD	0% (0)‡	0% (0)‡	0% (0)‡	0% (0)‡
	Chest pain frequency	NR	NR	NR	NR
	Hypertension	65.5% (5778)	60.2% (48,495)	57.5% (35,091)	57.5% (35,091)
	Diabetes	29.9% (2639)	26.4% (21,242)	25.0% (15,249)	25.0% (15,249)
	Hyperlipidemia	72.1% (6359)	64.6% (52056)	65.1% (39,737)	65.1 (39,737)
	Current smoker	2.5 (218)	2.3 (1896)	2.1 (1268)	2.1 (1268)
Test details	CT images (slice)	NR	NA	NA	NA
	CACS performed	NR	NA	NA	NA
	Type of stressor	NA	NR	Exercise or pharmacologic stress (types NR)	Exercise or pharmacologic stress (types NR)
	Contrast (dose)	NA	NR	NA	NA
Study	Setting	Outpatient	Outpatient	Outpatient	Outpatient

Author (year)		Shreibati (2011)[6]			
characteristics	Followup period % completed followup (n)	6 months 100 (8820)	6 months 100% (80,604)	6 months 100% (61,063)	6 months 100% (61,063)
	Study Design	Retro admin database	Retro admin database	Retro admin database	Retro admin database
	Study Quality	Fair	Fair	Fair	Fair

CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; Echo = echocardiogram; ED = emergency department; IM = intermediate risk; MI = myocardial infarction; MPI = myocardial perfusion imaging; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention

*As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.

† Within previous 12 months.

‡ Within previous 9 months.

Table E8. Clinical outcomes from observational studies including populations with mixed risk for coronary artery disease and comparing anatomical testing with functional testing

Author, Year Study Design	Test, Sample Size, Final Followup	Mortality	Myocardial infarction	Heart failure, unstable angina	Major Adverse Cardiac Events	New onset angina	Quality of Life*
Yamauchi, 2012[7*] Prospective observational	CCTA (n=625) Median 17 months	NR	NR	NR	2.1% (13)	NR	NR
	Nuclear MPI (n=1205) Median 17 months	NR	NR	NR	2.6% (31)†	NR	NR
Tandon, 2012[8] Prospective registry	CCTA‡ (n=1221) 6 months	0.2% (3) (cardiac)	0.5% (6)	NR	NR	NR	NR
	SPECT‡ (n=1221) 6 months	NR	NR	NR	NR	NR	NR
Min, 2008[9] Administrative database	CCTA (n=1938) 9 months	NR	0.4% (8)	NR	NR	3.0% (58)	NR
	SPECT (n=7752) 9 months	NR	0.6% (43)	NR	NR	3.5% (272)	NR
Shreibati, 2011[6] Administrative database	CCTA (n=8820) 6 months	1.05% (93) (all-cause)	NR	NR	NR	NR	NR
	Stress Echocardiography (n=80,604) 6 months	0.95% (765) (all-cause)	NR	NR	NR	NR	NR
	Exercise ECG (n=61,063) 6 months	0.78% (479) (all-cause)	NR	NR	NR	NR	NR
	Nuclear MPI (n=132,343) 6 months	1.28% (1694) (all-cause)	NR	NR	NR	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography
*The n values wee backcalculated from percent given.
†MACE=death, acute MI, other major cardiac event, late (>3months) revascularization.
‡CCTA patients were enrolled consecutively and matched to SPECT patients from the same time period.

Table E9. Clinical management and hospitalization outcomes from observational studies including populations with mixed risk for coronary artery disease and comparing anatomical testing with functional testing

Author, Year Study Design	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Revascular-ization	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Any Additional Noninvasive Testing	Hospitali-zation	Cardiovascular Outpatients Visit
Yamauchi, 2012[7*]	CCTA (n=625) Median 17 months	31% (194)	NR†	NR	NR	2.0% (13)	NR	NR
Prospective observational	Nuclear MPI (n=1205) Median 17 months	33% (398)	NR†	NR	NR	1.0% (12)	NR	NR
Tandon, 2012[8]	CCTA‡ (n=1221) 6 months	10.6% (129)	6.2% (76)	3.9% (48)	2.3% (28)	NR	NR	NR
Prospective registry	SPECT‡ (n=1221) 6 months	10.2% (125)	5.9% (72)	4.0% (49)	1.9% (23)	NR	NR	NR
Min, 2008[9*§]	CCTA (n=1938) 9 months	6.2% (120)	2.1% (41)	1.4% (27)	0.7% (14)	8.3% (161)§	4.2% (82) cardiac-related	17.4% (338)
Administrative database	SPECT (n=7752) 9 months	9.5% (736)	1.6% (124)	1.1% (85)	0.5% (39)	2.1% (163)**	4.1% (320) cardiac-related	13.3% (1030)
Shreibati, 2011[6] Administrative database	CCTA (n=8820) 6 months	22.94% (2023)	11.41% (1006)	7.85% (692)	3.71% (327)	4.98% (439)††	0.19% For acute MI	NR
	Stress Echocardiography (n=80,604) 6 months	9.50% (7659)	4.22% (3403)	2.61% (2100)	1.69% (1365)	5.57% (4492)‡‡	0.32% (255) for acute MI	NR
	Exercise ECG (n=61,063) 6 months	9.04% (5520)	4.31% (2632)	2.57% (1569)	1.82% (1112)	19.34% (11,812)§§	0.32% (195) for acute MI	NR
	Nuclear MPI (n=132,343) 6 months	12.13% (16,058)	4.59% (6078)	3.37% (4465)	1.29% (1709)	3.22% (4257)***	0.43% (575) for acute MI	NR

CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; MI = myocardial infarction; NR = not reported; SPECT = single photon emission computed tomography

*The n values were back-calculated from the percent given.

†Percent NR, OR=1.62 (95% CI, 1.20 to 2.18), p=0.002; higher in CCTA groups.

‡CCTA patients were enrolled consecutively and matched to SPECT patients from the same time period.

§Additional testing consisted of CCTA (0.8%, n=16) and SPECT (7.5%, n=145).

**Additional testing consisted of CCTA (0.7%, n=54) and SPECT (1.4%, n=109).

††Includes: MPI (2.74%, n=242); CCTA (0.87%, n=77), stress echo (0.71%, n=63), Ex ECG 1.47% (n=130)
‡‡Includes: MPI (4.03%, n=3248); CCTA (0.68%, n=551), stress echo (0.74%, n=593), Ex ECG 0.95% (n=762)
§§Includes: MPI (16.47%, n=10,060); CCTA (0.76%, n=465) stress echo (1.75%, n=1067), Ex ECG 2.57% (n=1569)
***Includes: MPI (1.64%, n=2165); CCTA (0.95%, n=1261) stress echo (0.27%, n=356), Ex ECG 0.68% (n=906)

Table E10. Demographics for included RCTs in populations considered to be at high risk for coronary artery disease

Author (year)		**Sabharwal (2007)[2]**	
Test **Sample size**		SPECT (n=45)*	Exercise ECG (n=61)*
Patient demographics	Female, % (n)	44.4% (111)	42.5% (88)
	Age (years); mean ± SD	59.7 ± 12.2	58.9 ± 911.4
	Race, % (n)	White: 55.6% (139)	White: 46.9% (97)
	Pretest risk, % (n)†	Low: 10.8% (27) IM: 71.2% (178) High: 18.0% (45)	Low: 21.3% (44) IM: 49.3% (102) High: 29.5% (61)
	Subgroup	None	None
Cardiac risk factors, % (n)	Chest pain	100% (250)	100% (207)
	Typical angina	NR	NR
	Atypical angina	NR	NR
	Unstable angina	NR	NR
	Nonspecific chest pain	NR	NR
	Nonangina	NR	NR
	Noncardiac angina	NR	NR
	Silent ischemia	NR	NR
	Dyspnea	NR	NR
	Prior MI	0% (0)	0% (0)
	Prior revascularization	NR	NR
	Prior CABG/PCI	NR	NR
	Known CAD	0% (0)	0% (0)
	Chest pain frequency	NR	NR
	Hypertension	53.2% (133)	46.3% (96)
	Diabetes	19.2% (48)	14.5% (30)
	Hyperlipidemia	NR	NR
	Current smoker	12.8% (32)	16.4% (34)
Test details	CT images (slice)	NA	NA
	CACS performed	NA	NA
	Type of stressor	Exercise (treadmill 62%) and/or pharmacologic stress (dipyradimole 38% [or dobutamine if contraindication])	Treadmill (Bruce protocol)
	Contrast (dose)	Radiotracer: Tc-99m sestamibi	NA
Study characteristics	Setting	Outpatient	Outpatient
	Followup period % completed followup (n)	Mean 19.6 months 96.9% (443/457)‡	Mean 19.6 months 96.9% (443/457)‡
	Study Design	RCT	RCT
	Study Quality	Fair	Fair

CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; ECG = electrocardiogram; IM = intermediate risk; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography
*Subgroup of high pretest risk patients; demographics represent the entire population (not reported separately for groups stratified by high risk).

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.
‡Loss-to-followup not reported by group; 10 patients did not have followup data and there were 2 deaths in each group (SPECT: 2 malignancy; ECG: 1 malignancy and 1 cardiac).

Table E11. Clinical outcomes from randomized controlled trials including patients considered to be at high risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure	Stroke	Major Adverse Cardiac Events	Unstable Angina	Dysrhythmia	Quality of Life
Sabharwal, 2007[2]*	SPECT (n=45) Mean 21.7 ± 6.4 months	NR†	NR†	NR	NR	NR	NR	NR	NR
	Exercise ECG (n=61) Mean 21.7 ± 6.4 months	NR†	NR†	NR	NR	NR	NR	NR	NR

CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography

*Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the low risk group only are reported here.

†Mortality and myocardial infarction for SPECT and Exercise ECG are not reported by pretest risk; these outcomes are reported in the mixed population table, Table E2.

Table E12. Clinical management outcomes from randomized controlled trials including patients considered to be at high risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Re-vascularization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Medical Therapy	Outpatient Cardiovascular Visit
Sabharwal, 2007[2]*	SPECT (n=45) Mean 21.7 ± 6.4 months	44.4% (20)	NR†	NR	NR	0% (0) (imaging)	55.5% (25)	NR
	Exercise ECG (n=61) Mean 21.7 ± 6.4 months	85.2% (52)	NR†	NR	NR	4.9% (3) (imaging)	9.8% (6)	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography
*Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the low risk group only are reported here.
† Revascularization for SPECT and Ex ECG are not reported by pretest risk, these outcomes are reported in the mixed population table, Table E2.

Table E13. Hospital and emergency department outcomes from randomized controlled trials including patients considered to be at high risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Hospitalization (any)	Hospitalization (cardiac)	Emergency Department Revisit
Sabharwal, 2007[2]*	SPECT (n=45) Mean 21.7 ± 6.4 months	NR†	NR†	NR†
	Exercise ECG (n=61) Mean 21.7 ± 6.4 months	NR†	NR†	NR†

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography
*Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the low risk group only are reported here.
† Hospitalization and ER revisit are not reported stratified by pretest risk group, these outcomes are reported in the mixed population table, Table E2.

Table E14. Demographics for the included RCT in a population considered to be at intermediate to high risk for coronary artery disease

Author (year)		**Min (2012)[10]**	
Test **Sample size**		CCTA (n=91)	SPECT (n=89)
Patient demographics	Female, % (n)	41.8% (38)*	57.3% (51)*
	Age (years); mean ± SD	55.9±10*	58.9±9.5*
	Race, % (n)	NR	NR
	Pretest risk, % (n)†	Mixed (results not stratified): Low 4.1% (4) IM: 62.6% (57) High: 33.0% (30)	Mixed (results not stratified): Low: 9.0% (8) IM: 67.4% (60) High: 23.6% (21)
	Subgroup	None	None
Cardiac risk factors, % (n)	Chest pain	NR	NR
	Typical angina	31.9% (29)	22.5% (20)
	Atypical angina	23.1% (21)	24.7% (22)
	Unstable angina	NR	NR
	Nonspecific chest pain	NR	NR
	Nonangina	NR	NR
	Noncardiac angina	27.5% (25)	24.7% (22)
	Silent ischemia	NR	NR
	Dyspnea	NR	NR
	Prior MI	0% (0)	0% (0)
	Prior revascularization	0% (0)	0% (0)
	Prior CABG/PCI	NR	NR
	Known CAD	0% (0)	0% (0)
	Chest pain frequency	NR	NR
	Hypertension	61.5% (56)	68.5% (61)
	Diabetes	23.1% (21)	21.3% (19)
	Hyperlipidemia	52.7% (48)	60.7% (54)
	Current smoker	58.2% (53)	42.7% (38)
Test details	CT images (slice)	64	NA
	CACS performed	No	NA
	Type of stressor	NA	Exercise (treadmill) or pharmacologic (adenosine)
	Contrast (dose)	Iodinated contrast	Tc-99m sestamibi (some had dual isotope imaging thallium-201)
Study characteristics	Setting	Outpatient	Outpatient
	Followup period % completed followup (n)	mean 55 ± 34 days Overall: 96.1% (173/180)	mean 55 ± 34 days Overall: 96.1% (173/180)
	Study Design	RCT	RCT
	Study Quality	Poor	Poor

CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; IM = intermediate risk; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography

*p<0.05

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.

Table E15. Clinical outcomes, clinical management outcomes, and hospitalization outcomes from randomized controlled trials including patients considered to be at intermediate to high risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure, Stroke, MACE	Change in Angina*	Quality of Life*	Invasive Coronary Angiography	Re-vascularization (any)†	Additional Noninvasive Testing (any)	Hospitalization (CAD-related)
Min, 2012[10‡]	CCTA (n=91) Mean 55 ± 34 days	0% (0)	0% (0)	NR	Stability: 30.0 ± 37.0 Frequency: 10.2 ± 16.4	13.5 ± 22.6	13% (12)	8% (7)	3% (3)	12.1% (11)
	SPECT (n=89) Mean 55 ± 34 days	0% (0)	0% (0)	NR	Stability: 22.9 ± 30.1 Frequency: 7.6 ± 14.8	11.6 ± 19.0	8% (7)	1% (1)	10% (9)	11.2% (10)

CAD = coronary artery disease; CCTA = coronary computed tomography angiography; MACE = major adverse cardiac events; NR = not reported; SPECT = single photon emission computed tomography

*Change in angina reported as difference from baseline (± standard deviation) to final followup in Seattle Angina Questionnaire subscales "angina stability" and "angina frequency". Quality of life reported as difference from baseline (± standard deviation) to final followup in Seattle Angina Questionnaire subscale "disease perception/quality of life".

†Study did not report percutaneous coronary intervention and coronary artery bypass graft separately.

‡For the outcomes any noninvasive testing, invasive coronary angiography, and subsequent revascularization, cases were calculated from percentage given.

§Study also reports increased incident aspirin use (22% versus 8%) and statin use (7% versus 23.5%) in the CCTA versus SPECT groups, no differences noted for other medications

Table E16. Demographics for the included observational study in populations considered to be at intermediate to high risk for coronary artery disease

Author (year)		**Hachamovitch (2012) / Hlatky (2014)[11, 12]**	
Test **Sample size**		SPECT (n=565)*	PET (n=548)*
Patient demographics	Female, % (n)	51% (286)	59% (323)
	Age (years); mean ± SD	60 ± 11	63 ± 11
	Race, % (n)	White: 68% (386)	White: 80% (439)
	Pretest risk, % (n)†	Intermediate-high risk	Intermediate-high risk
	Subgroup	None	None
Cardiac risk factors, % (n)	Chest pain	NR	NR
	Typical angina	79% (449)	68% (370)
	Atypical angina	NR	NR
	Unstable angina	NR	NR
	Nonspecific chest pain	4% (23)	5% (27)
	Dyspnea	24% (136)	44% (239)
	Prior MI	NR	NR
	Prior revascularization	NR	NR
	Prior CABG/PCI	NR	NR
	Known CAD	0% (0)	0% (0)
	Chest pain frequency	NR	NR
	Hypertension	66% (371)	73% (398)
	Diabetes	31% (173)	41% (225)
	Hyperlipidemia	60% (338)	65% (356)
	Smoker (past or current)	20% (110) within 5 years	12% (64) within 5 years
Test details	Type of stressor	Exercise, pharmacologic or combination (types NR)	Pharmacologic (type NR)
	Radioisotope	NR	NR
Study characteristics	Setting	Hospital, outpatient, academic, nonacademic sites, and community and tertiary care centers	Hospital, outpatient, academic, nonacademic sites, and community and tertiary care centers
	Followup period % completed followup (n)	3 months %NR	3 months %NR
	Study Design	Prospective	Prospective
	Study Quality	Fair	Fair

CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; PET = positron emission tomography; SD = standard deviation; SPECT = single photon emission computed tomography

*Demographics and results reported only for those patients who completed 90-day followup. Of 1717 total patients (includes CCTA group described elsewhere), 1703 (99.2%) had complete followup (loss-to-followup not reported by test group).

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.

Table E17. Clinical outcomes, clinical management outcomes, and hospitalization outcomes from prospective observational studies including patients considered to be at low to intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure, Stroke, MACE, Change in Angina, QOL	Invasive Coronary Angiography	Revascular-ization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Non-invasive Testing (any)	Hospital-ization (CAD-related)
Hachamovitch 2012/Hlatky 2014[11, 12‡]	PET (n=548) 24 months	5.5% (30)	1.1% (6)	NR	3 mos: 11.5% (63) 24 mos: 15.5% (82)	3 mos: 6.2% (34) 24 mos: 7.7% (42)	3 mos: 4.6% (25) 24 mos: 5.7% (31)	3 mos: 1.6% (9) 24 mos: 2.0% (11)	NR	NR
	SPECT (n=565) 24 months	1.6% (9)	1.2% (7)	NR	3 mos: 4.2% (24) 24 mos: 6.7% (38)	3 mos: 1.8% (10) 24 mos: 2.3% (13)	3 mos: 1.4% (8) 24 mos: 1.9% (11)	3 mos: 0.4% (2) 24 mos: 0.4% (2)	NR	NR

CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; MACE = major adverse cardiac events; NR = not reported; PET = positron emission tomography; QOL = quality of life; SPECT = single photon emission computed tomography

*Unless otherwise noted, relative risk and 95% confidence interval estimates were calculated by the EPC and are not adjusted.

†Authors report odds ratio adjusted for baseline characteristics for PET compared with SPECT.

‡ Also report medication usage/change, "The frequency pattern of medication use was similar across all imaging arms, with the exception of the lipid-lowering agent use, which was slightly higher in patients referred for PET and CCTA (52.6% and 50.0%, respectively)."

Table E18. Demographics for included RCTs in populations considered to be at intermediate risk for coronary artery disease

Author (year)		**Hoffman (2012)[13]**		**Chang (2008)[1]**		**Shaw (2011)[14]**		**Sabharwal (2007)[2]**	
Test Sample size		CCTA (n=501)	Usual Care (n=499)	CCTA (n=55)*	Usual Care (n=56)*	SPECT (n=412)*	Exercise ECG (n=412)*	SPECT (n=178)*	Exercise ECG (n=102)*
Patient demographics	Female, % (n)	47.9% (240)	46.1 (230)	39% (52)	38% (51)	100% (384)	100% (388)	44.4% (111)	42.5% (88)
	Age (years); mean ± SD	54±8	54±8	57 ± 14	58 ± 14	median (IQR): 62 (58–68)	median (IQR): 63 (60–69)	59.7 ± 12.2	58.9 ± 911.4
	Race, % (n)	White: 65.9% (330) Black: 28.1% (141) Asian: 3.6% (18) Other: 2.4% (12)	White: 66.1% (330) Black: 28.3% (141) Asian: 2.6% (13) Other: 3.6% (18)	NR	NR	NR	NR	White: 55.6% (139)	White: 46.9% (97)
	Pretest risk, % (n)†	NR	NR	Low: 37.6% (50) IM: 41.4% (55) High: 21.1% (28)	Low: 36.8% (49) IM: 42.1% (56) High: 21.1% (28)	IM: 100% (384)	IM: 100% (384)	Low: 10.8% (27) IM: 71.2% (178) High: 18.0% (45)	Low: 21.3% (44) IM: 49.3% (102) High: 29.5% (61)
	Subgroup	NR	NR	NR	NR	Women (100%)	Women (100%)	None	None
Cardiac risk factors, % (n)	Chest pain	100% (501)	100% (499)	100% (133)	100% (133)	90.0% (346)	89.4% (347)	100% (250)	100% (207)
	Typical angina	89.0% (446)	91.0% (454)	NR	NR	59.8% (230)	61.2% (237)	NR	NR
	Atypical angina	11.0% (55)	9.0% (45)	NR	NR	9.3% (36)	9.1% (35)	NR	NR
	Unstable angina	NR	NR	NR	NR	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR	27.8% (107)	27.0% (105)	NR	NR
	Nonangina	NR	NR	NR	NR	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR	NR	NR	NR
	Dyspnea	1.4% (7)	2.0% (10)	NR	NR	48.3% (185)	53.5% (208)	NR	NR
	Prior MI	0% (0) (1.6% (8) at index visit)‡	0% (0) (3.0% (15) at index visit)‡	NR	NR	NR	NR	0% (0)	0% (0)
	Prior revascularization	0% (0)‡	0% (0)‡	NR	NR	NR	NR	NR	NR
	Prior CABG/PCI	0% (0)‡	0% (0)‡	NR	NR	NR	NR	NR	NR
	Known CAD	0% (0)‡	0% (0)‡	12% (16)	17% (23)	0% (0)	0% (0)	0% (0)	0% (0)
	Chest pain	NR	NR	NR	NR	Within 4 wks	Within 4 wks	NR	NR

Author (year)		Hoffman (2012)[13]		Chang (2008)[1]		Shaw (2011)[14]		Sabharwal (2007)[2]	
	frequency					Daily: 18.5% (71); ≥3 episodes/ wk: 25.9% (99)	Daily: 16.3% (63); ≥3 episodes/ wk: 29.3% (114)		
	Hypertension	53.7% (269)	54.5% (272)	46% (61)	41% (55)	52.0% (200)	55.2% (214)	53.2% (133)	46.3% (96)
	Diabetes	17.2% (86)	17.4% (87)	16% (21)	19% (25)	14.2% (55)	12.6% (49)	19.2% (48)	14.5% (30)
	Hyperlipidemia	45.9% (230)	44.9% (224)	29% (39)	25% (33)	53.7% (206)	50.0% (194)	NR	NR
	Current smoker	49.7% (249)	48.7% (243)	17% (23)	23% (31)	42.4% (163)	48.8% (189)	12.8% (32)	16.4% (34)
Test details	CT images (slice)	64+	NA	64	NA	NA	NA	NA	NA
	CACS performed	Yes	NA	NR	NR	NA	NA	NA	NA
	Type of stressor	NA	exercise or pharmacologic stress	NA	NA	Exercise (type NR)	Treadmill (Bruce protocol)	Exercise (treadmill 62%) and/or pharmacologic stress (dipyradimole 38% [or dobutamine if contraindication])	Treadmill (Bruce protocol)
	Contrast (dose)	NR (iodinated contrast agent)	NA	Lomeprol (80mL lomeron 400; Bracco, Milan, Italy)	NA	Tc-99m tetrofosmin; dual-isotope imaging with thallium 201 (n=94)	NA	Radiotracer: Tc-99m sestamibi	NA
Study characteristics	Setting	ED	ED	ED	ED	Outpatient	Outpatient	Outpatient	Outpatient
	Followup period % completed followup (n)	28 days 99.2% (497)	28 days 98.2% (490)	30 days	30 days	24 months 94.2% (388/412)	24 months 93.2% (384/412)	Mean 19.6 months 96.9% (443/457)§	Mean 19.6 months 96.9% (443/457)§
	Study Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair

CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; ED = emergency department; IM = intermediate risk; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography

*Subgroup of patients with intermediate pretest risk; demographics are reported for the entire population (not reported separately by group stratified by intermediate risk).

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.

‡MI, Revascularization, CABG, CAD, were abstracted from protocol on clinicaltrials.gov

§Loss-to-followup not reported by group; 10 patients did not have followup data and there were 2 deaths in each group (SPECT: 2 malignancy; ECG: 1 malignancy and 1 cardiac).

Table E19. Clinical outcomes from randomized controlled trials including patients considered to be at intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure	Stroke	Major Adverse Cardiac Events*	Unstable Angina	Worsening Angina Frequency or Stability†	Angina-free	Quality of Life, Dysrhythmia
Hoffman, 2012[13]	CCTA (n=501) 28 days	Index: 0% (0) 28 days: 0% (0)	Index: 1.6% (8) 28 days: 0.2% (1)	NR	NR	28 days: 0.4% (2)	Index: 7.0% (35) 28 days: 0.2% (1)‡	NR	NR	NR
	Usual Care (n=499) 28 days	Index: 0% (0) 28 days: 0% (0)	Index: 3.0% (15) 28 days: 0.8% (4)	NR	NR	28 days: 1.2% (6)	Index: 3.4% (17) 28 days: 0.4% (2)‡	NR	NR	NR
Chang, 2008[1§]	CCTA (n=55) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 9% (5) 30 days: NR	NR	NR	NR	Index: 27% (15) 30 days: NR	NR	NR	NR
	Usual Care (n=56) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 9% (5) 30 days: NR	NR	NR	NR	Index: 24% (13) 30 days: NR	NR	NR	NR
Shaw, 2011[14**]	SPECT (n=384) 24 months	1.0% (4)	NR	NR	NR	2.3% (9)	NR	5% (19)	6 mos: 51.0% (196) 12 mos: 49.5% (190) 24 mos: 64.9% (249)	NR
	Exercise ECG (n=388) 24 months	0.5% (2)	NR	NR	NR	1.7% (7)	NR	5% (19)	6 mos: 50.6% (196) 12 mos: 48.9% (190) 24 mos: 60.4% (234)	NR
Sabharwal, 2007[2§‡]	SPECT (n=178) Mean 21.7 ± 6.4 months	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Exercise ECG (n=102) Mean 21.7 ± 6.4 months	NR	NR	NR	NR	NR	NR	NR	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; mos = months; NR = not reported; SPECT = single photon emission tomography.

*For Hoffman 2012, includes death, myocardial infarction, unstable angina, or urgent coronary revascularization; for Shaw 2011, includes death, nonfatal myocardial infarction, or hospital admission for an acute coronary syndrome or heart failure.

†As measured by the corresponding subscales of the Seattle Angina Questionnaire.

‡Requiring percutaneous coronary intervention.

§Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the intermediate risk group only are reported here.

**Shaw also reported cardiac death, myocardial infarction, and heart failure through 24 months followup but did not report events by test group; thus, for the entire population, rates were 0.1% (1/772), 0.4% (3/772), and 0.1% (1/772), respectively. The six deaths listed in the table are non-cardiac deaths.

Table E20. Clinical management outcomes from randomized controlled trials including patients considered to be at intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Revascularization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Single Positron Emission Computed Tomography	Stress Echo-cardiography	Exercise Electro-cardiography	Medical Therapy
Hoffman 2012[13]	CCTA (n=501) 28 days	Index: 11% (54) 28 days: 1.0% (5)	Index: 5.8% (29) 28 days: 0.6% (3)	Index: 5.0% (24) 28 days: 0.6% (3)	Index: 1.0% (5) 28 days: 0% (0)	Index: 16.4% (82) 28 days: 3.6% (18)	Index: 10% (50) 28 days: 1.6% (8)	Index: 4% (20) 28 days: 0% (0)	Index: 2% (12) 28 days: 1.9% (10)	NR
	Usual Care (n=499) 28 days	Index: 7% (36) 28 days: 0.8% (4)	Index: 3.6% (18) 28 days: 0.6% (3)	Index: 3% (14) 28 days: 0.6% (3)	Index: 1.0% (4) 28 days: 0% (0)	Index: 74.7% (373) 28 days: 4.8% (24)	Index: 25% (124) 28 days: 1.8% (9)	Index: 20% (102) 28 days: 0% (0)	Index: 29% (147) 28 days: 3.0% (15)	NR
Chang 2008[1*]	CCTA (n=55) 30 days	Index: 42% (23) 30 days: NR	Index: 20% (11) 30 days: NR	NR	NR	Index: 0% (0) 30 days: NR	NR	NR	NR	NR
	Usual Care (n=56) 30 days	Index: 46% (26) 30 days: NR	Index: 23% (13) 30 days: NR	NR	NR	Index: 50% (28) 30 days: NR	NR	NR	NR	NR
Shaw 2011[14†]	SPECT (n=384) 24 months	65.7% (22)	2.1% (8)	NR	NR	9.4% (36)	9.1% (35)	NR	0.3% (1)	NR
	Exercise ECG (n=388) 24 months	6.4% (25)	1.0% (4)	NR	NR	18.6% (72)	18.0% (70)	NR	0.5% (2)	NR
Sabharwal 2007[2*]	SPECT (n=178) Mean 21.7 ± 6.4 months	10.6% (19)	NR	NR	NR	0% (0) (imaging)	NR	NR	NR	89.3% (159)
	Exercise ECG (n=102) Mean 21.7 ± 6.4 months	43.1% (44)	NR	NR	NR	38.2% (39) (imaging)	NR	NR	NR	18.6% (19)

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography.
*Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the intermediate risk group only are reported here.
†For Shaw 2011: of the invasive coronary angiographies performed, nearly half occurred within 2 months of followup (not reported by test group), of the patients who underwent single positron emission tomography and had a subsequent revascularization, 0.5% (n=2) had an urgent revascularization after an acute coronary syndrome.

Table E21. Hospital and emergency department outcomes from randomized controlled trials including patients considered to be at intermediate risk for coronary artery disease

	Test, Sample Size, Final Followup	Hospitalization (any)	Hospitalization (cardiac)	Emergency Department Revisit
Hoffman 2012[13]	CCTA (n=501) 28 days	Index: 21.3% (107) 28 days: 1.4% (7)	NR	28 days: 2.8% (14)
	Usual Care (n=499) 28 days	Index: 25.1% (125) 28 days: 1.4% (7)	NR	28 days: 3.8% (19)
Chang 2008[1*]	CCTA (n=55) 30 days	Index: 47% (26) 30 days: NR	Index: 36% (20)† 30 days: NR	NR
	Usual Care (n=56) 30 days	Index: 55% (31) 30 days: NR	Index: 32% (18)† 30 days: NR	NR
Shaw 2011[14]	SPECT (n=384) 24 months	43.9% (15)	43.9% (15)‡	NR
	Exercise ECG (n=388) 24 months	3.1% (12)	3.1% (12)‡	NR
Sabharwal 2007[2§‡]	SPECT (n=178) Mean 21.7 ± 6.4 months	NR	NR	NR
	Exercise ECG (n=102) Mean 21.7 ± 6.4 months	NR	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography
*Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the intermediate risk group only are reported here.
†Includes hospitalization for non-ST-segment elevation myocardial infarction or unstable angina, which are also reported separately under clinical outcomes.
‡For chest pain, same patients as included under any hospitalization.

Table E22. Demographics for the included RCT in a population considered to be at intermediate risk for coronary artery disease comparing CCTA to various functional tests

Author (year)		**Douglas (2015)[15]**	
Test Sample size		CCTA (n=4996)	Functional testing (n=5007) Nuclear Stress Imaging: 63.09% (3159/5007) Stress Echocardiography: 21.09% (1056/5007) Exercise ECG: 9.53% (477/5007)
Patient demographics	Female, % (n)	51.9% (2593)	53.4% (2673)
	Age (years); mean ± SD	60.7 ± 8.3	60.9 ± 8.3
	Race, % (n)	Racial or ethnic minority: 23.5%	Racial or ethnic minority: 21.8%
	Pretest risk, % (n)*	Pre-test probability of CAD:† Low: 2.5% IM: 92.6% High: 4.9%	Pre-test probability of CAD:† Low: 2.5% IM: 92.6% High: 4.9%
	Subgroup	None	None
Cardiac risk factors, % (n)	Chest pain	73.6% (3673/4992)	71.9% (3599/5004)
	Typical angina	11.8% (590)	11.5% (576)
	Atypical angina	77.5% (3873)	77.9% (3900)
	Unstable angina	NR	NR
	Nonspecific chest pain	NR	NR
	Nonangina	10.7% (533)	10.6% (531)
	Noncardiac angina/ other pain‡	12.2% (607/4992)	12.5% (627/5004)
	Silent ischemia	NR	NR
	Dyspnea on exertion	14.3% (712/4992)	15.5% (778/5004)
	Prior MI	0% (0)	0% (0)
	Prior revascularization	0% (0)	0% (0)
	Prior CABG/PCI	NR	NR
	Known CAD	0% (0)	0% (0)
	Peripheral arterial or cerebrovascular disease	5.3% (263)	5.8% (289)
	Chest pain frequency	NR	NR
	Hypertension	65% (3247)	65% (3254)
	Diabetes	21.3% (1065)	21.5% (1079)
	Hyperlipidemia	67.4% (3365/4995)	67.9% (3402)
	Current smoker	50.7% (2533/4994)	51.4% (2571/5006)
Test details	CT images (slice)	≥64-slice	NA
	CACS performed	No	NA
	Type of stressor	NR	NR
	Contrast (dose)	NR	NR
Study characteristics	Setting	Outpatient	Outpatient
	Followup period % completed followup (n)	Median 25 months (IQR 18-34 months, 93.5% (9350/10,003)	Median 25 months (IQR 18-34 months, 93.5% (9350/10,003)

Author (year)		Douglas (2015)[15]	
	Study Design	RCT	RCT
	Study Quality	Good	Good

CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; IM = intermediate risk; IQR = interquartile range; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; RCT = randomized controlled trial

*As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.

†Also reports pre-test risk assessment, mean combined Diamond-Forrester/CASS risk score, cad risk factor equivalent present, ten year risk of events

‡Other pain (in descending order of frequency): fatigue or weakness, arm or shoulder pain, palpitations, dizziness or light-headedness, neck or jaw pain

Table E23. Clinical outcomes for the included RCT in a population considered to be at intermediate risk for coronary artery disease comparing CCTA to various functional tests

Author, Year	Test, Sample Size, Final Followup	Mortality (all-cause)	Myocardial Infarction (nonfatal)	Heart Failure	Stroke	Unstable Angina	Change in Angina	Quality of Life
Douglas, 2015[15]	CCTA (n=4996)	12 months: 0.4% (21/4996) Median 25 months: 1.5% (74/4996)	12 months: 0.4% (18/4996) Median 25 months: 0.6% (30/4996)	NR	NR	NR	NR	NR
	Functional imaging (n=5007)	12 months: 0.6% (32/5007) Median 25 months: 1.5% (75/5007)	12 months: 0.5% (27/5007) Median 25 months: 0.8% (40/5007)	NR	NR	NR	NR	NR

CCTA = coronary computed tomography angiography; NR = not reported

Table E24. Clinical management outcomes from randomized controlled trials including patients considered to be at intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Re-vascularization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Medical Therapy
Douglas, 2015[15]	CCTA (n=4996) 90 days	12.2% (609/4996)	6.2% (311/4996)	NR	1.4% (72/4996)	NR	NR
	Functional imaging (n=5007) 90 days	8.1% (406/5007)*	3.2% (158/5007)	NR	0.75% (38/5007)	NR	NR

CCTA = coronary computed tomography angiography; NR = not reported

*Also report proportion of patients with invasive catheterization showing no obstructive CAD.

Table E25. Hospital and emergency department outcomes for the included RCT in a population considered to be at intermediate risk for coronary artery disease comparing CCTA to various functional tests

Author, Year	Test, Sample Size, Final Followup	Hospitalization (any)	Hospitalization (unstable angina)	Emergency Department Revisit
Douglas, 2015[15]	CCTA (n=4996)	Median 25 months: 0% (0/4996)	12 months: 0.98% (49/4996) Median 25 months: 1.2% (61/4996)	NR
	Functional imaging (n=5007)	Median 25 months: 0.10% (5/5007)	12 months: 0.68% (34/5007) Median 25 months: 0.8% (41/5007)	NR

CCTA = coronary computed tomography angiography; NR = not reported

Table E26. Demographics for the included RCT in a population considered to be at intermediate risk for coronary artery disease comparing CCTA to SPECT

Author (year)		**Levsky (2015)[16]**	
Test Sample size		CCTA (n=200)	SPECT (n=200)
Patient demographics	Female, % (n)	63.0% (126)	62.5% (125)
	Age (years); mean ± SD	56.8 ± 11.8	56.3 ± 10.5
	Race, % (n)	White: 4.0% (8) Hispanic: 52.5% (108) Black: 39.0% (78) Asian: 3.5% (7) Other: 0.5% (1)	White: 5.0% (10) Hispanic: 54.0% (108) Black: 33.5% (67) Asian: 5.5% (11) Other: 1.0% (2)
	Pretest risk, % (n)*	Intermediate	Intermediate
	Subgroup	None	None
Cardiac risk factors, % (n)	Chest pain	100% (200)	100% (200)
	Typical angina	NR	NR
	Atypical angina	NR	NR
	Unstable angina	NR	NR
	Nonspecific chest pain	NR	NR
	Nonangina	NR	NR
	Silent ischemia	NR	NR
	Dyspnea on exertion	NR	NR
	Prior MI	NR	NR
	Prior revascularization	NR	NR
	Known CAD	0% (0)	0% (0)
	Chest pain frequency	NR	NR
	New pain on exertion within last 2 weeks	36.0% (72)	39.5% (79)
	Exertional pain	38.5% (77)	41.5% (83)
	Retrosternal pain	67.0% (134)	72.0% (144)
	Hypertension	70.5% (141)	73.5% (147)
	Diabetes	33.0% (66)	30.5% (61)
	Dyslipidemia	48.5% (97)	54.5% (109)
	Current smoker	16.5% (33)	13.0% (26)
Test details	CT images (slice)	64-row	NA
	CACS performed	Yes	NA
	Type of stressor	NR	Treadmill (preferred); if patient unable to exercise then pharmacologic stress (adenosine or regadenoson) was used ± low-level exercise
	Contrast (dose)	Iodixanol-320	201 TI rest/99m-Tc-sestamibi stress OR 99m-TC-sestamibi rest/stress
Study	Setting	Inpatient (telemetry unit)	Inpatient (telemetry unit)

Author (year)		Levsky (2015)[16]	
characteristics	Followup period % completed followup (n)	≥12 months, 95.0% (190); 6-12 months symptoms: 88.5% (177)	≥12 months, 95.5% (191); 6-12 months symptoms: 90.0% (180)
	Study Design	RCT	RCT
	Study Quality		

CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; MI = myocardial infarction; NA = not applicable; NR = not reported; RCT = randomized controlled trial

*Also reports pre-test risk probability using Diamond-Forrester prediction rules (36% for CCTA vs. 37% for SPECT groups); and mean TIMI score (1.3 ± 1.0 for CCTA vs. 1.2 ± 1.0 for SPECT group)

Table E27. Clinical outcomes for the included RCT in a population considered to be at intermediate risk for coronary artery disease comparing CCTA to SPECT

Author, Year	Test, Sample Size, Final Followup	Mortality (all-cause)	Myocardial Infarction (non-fatal)	Heart Failure	Stroke	Unstable Angina	Change in Angina	Quality of Life
Levsky, 2015[16]	CCTA (n=200)	Median 24.5 months: 0.5% (1/200)	NR	NR	NR	NR	Chest pain described as same or worse: 15.8% (28/177)	NR
	SPECT (n=200)	Median 24.5 months: 3.0% (6/200)	NR	NR	NR	NR	Chest pain described as same or worse: 12.7% (23/180)	NR

CCTA = coronary computed tomography angiography; NR = not reported

Table E28. Clinical management outcomes for the included RCT in a population considered to be at intermediate risk for coronary artery disease comparing CCTA to SPECT

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Re-vascularization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Medical Therapy
Levsky (2015)[16]	CCTA (n=200) 12 months	15.0% (30/200)	7.5% (15/200)	4.0% (8/200)	3.5% (7/200)	22.5% (45/200)	New aspirin Rx: 39.5% (79/200) New statin Rx: 25.0% (50/25) Increased statin dose: 3.0% (6/200)
	SPECT (n=200) 12 months	16.0% (32/200)	6.0% (12/200)	5.5% (11/200)	0.5% (1/200)	22.5% (45/200)	New aspirin Rx: 34.0% (68/200) New statin Rx: 18.0% (36/25) Increased statin dose: 3.0% (6/200)

CCTA = coronary computed tomography angiography; MPI = myocardial perfusion imaging; NR = not reported

*Also report proportion of patients with invasive catheterization but did not undergo revascularization (7.5% [15/200] for CCTA vs. 10% [10/200] for SPECT)

Table E29. Hospital and emergency department outcomes for the included RCT in a population considered to be at intermediate risk for coronary artery disease comparing CCTA to SPECT

Author, Year	Test, Sample Size, Final Followup	Hospitalization (cardiac)	Hospitalization (unstable angina)	Emergency Department Revisit (cardiac)
Levsky, 2015[16]	CCTA (n=200) Median 40.4 months	25.0% (50/200)	NR	20.5% (41/200)
	SPECT (n=200) Median 40.4 months	30.5% (61/200)	NR	20.0% (40/200)

CCTA = coronary computed tomography angiography; NR = not reported

Table E30. Demographics for the included observational study in populations considered to be at intermediate risk for coronary artery disease

Author (year)		**Henzler (2013)/ Gruettner (2013)[17, 18]**	
Test **Sample size**		CCTA (n=100)	Usual Care (n=100)
Patient demographics	Female, % (n)	48% (48)	39% (39)
	Age (years); mean ± SD	58 (range, 27-95)	66 (range, 36-87)
	Race, % (n)	NR	NR
	Pretest risk, % (n)*	Intermediate	Intermediate
	Subgroup	None	None
Cardiac risk factors, % (n)	Chest pain	100% (100)	100% (100)
	Typical angina	NR	NR
	Atypical angina	NR	NR
	Unstable angina	NR	NR
	Noncardiac angina	NR	NR
	Nonangina	NR	NR
	Noncardiac angina	NR	NR
	Silent ischemia	NR	NR
	Dyspnea	NR	NR
	Prior MI	0% (0)[18]	NR
	Prior revascularization	NR	NR
	Prior CABG/PCI	0% (0)	0% (0)
	Known CAD	9% (9)	10% (10)
	Chest pain frequency	NR	NR
	Hypertension	59% (59)	71% (71)
	Diabetes	24% (24)	29% (29)
	Hyperlipidemia	30% (30)	40% (40)
	Smoker (past or current)	54% (54)	47% (47)
Test details	CT images (slice)	320[18]	NA
	CACS performed	Yes[18]	NA
	Type of stressor	NA	NR
	Contrast (dose)	Iomeron 400[18]	NA
Study characteristics	Setting	ED	ED
	Followup period % completed followup (n)	90 days 100% (100)	90 days 87% (87)
	Study Design	Retrospective cohort	Retrospective cohort
	Study Quality	Poor	Poor

CABG = coronary artery bypass graft; CACS = coronary artery calcium scoring; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ED = emergency department; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation
*As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.

Table E31. Clinical outcomes, clinical management outcomes, and hospital outcomes from observational studies including patients considered to be at intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure	Stroke	Major Adverse Cardiac Events*	Change in Angina	Invasive Coronary Angiography†	Hospitalization (recurrent chest pain)
Henzler/ Gruettner (2013)[17, 18]	CCTA (n=100) 3 months	0% (0)	0% (0)	0% (0)	NR	0% (0)	NR	40% (40)	0% (0)
	Usual Care (n=100) 3 months	0% (0)	0% (0)	0% (0)	NR	0% (0)	NR	87% (80)	3% (3)

CCTA = coronary computed tomography angiography; NR = not reported

*Includes (1) death, (2) acute myocardial infarction, (3) unstable angina requiring hospitalization, (4) development or progression of heart failure requiring hospitalization and (5) lethal ventricular arrhythmias requiring appropriate discharge from external or internal defibrillators.

†CCTA patients received invasive coronary angiography per study protocol if CCTA found stenosis > 50%; usual care group received invasive coronary angiography in the course of usual clinical care with no details provided.

Table E32. Demographics for included RCTs in populations considered to be at low to intermediate risk for coronary artery disease

Author (year)		**Litt (2012)[19]**		**Miller (2011)[20]**		**Goldstein (2011)[21]**		**Hamilton-Craig (2014)[22]**		**Goldstein (2007)[23]**	
Test Sample size		CCTA (n=908)	Usual Care (n=462)	CCTA + Usual Care (n=30)	Usual Care (n=30)	CCTA (n=375)*	SPECT (n=374)*	CCTA (n=322)	Exercise ECG (n=240)	CCTA (n=99)*	SPECT (n=98)*
Patient demographics	Female, % (n)	51.2% (465)	56.3% (260)	57% (17)	43% (13)	54.8% (198)	53.0% (179)	43.5% (140)	41.6% (100)	57.6 (57)	42.9 (42)
	Age (years); mean ± SD	49±9	50±10	51±10	51±10	50±10	50±10	52.2±10.7	52.3±9.8	48±11	51±12
	Race, % (n)	White: 39.8% (361) Black: 57.8% (525) Asian: 1.2% (11) Other: 1.8% (16)	White: 35.1% (162) Black: 62.3% (288) Asian: 1.5% (7) Other: 2.2% (10)	White: 23.3% (7) Black: 46.7% (14) Asian: 0% (0) Hispanic: 30.0% (9)	White: 13.3% (4) Black: 46.7% (14) Asian: 3.3% (1) Other: 36.7% (11)	NR	NR	NR	NR	NR	NR
	Pretest risk, % (n)†	Low-to-intermediate (%NR)	Low-to-intermediate (%NR)	Low-to-intermediate (%NR)	Low-to-intermediate (%NR)	Low-to-intermediate	Low-to-intermediate	Low-to-intermed-iate (%NR)	Low-to-intermed-iate (%NR)	Very low-to-low	Very low-to-low
	Subgroup	NR	NR	NR	NR	None	None	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	100% (908)	100% (462)	100% (30)	100% (30)	100% (361)	100% (338)	100% (322)	100% (240)	100 (99)	100 (98)
	Typical angina	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Unstable angina	NR	NR	NR	NR	0.8% (3)	0.9% (3)	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Nonangina	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Prior MI	1% (10)	1% (6)	NR	NR	0.3% (1)	1.5% (5)	NR	NR	NR	NR
	Prior revascularization	NR	NR	0% (0)	0% (0)	NR	NR	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	0% (0)	0% (0)	NR	NR	NR	NR	NR	NR
	Known CAD	NR	NR	0% (0)	0% (0)	NR	NR	0% (0)	0% (0)	0 (0)	0 (0)
	Chest pain frequency	NR	NR	NR	NR	NR	NR	NR	NR	In last 24 hrs: 77 (76)	In last 24 hrs: 65 (66)

Author (year)		Litt (2012)[19]		Miller (2011)[20]		Goldstein (2011)[21]		Hamilton-Craig (2014)[22]		Goldstein (2007)[23]	
	Hypertension	51.0% (463)	50.2% (232)	NR	NR	35.5% (128)	38.8% (131)	30.7% (99)	30.8% (74)	39 (38)	38 (37)
	Diabetes	14.3% (130)	13.9% (64)	NR	NR	5.5% (20)	8.3% (28)	7.1% (23)	6.3% (15)	8.2 (8)	12.2 (12)
	Hyperlipidemia	27.4% (249)	25.5% (118)	NR	NR	31.0% (112)	36.1% (122)	25.2% (81)	23.8% (57)	34 (33)	38 (37)
	Smoker (past or current)	32.0% (291)	33.8% (156)	NR	NR	25.2% (91)	30.5% (103)	23.9% (77)	22.9% (55)	15 (15)	20 (20)
Test details	CT images (slice)	64+	NA	64	NA	64–320	NA	64–128	NA	64	NA
	CACS performed	Yes	NA	Yes	NA	Yes	NA	No	NA	Yes	NA
	Type of stressor	NA	exercise or pharmaco-logic	NA	NR	NA	Exercise (treadmill) or pharmacologic (adenoside or dipyridamole)‡	NA	Treadmill (Bruce protocol)	NA	Exercise (type NR)
	Contrast (dose)	NR	NA	NR	NA	Ultravist 300	Tc-99m sestamibi	Iomeron 350	NA	Visipaque	Tc-99m sestamibi
Study characteristics	Setting	ED	ED	ED	ED	ED	ED	ED	ED	ED	ED
	Followup period % completed followup (n)	30 days 98.9% (898)	30 days 98.9% (457)	90 days 100% (30)	90 days 100% (30)	6 months 88.0% (330)	6 months 79.4% (297)	12 months Overall: 100%	12 months Overall: 100%	6 months Overall: 97.0% (197/203)	6 months Overall: 97% (197/203)
	Study Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Poor	Poor	Good	Good	Fair	Fair	Fair	Fair

CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; ED = emergency department; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography

*Demographics reported only for those who completed the protocol and did not withdraw consent (Goldstein 2011) or who completed followup (2007).

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.

‡Rest imaging was done in all patients and stress testing was only done if the resting studies were normal

Table E33. Clinical outcomes from randomized controlled trials including patients considered to be at low to intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure	Stroke	Major Adverse Cardiac Events*	Unstable Angina	Quality of Life*
Litt, 2012[19]	CCTA (n=908) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 1.0% (9) 30 days: 0.1% (1)	NR	NR	NR	Index: 3.1% (28) 30 days: NR	NR
	Usual Care (n=462) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 0.9% (4) 30 days: 0.2% (1)	NR	NR	NR	Index: 1.5% (7) 30 days: NR	NR
Miller, 2011[20]	CCTA (n=30) 3 months	NR	NR	NR	NR	NR	NR	SF-12 PCS (n=15): 1.0 ± 7.4 SF-12 MCS (n=15): –0.5 ± 11.5
	Usual Care (n=30) 3 months	NR	NR	NR	NR	NR	NR	SF-12 PCS (n=17): –2.3 ± 13.4 SF-12 MCS (n=17): –0.7 ± 11.9
Goldstein, 2011[21]	CCTA (n=361) 6 months	Index: 0% (0) 6 mos: 0% (0)	Index: 0.3% (1) 6 mos: 0% (0/330)	NR	NR	NR	Index: 0.8% (3) 6 mos: 0% (0/330)	NR
	SPECT (n=338) 6 months	Index: 0% (0) 6 mos: 0% (0)	Index: 1.5% (5) 6 mos: 0% (0/297)	NR	NR	NR	Index: 10.9% (3) 6 mos: 0% (0/297)	NR
Hamiton-Craig, 2014[22]†	CCTA (n=322) 12 months	Index: NR 30 days: 0% (0) 12 mos: 0.6% (2)‡	Index: 1.9% (6) 30 days: 0% (0) 12 mos: NR	NR	NR	NR	Index: 3.4% (11) 30 days: 0% (0) 12 mos: NR	NR
	Exercise ECG (n=240) 12 months	Index: NR 30 days: 0% (0) 12 mos: 0.4% (1)‡	Index: 1.7% (4) 30 days: 0% (0) 12 mos: NR	NR	NR	NR	Index: 1.3% (3) 30 days: 0% (0) 12 mos: NR	NR
Goldstein, 2007[23]	CCTA (n=99) 6 months	Index: 0% (0) 6 mos: 0% (0)	Index: 0% (0) 6 mos: 0% (0)	NR	NR	NR	Index: NR 6 mos: 0% (0)	NR
	SPECT (n=98) 6 months	Index: 0% (0) 6 mos: 0% (0)	Index: 0% (0) 6 mos: 0% (0)	NR	NR	NR	Index: NR 6 mos: 0% (0)	NR

CCTA = coronary computed tomography angiography;; ECG = electrocardiography;; mos = months;; NR = not reported;; SF-12 MCS = Short Form 12 Mental Component Score;; SF-12 PCS = Short Form 12 Physical Component Score;; SPECT = single photon emission computed tomography

*Scores are reported as difference from baseline to final followup (3 months).

†All events were back-calculated using the percentages provided.

‡For CCTA, deaths were due to urosepsis and multi-organ failure during elective aortic valve replacement; for ECG, the one death was due to complications from cancer therapy.

Table E34. Clinical management outcomes from randomized controlled trials including patients considered to be at low to intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Re-vascularization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Stress Testing With Imaging	Stress Testing Without Imaging	Resting Echo-cardiography	Outpatient Cardiology Visit
Litt, 2012[19]	CCTA (n=908) 30 days	Index: 4% (37) 30 days: 0.9% (8/887)	Index: 3% (23) 30 days: 0.1% (1/893)	NR	NR	30 days: 23.1% (206/891)	30 days: 16% (140/891)	30 days: 1% (11/886)	30 days: 6% (55/888)	30 days: 7% (62/787)
	Usual Care (n=462) 30 days	Index: 4% (18) 30 days: 0.2% (1/454)	Index: 1% (4) 30 days: 0.4% (2/457)	NR	NR	30 days: 66.4% (304/458)	30 days: 58% (264/458)	30 days: 2% (10/454)	30 days: 7% (30/454)	30 days: 4 (17/451)
Miller, 2011[20]	CCTA (n=30) 3 months	13% (4)	3.3% (1)	3.3% (1)	0% (0)	33.3% (10)	20.0% (6)*	6.7% (2)*	6.7% (2)	10.0% (3)†
	Usual Care (n=30) 3 months	13% (4)	0% (0)	0% (0)	0% (0)	60.0% (18)	23.3% (7)*	20.0% (6)*	16.7% (5)	16.7% (5)†
Goldstein, 2011[21]	CCTA (n=361) 6 months	Index: 6.7% (24) 6 mos: 0.6% (2/330)	Index: 3.6% (13) 6 mos: 0.3% (1/330)	Index: 2.5% (9) 6 mos: 0.3% (1/330)	Index: 1.1% (4) 6 mos: 0% (0/330)	Index: 10.9% (37)‡ 6 mos: NR	Index: 10.9% (37)‡ 6 mos: NR	NR	NR	NR
	SPECT (n=338) 6 months	Index: 6.2% (21) 6 mos: 0.3% (1/297)	Index: 2.4% (8) 6 mos: 0% (0/297)	Index: 2.4% (8) 6 mos: 0% (0/297)	Index: 0% (0) 6 mos: 0% (0/297)	Index: 1.8% (6)‡ 6 mos: NR	NR	NR	NR	NR
Hamiton-Craig, 2014[22]	CCTA (n=322) 12 months	12 mos: 9.0% (29)	12 mos: 4.3% (14)	12 mos.3.7% (12)	12 mos: 0.62% (2)	12 mos: 4.3% (14)	12 mos: 4.3% (14)§	NR	NR	NR
	Exercise ECG (n=240) 12 months	12 mos: 4.2% (10)	12 mos: 1.3% (3)	NR	NR	12 mos: 8.8% (21)	12 mos: 8.8% (21)§	NR	NR	NR
Goldstein, 2007[23]	CCTA (n=99) 6 months	Index: 11.1% (11) 6 mos: 1.0% (1)	Index: 5.1% (5) 6 mos: 1.0% (1)	Index: 3.0% (3) 6 mos: 1.0% (1)	Index: 2.0% (2) 6 mos: 0% (0)	Index: 24.2% (24) 6 mos: 1.0% (1)	NR	NR	NR	6 mos: 2.0% (2)
	SPECT (n=98) 6 months	Index: 3.1% (3) 6 mos: 4.1% (4)	Index: 1.0% (1) 6 mos: 0% (0)	Index: 1.0% (1) 6 mos: 0% (0)	Index: 0% (0) 6 mos: 0% (0)	Index: 24.2% (24) 6 mos: 1.0% (1)	NR	NR	NR	6 mos: 2.0% (2)

CCTA = coronary computed tomography angiography; ECG = electrocardiography; mos = months; NR = not reported; SPECT = single photon emission computed tomography
*For the CCTA group, stress testing with imaging consisted of stress echocardiography (10%, n=3) and nuclear perfusion (10%, n=3); for usual care, stress echocardiography (3.3%, n=1) and nuclear perfusion (20%, n=6). Stress testing without imaging consisted of exercise electrocardiography for both test groups.

†Primary care/other visits were also reported in the CCTA group (50%, n=15) and the usual care group (70%, n=21) during followup.
‡Additional testing for the CCTA group consisted of single photon emission computed tomography (SPECT) and for the SPECT group, CCTA.
§For the CCTA group, stress testing with imaging consisted of single photon emission computed tomography (2.2%, n=7) and stress echocardiography (2.2%, n=7); for the exercise electrocardiography group, single photon emission computed tomography (7.5%, n=18) and stress echocardiography (1.3%, n=3).

Table E35. Hospital and emergency department outcomes from randomized controlled trials including patients considered to be at low to intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Hospitalization (any)	Hospitalization (cardiac)	Emergency Department Revisit
Litt, 2012[19]	CCTA (n=908) 30 days	Index: 50.4% (458) 30 days: 3% (28/889)	NR	30 days: 8% (71/885)
	Usual Care (n=462) 30 days	Index: 77.3% (357) 30 days: 2% (11/456)	NR	30 days: 8% (34/452)
Miller, 2011[20]	CCTA (n=30) 3 months	20.0% (6)	NR	16.7% (5)
	Usual Care (n=30) 3 months	53.3% (16)	NR	33.3% (10)
Goldstein, 2011[21]	CCTA (n=361) 6 months	Index: 27.4% (99)* 6 months: NR	Index: NR 6 months: 0% (0/330)	6 months: 0.6% (2/330)
	SPECT (n=338) 6 months	Index: 19.2% (65)* 6 months: NR	Index: NR 6 mos: 0% (0/297)	6 months: 1.3% (4/297)
Hamilton-Craig, 2014[22]†	CCTA (n=322) 12 months	12 months: 10.2% (33)	NR	12 months: 12.7% (41)‡
	Exercise ECG (n=240) 12 months	12 months: 10.8% (26)	NR	12 months: 10.5% (25)‡
Goldstein, 2007[23]	CCTA (n=99) 6 months	Index: 11.1% (11)§ 6 months: NR	NR	6 months: 6.1% (6)
	SPECT (n=98) 6 months	Index: 3.1% (3)§ 6 months: NR	NR	6 months: 6.1% (6)

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography
*Authors reported the number of patients discharged home after index visit; we inferred that those not discharged were admitted or kept for observation
†All events back-calculated using percentages provided.
‡For chest pain/symptoms.
§Authors reported the number of patients who were discharged to home; we reported the difference as those who were hospitalized or kept for observation at index.

Table E36. Demographics for included observational studies in populations considered to be at low to intermediate risk for coronary artery disease

Author (year)		Poon (2013)[24]		Cheezum (2011)[25]		Nielsen (2011/2013)[26, 27]	
Test **Sample size**		CCTA (n=894)*	Usual Care (n=894)*	CCTA (n=252)†	SPECT (n=241)	CCTA (n=251)	Exercise ECG (n=247)
Patient demographics	Female, % (n)	52% (464)	52% (464)	44% (111)	45% (108)	51.0% (128)	46.6% (115)
	Age (years); mean ± SD	49±11	49±12	53±10	53±11	55±11	56±12
	Race, % (n)	Minority: 18% (158)	Minority: 20% (176)	NR	NR	NR	NR
	Pretest risk, % (n)‡	Low-to-intermediate (score NR)	Low-to-intermediate (score NR)	Low: 16% (40) IM: 84% (212)	Low: 19% (46) IM: 81% (195)	Low: 27% (68) IM: 69% (173) High: 4% (10)	Low: 28% (68) IM: 69% (171) High: 3% (8)
	Subgroup (%)	None	None	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	100% (894)	100% (894)	90% (227)	88% (212)	100% (251)	100% (247)
	Typical angina	NR	NR	0% (0)	0% (0)	5.6% (14)	5.7% (14)
	Atypical angina	NR	NR	NR	NR	18.7% (47)	21.9% (54)
	Unstable angina	NR	NR	NR	NR	NR	NR
	Nonangina	NR	NR	NR	NR	75.7% (190)	72.5% (179)
	Noncardiac angina	0% (0)	0% (0)	NR	NR	NR	NR
	Dyspnea	NR	NR	10% (25)	12% (29)	NR	NR
	Prior MI	NR	NR	NR	NR	NR	NR
	Prior revascularization	NR	NR	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR	NR	NR
	Known CAD	0% (0)	0% (0)	NR	NR	0% (0)	0% (0)
	Hypertension	33% (294)	33% (294)	60.3% (152)	62.7	59.4% (149)	53.0% (131)
	Diabetes	6% (56)	6% (56)	11% (28)	11 (27)	8.4% (21)	9.7% (24)
	Hyperlipidemia	16% (141)	16% (141)	NR	NR	80.9% (203)	84.2% (208)
	Smoker (current or past)	29% (257)	29% (257)	17% (43)	14 (34)	51.0% (128)	44.5% (110)
Test details	CT images (slice)	64 slice	64 slice	64 slice	NA	64 slice	NA
	CACS performed	NR	NA	Yes	NA	NR	NA
	Type of stressor	NA	NR	NA	Exercise (treadmill 72%); pharmacologic (persantine 25%, adenosine 3%)	NA	Bicycle ergometer
	Contrast/radioisotope	Ultravist 370 (75 ml or 110 ml)	NR	Visapaque	Tc-99m sestamibi	NR (iodinated contrast)	NA
Study characteristics	Setting	Emergency department	Emergency department	Outpatient; Inpatient (9.5%),	Outpatient; Inpatient (10.4%)	Outpatient	Outpatient
	Followup period % completed followup (n)	30 days (100%)	30 days (100%)	Mean 29±7 months; 96.8% (244/252)	Mean 30±8 months 97.5% (235/241)	12 months 100% (251)	12 months 100% (247)
	Study Design	Retro cohort	Retro cohort	Retro cohort	Retro cohort	Retro cohort	Retro cohort

Author (year)		Poon (2013)[24]		Cheezum (2011)[25]		Nielsen (2011/2013)[26, 27]	
	Study Quality	Fair	Fair	Fair	Fair	Fair	Fair

CABG = coronary artery bypass graft; CAD = coronary artery disease; ECG = electrocardiogram; IM = intermediate; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; Retro = retrospective; SD = standard deviation; SPECT = single photon emission computed tomography

*Propensity matched analysis.

†CCTA group was selected through patient matching.

‡As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.

Table E37. Clinical outcomes from retrospective observational studies including patients considered to be at low to intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Mortality*	Myocardial Infarction	Major Adverse Cardiac Events	Unstable Angina	Heart Failure	Stroke
Poon, 2013[24]	CCTA (n=894) 30 days	0% (0)	0.3% (3)*	NR	NR	NR	NR
	Usual Care (n=894) Usual Care	0% (0)	0.6% (6)*	NR	NR	NR	NR
Cheezum, 2011[25]	CCTA (n=244) Mean 30 ± 7 months	2.4% (1)†	NR	0.4% (1)‡	NR	NR	NR
	SPECT (n=235) Mean 30 ± 7 months	2.4% (1)†	NR	0.9% (2)‡	NR	NR	NR
Nielsen, 2011/2013[26, 27]	CCTA (n=251) 12 months	0% (0)	0% (0)	NR	NR	NR	NR
	Exercise ECG (n=247) 12 months	0% (0)	1.2% (3)	NR	NR	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography
*All acute MIs occurred during the index visit in the emergency department.
†The two death reported are both due to unknown causes and identified on review of medical records. No cardiac-related deaths were reported in either group.
‡Includes revascularization, myocardial infarction, acute coronary syndrome or cardiac death.

Table E38. Clinical management outcomes from retrospective observational studies including patients considered to be at low to intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Re-vascular-ization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Stress Testing With Imaging*	Stress Testing Without Imaging†	Coronary Computed Tomography Angiography	Outpatient Cardiology Visit
Poon, 2013[24]	CCTA (n=894) 30 days	1% (8)	3% (23)	NR	NR	4% (33)	1% (8)	3% (25)	NR	NR
	Usual Care (n=894) 30 days	3% (27)	2% (19)	NR	NR	21% (184)	11% (102)	9% (82)	NR	NR
Cheezum, 2011[25†‡]	CCTA (n=244) Mean 30 ± 7 months	3.3% (8)	NR	NR	NR	9.8% (24)	6.9% (17)	2.5% (6)	0.4% (1)	11.9% (29)
	SPECT (n=235) Mean 30 ± 7 months	8.1% (19)	NR	NR	NR	13.6% (32)	6.8% (16)	2.1% (5)	4.7% (11)	11.9% (28)
Nielsen, 2011/ 2013[26, 27]	CCTA (n=251) 12 months	17.5% (44)	5.6% (14)	3.6% (9)	2.0% (5)	4.8% (12)	4.0% (10)	0.8% (2)	0% (0)	NR
	Exercise ECG (n=247) 12 months	22.7% (56)	4.5% (11)	4.0% (10)	0.4% (1)	13.4% (33)	8.9% (22)	0% (0)	4.5% (11)	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography

*For Poon 2013, additional stress testing with imaging included nuclear stress tests (not further specified); for Cheezum 2011, single photon emission computed tomography and exercise echocardiography (rates in the CCTA group and SPECT group respectively were 5.7% [n=14] and 1.2% [n=3] versus 6.0% [n=14] and 0.9% [n=2]); and for Nielsen, patients received stress myocardial perfusion imaging (not specified further).

†Exercise electrocardiography for all three studies.

‡Also reports total downstream clinical resource utilization, CCTA 24.6% (60), SPECT 27.7% (65); Includes post-test referral to specialist, ED visits, hospital admissions, and additional testing; per-patient composite rates

Table E39. Hospital or emergency department outcomes from retrospective observational studies including patients considered to be at low to intermediate risk for coronary artery disease*

Author, Year	Test, Sample Size, Final Followup	Hospitalization (any)	Hospitalization (cardiac)	Emergency department visit (cardiac)
Poon, 2013[24]	CCTA (n=894) 30 days	14% (123)†	NR	1% (12)
	Usual Care (n=894) 30 days	40% (358)†	NR	4% (32)
Cheezum, 2011[25]	CCTA (n=244) Mean 30 ± 7 months	NR	6.6% (16)	13.1% (32)
	SPECT (n=235) Mean 30 ± 7 months	NR	4.3% (10)	14.0% (33)
Nielsen, 2011/ 2013[26, 27]	CCTA (n=251) 12 months	NR	NR	NR
	Exercise ECG (n=247) 12 months	NR	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography
*Heart Failure and stroke were not reported in retrospective observational studies including patients considered to be at low-to-intermediate risk.
†Admission following index emergency department assessment.

Table E40. Demographics for included RCTs in populations considered to be at low risk for coronary artery disease

Author (year)		**Chang (2008)[1]**		**Sabharwal (2007)[2]**	
Test **Sample size**		CCTA (n=50)*	Usual Care (n=49)*	SPECT (n=27)*	Exercise ECG (n=44)*
Patient demographics	Female, % (n)	39% (52)	38% (51)	44.4% (111)	42.5% (88)
	Age (years); mean ± SD	57 ± 14	58 ± 14	59.7 ± 12.2	58.9 ± 911.4
	Race, % (n)	NR	NR	White: 55.6% (139)	White: 46.9% (97)
	Pretest risk, % (n)†	Low: 37.6% (50) IM: 41.4% (55) High: 21.1% (28)	Low: 36.8% (49) IM: 42.1% (56) High: 21.1% (28)	Low: 10.8% (27) IM: 71.2% (178) High: 18.0% (45)	Low: 21.3% (44) IM: 49.3% (102) High: 29.5% (61)
	Subgroup	NR	NR	None	None
Cardiac risk factors, % (n)	Chest pain	100% (133)	100% (133)	100% (250)	100% (207)
	Typical angina	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR
	Unstable angina	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR
	Nonangina	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR
	Prior MI	NR	NR	0% (0)	0% (0)
	Prior revascularization	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR
	Known CAD	12% (16)	17% (23)	0% (0)	0% (0)
	Chest pain frequency	NR	NR	NR	NR
	Hypertension	46% (61)	41% (55)	53.2% (133)	46.3% (96)
	Diabetes	16% (21)	19% (25)	19.2% (48)	14.5% (30)
	Hyperlipidemia	29% (39)	25% (33)	NR	NR
	Current smoker	17% (23)	23% (31)	12.8% (32)	16.4% (34)
Test details	CT images (slice)	64	NA	NA	NA
	CACS performed	NR	NR	NA	NA
	Type of stressor	NA	NA	Exercise (treadmill 62%) and/or pharmacologic stress (dipyradimole 38% (or dobutamine if contraindication))	Treadmill (Bruce protocol)
	Contrast (dose)	Lomeprol (80mL lomeron 400; Bracco, Milan, Italy)	NA	Radiotracer: Tc-99m sestamibi	NA

Author (year)		Chang (2008)[1]		Sabharwal (2007)[2]	
Study characteristics	Setting	ED	ED	Outpatient	Outpatient
	Followup period % completed followup (n)	30 days	30 days	Mean 19.6 months 96.9% (443/457)‡	Mean 19.6 months 96.9% (443/457)‡
	Study Design	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Fair	Fair

CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; ECHO = echocardiogram; ED = emergency department; IM = intermediate risk; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography

*Subgroup of patients at low pretest risk; demographics are reported for the entire population (demographics not reported separately for groups stratified by low risk).

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.

‡Loss-to-followup not reported by group; 10 patients did not have followup data and there were 2 deaths in each group (SPECT: 2 malignancy; ECG: 1 malignancy and 1 cardiac).

Table E41. Clinical outcomes from randomized controlled trials including patients considered to be at low risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Unstable Angina	Heart failure, stroke, MACE	Dysrhythmia	Quality of Life
Chang, 2008[1]*	CCTA (n=50) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 4% (2) 30 days: NR	Index: 2% (1) 30 days: NR	NR	NR	NR
	Usual Care (n=49) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 4% (2) 30 days: NR	Index: 2% (1) 30 days: NR	NR	NR	NR
Sabharwal, 2007[2]*	SPECT (n=27) Mean 21.7 ± 6.4 months	NR	NR	NR	NR	NR	NR
	Exercise ECG (n=44) Mean 21.7 ± 6.4 months	NR	NR	NR	NR	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; MACE = major adverse cardiac events; NR = not reported; SPECT = single photon emission computed tomography

*Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the low risk group only are reported here.

Table E42. Clinical management outcomes from randomized controlled trials including patients considered to be at low risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Re-vascularization (any)	Additional Noninvasive Testing (any)	Medical Therapy	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Outpatient Cardio-vascular Visits
Chang, 2008[1*]	CCTA (n=50) 30 days	Index: 6% (3) 30 days: NR	Index: 6% (3) 30 days: NR	Index: 0% (0) 30 days: NR	NR	NR	NR	NR
	Usual Care (n=49) 30 days	Index: 10% (5) 30 days: NR	Index: 2% (1) 30 days: NR	Index: 80% (39) 30 days: NR	NR	NR	NR	NR
Sabharwal, 2007[2*]	SPECT (n=27) Mean 21.7 ± 6.4 months	7.4% (2)	NR	0% (0) (imaging)	92.5% (25)	NR	NR	NR
	Exercise ECG (n=44) Mean 21.7 ± 6.4 months	0% (0)	NR	13.6% (6) (imaging)	75% (38)	NR	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography
*Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the low risk group only are reported here.

Table E43. Hospital and emergency department outcomes from randomized controlled trials including patients considered to be at low risk for coronary artery disease*

Author, Year	Test, Sample Size, Final Followup	Hospitalization (any)	Hospitalization (cardiac)
Chang, 2008[1†]	CCTA (n=50) 30 days	Index: 14% (7) 30 days: NR	Index: 6% (3)‡ 30 days: NR
	Usual Care (n=49) 30 days	Index: 16% (8) 30 days: NR	Index: 6% (3)‡ 30 days: NR
Sabharwal, 2007[2†]	SPECT (n=27) FF: Mean 21.7 ± 6.4 months	NR	NR
	Exercise ECG (n=44) FF: Mean 21.7 ± 6.4 months	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography
* Emergency department revisits were not reported in studies with patients at low risk
† Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the low risk group only are reported here.
‡Includes hospitalization for non-ST-segment elevation myocardial infarction or unstable angina, which are also reported separately under clinical outcomes.

Table E44. Pretest risk assessment in included studies

Author, Year	Study Design	Method Used to Assess Pretest Risk	Pretest Risk (as reported by authors)	Risk Scores or Percent of Patients
CCTA vs. Usual Care				
Henzler, 2013[17]	Retro cohort	TIMI risk score	• Intermediate (TIMI scores NR)	NR
Litt, 2012[19]	RCT	TIMI risk score	• Low-to-intermediate (TIMI score 0 to 2)	CCTA (n=908) • 0 (51%), 1 (36%), ≥2 (13%) Usual Care (n=462) • 0 (51%), 1 (36%), ≥2 (13%)
Miller, 2011[20]	RCT	"Established criteria" [see Table E41]	• Low-to-intermediate	NR
Hoffman, 2012[13]	RCT	NR	NR	Number of cardiovascular risk factors: • CCTA (n=501): 0-1 (36%), 2-3 (54%), ≥4 (10%) • Usual Care (n=499): 0-1 (38%), 2-3 (52%), ≥4 (10%)
Stress Echo vs. Ex ECG				
Dodi, 2001[28*]	Retro cohort	Diamond-Forrester risk algorithm	Mixed (results not stratified) • Low-to-intermediate (<70%) High (≥70%)	• Low-intermediate: 60% • High: 40% • Overall %: 56% ± 27%
Marwick, 2003[5]	Retro cohort	predicted annualized probability of cardiac death or MI, derived from a Cox proportional hazards model that included age, gender, diabetes, angina class, cigarette smoking, hypertension, diabetes, hyperlipidaemia, prior revascularization and previous MI [see Table E41]	• Low (<0.6%) • Intermediate (0.6-2.0%) • High (>2.0%)	Ex Echo (n=3860) • Low (11%), intermediate (58%), high (31%) Ex ECG (n=3796) • Low (12%), intermediate (60%), high (28%)
Sanfilippo, 2005[3]	RCT	NR	NR	NR
Ferrara, 1991[29*]	Pro cohort	NR	NR	NR
Severi, 1994[30*]	Pro cohort	CCS Angina Grading Scale, Classes I-III	NR	• Class I: 27% • Class II: 53% • Class III: 19%
Shreibati, 2011[6]	Retro database	NR	NR	NR
SPECT vs. Ex ECG				
Sabharwal, 2007[2]	RCT	determined from patient's symptoms and cardiac risk factors by use of the ACC/AHA guidelines (Diamond-Forrester) [see Table E41]	• Low • Intermediate • High	SPECT (n=250) • Low (11%), intermediate (71%), high (18%) Ex ECG (n=207) • Low (21%), intermediate (49%), high (29%)

Author, Year	Study Design	Method Used to Assess Pretest Risk	Pretest Risk (as reported by authors)	Risk Scores or Percent of Patients
Shaw, 2011[14]	RCT	defined as women age ≥50 years with typical or atypical angina or age ≥60 years with nonanginal symptoms	• Intermediate	NR
Shreibati, 2011[6]	Retro database	NR	NR	NR
PET vs. SPECT				
Hachamovitch, 2012/Hlatky, 2014[11, 12]	Pro cohort	method of Pryor et al [see Table E41]	• Intermediate-to-high	PET (n=548): 0.45 ± 0.33 SPECT (n=565): 0.38 ± 0.329
SPECT vs. Stress Echo				
Takeuchi, 1996[31]	Retro cohort	Diamond-Forrester risk algorithm	Mixed (results not stratified): • Low (<20%) • Intermediate (20-80%) • High (>80%)	Overall %: 56.8% ± 4.0% Low: 33% Intermediate: 26% High: 41% (risk not reported by test)
Shreibati, 2011[6]	Retro database	NR	NR	NR
CCTA vs. Ex ECG				
McKavanagh, 2014[4]	RCT	Diamond-Forrester risk algorithm	Mixed (results not stratified): • Low (<30%) • Intermediate (30-60%) • High (>60%)	CCTA (n=243) • Low (42%), intermediate (22%), high (37%) • Overall %: 47.8% ± 31.7% Ex ECG (n=245) • Low (44%), intermediate (25%), high (31%) • Overall %: 44.9% ± 30.2%
Nielsen, 2011/ 2013[26, 27]	Retro cohort	Diamond-Forrester risk algorithm	Mixed (results not stratified): • Low (<13.4%) • Intermediate (13.5-87.2%) • High (>87.2%)	CCTA (n=251) • Low (27%), intermediate (69%), high (4%) • Overall %: 26% ± 23% Ex ECG (n=247) • Low (28%), intermediate (69%), high (3%) • Overall %: 27% ± 23%
Hamilton-Craig, 2014[22]	RCT	Cardiac Society of Australia and New Zealand guidelines [see Table E41]	• Low-intermediate	NR
Shreibati, 2011[6]	Retro database	NR	NR	NR
CCTA vs. Stress Echo				
Shreibati, 2011[6]	Retro database	NR	NR	NR

Author, Year	Study Design	Method Used to Assess Pretest Risk	Pretest Risk (as reported by authors)	Risk Scores or Percent of Patients
CCTA vs. SPECT				
Min, 2012[10]	RCT	Diamond-Forrester risk algorithm	Mixed (results not stratified): • Low • Intermediate High	CCTA (n=91) • Low (4%), intermediate (63%), high (33%) SPECT (n=89) Low (9%), intermediate (67%), high (24%)
Goldstein, 2011[21]	RCT	Unclear – see inclusion criteria; TIMI risk score reported	Low-intermediate	CCTA (n=361) • TIMI score: 0.99 ± 0.84 SPECT (n=338) • TIMI score: 1.04 ± 0.87 Median TIMI score for both groups=1.0
Goldstein, 2007[23]	RCT	Goldman Reilly criteria [see Table E41]; TIMI score reported	Very low to low • Very low (score 0) • Low (score 2) • Moderate (score 3)	CCTA (n=99) • Very low (100%), low (0%) • TIMI score: 1.24 ± 0.8 SPECT (n=98) • Very low (99%), low (1%) • TIMI score: 1.33 ± 0.8 Median TIMI score for both groups=1.0
Cheezum, 2011[25]	Retro cohort	Diamond-Forrester risk algorithm	Very low-intermediate • Very low (<5%) • Low (5-10%) • Intermediate (10-90%)	CCTA (n=252) • Very low (1%), low (15%), intermediate (84%) SPECT (n=241) • Very low (5%), low (14%), intermediate (81%)
Tandon, 2012[8]	Pro cohort	Pretest probability calculated using age, gender and symptoms (scale NR) (Diamond-Forrester); Also report Morise score (based on pretest probability and cardiac risk factors)	NR	CCTA (n=1221) • Pretest probability (median, IQR): 12.3 (7-22) • Morise score: 10.7 ± 3.0 SPECT (n=1221) • Pretest probability (median, IQR): 12.3 (8-31) • Morise score: 10.7 ± 3.0
Yamauchi, 2012[7]	Pro cohort	NYHA Class (I-IV) and CCS Angina Grading Scale (1-4)	NR	CCTA (n=635) • NYHA class: I (81%), II (15%), III (2%), IV (3%) • CCS class: 1 (62%), 2 (32%), 3 (2%), 4 (4%) SPECT (n=1221) • NYHA class: I (92%), II (8%), III (0%), IV (0%) • CCS class: 1 (78%), 2 (21%), 3 (1%), 4 (0%)
Min 2008,[9]	Retro database	NR	NR	NR
Shreibati, 2011[6]	Retro database	NR	NR	NR

Author, Year	Study Design	Method Used to Assess Pretest Risk	Pretest Risk (as reported by authors)	Risk Scores or Percent of Patients
CCTA vs. Functional testing				
Douglas, 2015[15] (PROMISE trial)	RCT	Combined Diamond and Forrester / CASS risk score Also report risk burden (based on mean number of risk factors present)	CTA (n=4996) • Combined Diamond & Forrester/CASS: Mean 53.4 ± 21.4 • Risk burden: 2.4 ± 1.1 Functional (n=5007) • Combined Diamond & Forrester/CASS: Mean 53.2 ± 21.4 • Risk burden: 2.4 ± 1.1	NR

ACI-TIPI = Acute Cardiac Ischemia Time Insensitive Predictive Instrument; ACPS = acute chest pain syndromes; CCS = Canadian Cardiovascular Society; CCTA = coronary computer tomography angiography; CI = confidence interval; ECG = electrocardiogram; ECHO = echocardiogram; ICA = invasive coronary angiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; NYHA = New York Heart Association; RCT = randomized controlled trial; PET = positron emission tomography; pro = prospective; retro = retrospective; RR = risk ratio; SPECT = single photon-emission computed tomography; TIMI = thrombolysis in myocardial infarction

*Relevant clinical outcomes were not stratified by test; included for safety only.

Table E45. Definition of risk assessment in included studies

Risk Criteria	Description
Cardiac Society of Australia and New Zealand guidelines[32]	Low risk (<2%): Any pain Intermediate risk (2%-10%): Any pain and/or pain at rest, repetitive or prolonged pain High risk (>10%): Any pain, pain at rest, repetitive or prolonged pain, and changes on electrocardiogram or elevated troponin level Risk categories are based on the presence of clinical factors known to increase rates of myocardial infarction and death within 6 months.
CCS Angina Grading Scale[33]	Commonly used for the classification of severity of angina: Class I – Angina only during strenuous or prolonged physical activity Class II – Slight limitation, with angina only during vigorous physical activity Class III – Symptoms with everyday living activities, i.e., moderate limitation Class IV – Inability to perform any activity without angina or angina at rest, i.e., severe limitation
Diamond-Forrester risk algorithm[34]	"This model takes into account age, sex, and type of chest pain, which was classified as typical, atypical or non-anginal.9 The commonly used classification cut-offs of 30% and 70% were used.10 Consequently, a score below 30% was considered low, 30%-70% intermediate and >70% high risk of having significant CAD."
Established criteria[20]	"patients with very low likelihood atypical chest pain presentations (e.g., costochondral point tenderness) to high-risk patients (e.g., those manifesting a classic ST-elevation MI or arrhythmias or those with unstable hemodynamics) were screened for enrollment"
Framingham risk score[34]	"A multivariable risk function that predicts 10-year risk of developing cardiovascular disease events (coronary heart disease, stroke, peripheral artery disease or heart failure). The sex-specific scores incorporate age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetic status. A score below 10% is considered low, 10%-20% intermediate, and >20% high 10-year risk of cardiovascular events."
Goldman Reilly Criteria[23, 35, 36]	Low-risk: By these criteria, low-risk patients had no ECG evidence of acute infarction or ischemia (including new left bundle branch block), no pain that was worse than usual angina or like a previous myocardial infarction, no recent revascularization, no rates above both bases, and a systolic blood pressure that was greater than 110 mm Hg.
TIMI risk score[37]	% risk at 14 days of: all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization. • Score of 0-1=4.7% risk • Score of 2=8.3% risk • Score of 3=13.2% risk • Score of 4=19.9% risk • Score of 5=26.2% risk • Score of 6-7=at least 40.9% risk
Pryor et al.[38]	The probability of significant coronary artery disease was calculated as: $1/(1 + e^{-x})$ Where e=base of natural logarithm *Where* $x=a_1y_1 + a_2y_2 + \ldots + a_ky_k + B$ Where $y_1, y_2, \ldots, y_k$ are the characteristics, $a_1, a_2, \ldots, a_k$ are the corresponding logistic regression coefficients, and B is the intercept term (in this case, -7.376).

Risk Criteria	Description
Predicted annualized risk of death or MI[5]	Determining 10-year (short term) risk for developing CHD is carried out using Framingham risk scoring. The risk factors included in the Framingham calculation are age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking. Because of a larger database, Framingham estimates are more robust for total cholesterol than for LDL cholesterol. Note, however, that LDL cholesterol remains the primary target of therapy. Risk score is calculated using a downloadable excel file or risk assessment tool available here: http://cvdrisk.nhlbi.nih.gov/calculator.asp .

CAD = coronary artery disease; CASS = Coronary Artery Surgery Study risk score; CCS = Canadian Cardiovascular Society; ECG = electrocardiogram; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction

Table E46. Definitions for usual care in included studies

Author (year)	Definition of Usual Care
Hoffman (2012)[13*] RCT (ROMICAT II) Multicenter (9 sites)	Subjects will be evaluated according to each hospital's specific protocol to evaluate and manage patients with acute chest pain. Typically, the standard evaluation in the ED will include: • past and current medical history • physical examination • ECG • cardiac biomarker (troponin and CK-MB) as well as other routinely obtained blood testing Patients may undergo cardiac CT as part of Usual Care but only as a secondary diagnostic test. (Patients in the CT arm may undergo further diagnostic testing as well.) All admitted subjects will undergo each hospital's standard rule out myocardial ischemia protocol. This protocol typically consists of observation and monitoring including serial ECGs and repeated cardiac biomarker measurements as well as a noninvasive stress test (often imaging based) to evaluate for myocardial ischemia. The participating clinical sites perform routinely either: • nuclear perfusion imaging [SPECT] at rest and stress; • and/or stress echocardiography; • and/or exercise treadmill test [ETT] Depending on the results, subjects may undergo additional noninvasive or invasive testing (coronary angiography), and/or coronary revascularization during their hospital stay.

Litt (2012)[19*]
 	
RCT
Multicenter (5 sites)
	Patient's health care provider (ED physician) will make all disposition and management decisions:
	• Admit to hospital, admit to cardiac diagnostic unit, or discharge to home
	• ECG and serial markers (e.g., cardiac troponin) per Usual Care
	• Banked serum at up to 3 approximated time points: 0, 90 to 180 minutes, and 6 hours (blood sampling only up until the time of discharge) (performed only at HUP and PPMC sites)
	• Objective testing per attending during admission or as an outpatient:
	  o Stress testing with or without imaging [58% (267/462)]
	  o No objective assessment (i.e., stress test or cath) for ischemia or coronary artery disease [36% (167/462)]
	  o CCTA [6% (26/462)]
	  o Cardiac catheterization [4% (18/462)]

Miller (2011)[20] RCT Single center	Standard treatment included: • 12-lead ECG tracings • coronary biomarkers (troponin I) obtained at 0, 4, and 9 hours after ED arrival • continuous ECG monitoring All enrolled participants received: • aspirin (81 mg orally) and sublingual nitroglycerin (0.4 mg) for the chest pain until it was alleviated (up to three administrations, about 5 minutes apart) • cardiology consultation • and additional cardiac testing as required (types not specified) None of standard care group patients received a CCTA during the 90-days study period

Author (year)	Definition of Usual Care
Gruettner/ Henzler (2013)[17, 18] Retrospective cohort	The Usual Care diagnostic algorithm consisted of: • repetitive biomarker measurements • stress testing including exercise ECG, stress echocardiography, SPECT, and clinical observation • patients with positive/inconclusive or non-diagnostic stress test results as well as patients with mildly elevated Troponin values <0.5 µg/l were scheduled for ICC Usual Care group patients did not receive CCTA during the 90-days study period due to limited scanner availability (identified using clinical information and billing system) All Usual Care patients hospitalized at least one night. [ICC in 87% (87/100). The reminder (13/100) hospitalized for monitoring, including repeat ECG, cardiac biomarkers, and stress testing.]

CCTA = cardiac computed tomography angiogram; CK-MB = creatine kinase MB; ECG = electrocardiogram; ED = emergency department; ETT = exercise treadmill test; ICA = invasive coronary angiography; ICC = invasive coronary catheterization; RCT = randomized controlled trial; ROMICAT = rule out myocardial infarction using computer assisted tomography; SPECT = single-photon emission computerized tomography
*From published protocols.

Appendix F. Evidence Tables for Noncomparative Studies

Table F1. Demographics and study characteristics for noncomparative stress echocardiography studies with patients at low risk

		Exercise		Exercise or Pharmacologic
Author (year) Sample size		**Buchsbaum (2001)[39]** n=149	**Elhendy (2001)[40]** n=1618	**Innocenti (2014)[41]** n=626
Patient demographics	Female, % (n)	44% (64)	65% (1047)	42% (265)
	Age (years); mean ± SD	47 ± 9	54.1	67 ± 12
	Race, % (n)	NR	NR	NR
	Pretest risk	Low-risk	Low pretest probability (≤25%)	Very low-to-low
	Subgroup	None	NR	None
Cardiac risk factors, % (n)	Chest pain	NR	NR	NR
	Typical angina	NR	0% (0)	NR
	Atypical angina	NR	38.0% (615)	NR
	Unstable angina	NR	NR	NR
	Noncardiac angina	NR	NR	NR
	Atypical chest pain or dyspnea	NR	67.3% (1090)	NR
	Prior MI	NR	0% (0)	NR
	Prior revascularization	NR	0% (0)	NR
	Prior CABG/PCI	NR	0% (0)	NR
	Known CAD	NR	NR	26% (162)*
	Hypertension	26% (38)	30.9% (501)	62% (389)
	Diabetes	3% (4)	5% (78)	17% (104)
	Hyperlipidemia/ hypercholesterolemia	20% (29)	46.3% (750)	NR
	Smoker	52% (75)	43.5% (704)	NR
Test details	Type of stressor	Exercise (treadmill)	Dobutamine (73%) or dipyridamole (171%z) ECHO	Exercise or Dobutamine
Study characteristics	Followup period % completed followup (n)	6 months, 99% (148/149)	36 ± 18 months, % NR	Mean 2.3 ± 1.1 years, % NR
	Setting	ED	NR	ED

CABG = coronary artery bypass graft; CAD = coronary artery disease; ECHO = echocardiography; ED = emergency department; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation

* Results are for those without history of CAD; an additional 148 hand known CAD; Cardiac events included nonfatal ACS, fatal ACS and ventricular tachycardia over an average 4.5 years of followup. Authors excluded patients who died from noncardiac disease but do not report number for the group without a history of CAD

Table F2. Summary clinical outcomes from single arm studies of stress echocardiography in patients at low risk

Author (year) **Sample Size**		**Buchsbaum (2001)[39*]** n=149		**Elhendy (2001)[40]** N=1618		**Innocenti (2014)[41]** N=424	
Pretest risk		Low risk		Low pretest probability (≤25%)		Very low-to-low	
Followup		6 months		Median 3 yrs		Mean 4.5 years	
Test result **Sample size**		**Positive** (n=7)	**Negative** (n=138)	**Positive** (n=344)	**Negative** (n=1272)	**Positive** (n=94)	**Negative** (n=330)
Outcomes	Mortality % (n)	NR	NR	NR	NR	NR	NR
	MI % (n)	0% (0)	0.7% (1)*	NR	NR	NR	NR
	Any Cardiac Event	0% (0)	0.7% (1)*	2.6% (9)†	0.8% (10)†	5.3% (5)‡	0.8% (3)

CAD = coronary artery disease; CI = confidence interval; ECHO = echocardiography; MI = myocardial infarction; NR = not reported

*non-Q-wave MI 6 months after discharge

†cardiac death, nonfatal MI over median of 3 years

‡ Results are for those without history of CAD; an additional 148 hand known CAD. Cardiac events included nonfatal ACS, fatal ACS and ventricular tachycardia over an average 4.5 years of followup. Authors excluded patients who died from noncardiac disease but do not report number for the group without a history of CAD

Table F3. Demographics and study characteristics for single arm coronary artery calcium scoring studies with patients at intermediate risk

Author (year) **Sample Size**		**Petretta (2012)**[42] n=341	**Villines (2011)**[43] n=10,037	
Test Result		**Total population**	**Positive** (n=4909)	**Negative** (n=5128)
Patient demographics	Female, % (n)	33% (113)	57% (2798)	44% (2256)
	Age (years); mean ± SD	62 ± 12	61 ± 11	52 ± 12
	Race, % (n)	NR	NR	NR
	Pretest risk	Intermediate risk (15-85%)	Intermediate-risk (54%)	Intermediate risk (32%)
	Subgroup	NR	NR	NR
Cardiac risk factors, % (n)	Chest pain	100%	NR	NR
	Typical angina	32% (103)	16% (785)	13% (667)
	Atypical angina	63% (207)	NR	NR
	Unstable angina	0% (0)	NR	NR
	Noncardiac angina	5% (16)	NR	NR
	Atypical chest pain or dyspnea	NR	NR	NR
	Dyspnea	NR	37% (1816)	26% (1333)
	Prior MI	0% (0)	NR	NR
	Prior revascularization	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR
	Known CAD	0% (0)	0% (0)	0% (0)
	Hypertension	51% (167)	59% (2896)	44% (2256)
	Diabetes	12% (40)	18% (884)	9% (462)
	Hyperlipidemia/ Hypercholesterolemia	38% (124)	62% (3044)	51% (2615)
	Smoker	27% (89)	18% (884)	16% (820)
Test details	Type of stressor	NR	NR	NR
Study characteristics	Followup period % completed followup (n)	26 ± 12 months 95.6% (326/341)	Median 2.1 years 84.9% (4169/4909)	Median 2.1 years 92.3% (4738/5128)
	Setting	Outpatient	NR	NR

CABG = coronary artery bypass graft; CAD = coronary artery disease; ED = emergency department; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation

Table F4. Summary outcomes for single arm coronary artery calcium scoring studies with patients at intermediate risk

Author (year) **Sample Size**		**Petretta (2012)**[42] n=341		**Villines (2011)**[43] n=10,037	
Pretest risk		Intermediate (15-85%)		Diamond-Forrester pretest risk=43%	
Followup		26 ± 12 months		Median 2.1 years	
Test result **Sample size**		**Positive** (n=220)	**Negative** (n=106)	**Positive** (n=4909)	**Negative** (n=5128)
Outcomes	Mortality % (n)	0% (0)	0% (0)	1.8% (74)	0.4% (21)
	MI % (n)	0% (0)	0% (0)	1.1% (46)	0.2% (9)
	Any Cardiac Event	8.2% (28)*	0% (0)	4.8% (191)†	0.9% (44)†

CAD = coronary artery disease; CI = confidence interval; ECHO = echocardiography; MI = myocardial infarction; NR = not reported

* Includes nonfatal MI, cardiac death, and revascularization for unstable angina

† Major adverse events, includes all-cause mortality, nonfatal MI, or coronary revascularization occurring 90 days after testing.

Table F5. Demographics and study characteristics for single arm stress echocardiography studies with patients at low to intermediate risk

		Exercise		Exercise or Pharmacologic
Author (year) Sample Size		**Fine (2013)[44]** n=7,236		**Colon (1998)[45]** n=108
Test result		**Positive** (n=1275)	**Negative** (n=5961)	**Total population**
Patient demographics	Female, % (n)	21% (262)	32% (1899)	50% (54)
	Age (years); mean ± SD	60 ± 10	50 ± 10	54 ± 12
	Race, % (n)	NR	NR	NR
	Pretest risk	Low: 30% (386) Intermediate to High: 31% (396)	Low: 51% (3055) Intermediate to High: 42% (2488)	Low-moderate risk (mean 2.4 ± 1.3 risk factors)
	Subgroup	High exercise capacity	High exercise capacity	NR
Cardiac risk factors, % (n)	Chest pain	36% (465)	41% (2450)	100% (108)
	Typical angina	7% (85)	3% (204)	NR
	Atypical angina	27% (345)	33% (1993)	NR
	Unstable angina	NR	NR	NR
	Noncardiac angina	3% (35)	4% (253)	NR
	Dyspnea	18% (233)	19% (1109)	NR
	Prior MI	24% (306)	2% (148)	NR
	Prior revascularization	34% (432)	6% (371)	NR
	Prior CABG/PCI	NR	NR	NR
	Known CAD	39% (493)	7% (418)	NR
	Hypertension	52% (664)	34% (2053)	40% (43)
	Diabetes	9% (118)	6% (344)	11% (12)
	Hyperlipidemia	75% (960)	55% (3293)	31% (34)
	Smoker	50% (633)	39% (2332)	51% (55)
Test details	Type of stressor	Exercise (treadmill)	Exercise (treadmill)	Exercise (72%) or dobutamine (28%) echo
Study characteristics	Followup period % completed followup (n)	Mean 4.8 ± 1.7 years, %NR	Mean 4.8 ± 1.7 years, %NR	12.8 ± 7.2 months, %NR
	Setting	Clinic	Clinic	ED

CABG = coronary artery bypass graft; CAD = coronary artery disease; ED = emergency department; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation

Table F6. Summary outcomes for single arm stress echocardiography studies with patients at low to intermediate risk

		Exercise		Exercise or Pharmacologic	
Author (year) **Sample size**		**Fine (2013)**[44] n=7,236		**Colon (1998)**[45] n=108	
Pretest risk		Low: 30% (386) Intermediate to high: 31% (396)	Low: 51% (3055) Intermediate to high: 42% (2488)	Low-moderate risk (mean 2.4 ± 1.3 risk factors)	Low-moderate risk (mean 2.4 ± 1.3 risk factors)
Followup		Mean 4.8 ± 1.7 years		12 months	
Test result **Sample size**		**Positive** (n=1275)	**Negative** (n=5961)	**Positive** (n=8)	**Negative** (n=100)
Outcomes	Mortality % (n)	Ischemia* 0.53 (0.33 to 0.80) Fixed* 0.93 (0.56 to 1.31)	0.30 (0.24 to 0.37)*	0% (0)	0% (0)
	MI % (n)	NR	NR	NR	NR
	Any Cardiac Event	NR	NR	75% (6)†	0% (0)

MI = myocardial infarction; NR = not reported
*Annualized mortality rates per person year of followup (95% CI)
†Calculated from author reported cardiac event-free rate

Table F7. Demographics and study characteristics for single arm stress electrocardiogram (ECG) studies with patients at low to intermediate risk

		Exercise		Exercise or Pharmacologic	
Author (year) Sample size		**Cho (2012)[46]** n=2977	**Dedic (2011)[47*]** n=422	**Hachamovitch (1996)[48]** n=2268†	**Colon (1998)[45]** n=108
Patient demographics	Female, % (n)	50% (1501)	49 (205)	40% (845/2113)	50% (54)
	Age (years); mean ± SD	50 ± 10	56 ± 9.9	61 ± 12	54 ± 12
	Race, % (n)	NR	NR	NR	NR
	Pretest risk	Very low (<5%): 8% (239) Low (6-9%): 28% (823) Intermediate (10-90%): 61% (1825) High (>90%): 3% (90)	Low-to-intermediate	Low: 8% Intermediate: 46% High: 3%	Low-moderate risk (mean 2.4 ± 1.3 risk factors)
	Subgroup	NR	None	NR	NR
Cardiac risk factors, % (n)	Chest pain	NR	100% (422)	30% (628/2113)	100% (108)
	Typical angina	NR	32% (136)	9.0% (191/2113)	NR
	Atypical angina	NR	52% (220)	20.6% (437/2113)	NR
	Unstable angina	NR	NR	NR	NR
	Noncardiac angina	NR	16% (66)	70% (1485/2113)	NR
	Dyspnea	NR	NR	2.5% (54/2113)	NR
	Prior MI	NR	NR	0%	NR
	Prior revascularization	0% (0)	NR	0%	NR
	Prior CABG/PCI	0% (0)	NR	0%	NR
	Known CAD	NR	0% (0)	NR	NR
	Hypertension	48% (1413)	50% (213)	39% (825/23113)	40% (43)
	Diabetes	16% (455)	14% (58)	9% (182/2113)	11% (12)
	Hyperlipidemia/ Hypercholesterolemia/ Dyslipidemia	44% (1300)	59% (249)	40% (849/2113)	31% (34)
	Smoker	13% (397)	27% (116)	17% (369/2113)	51% (55)
Test details	Type of stressor	Treadmill	Exercise (bicycle)	Treadmill	Exercise (72%) or dobutamine (28%) echo
Study characteristics	Followup period % completed followup (n)	Median 3.34 years (IQR 2.33 to 4.55), %NR	Mean 2.6 years, 90% (424)	Mean 566 ± 142 days 93.1% (2113/2268)‡	12.8 ± 7.2 months, %NR
	Setting	NR	Outpatient	NR	ED

CABG = coronary artery bypass graft; CAD = coronary artery disease; ED = emergency department; IQR = interquartile range; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation

* Also includes groups who underwent calcium scoring or computed tomography angiography included for other comparisons; demographics based on overall population, calculated using weighted means; demographics only reported for patients with followup.

† Originally stated they enrolled 2268, have data on 2200 patients, but table 1 demos only report on 2113 patients, as they censored 89 patients for undergoing early revascularization (<60 days after testing).

‡ Patients lost to followup include 87 who were censored from demographics and results for receiving early revascularization/revascularization in the first 60 days after nuclear testing.

Table F8. Summary outcomes for single arm stress echocardiography studies with patients at low to intermediate risk

Author (year) **Sample size**		**Cho (2012)**[46] n=2977		**Dedic (2011)**[47*] n=422		**Hachamovitch (1996)**[48] n=2268†		**Colon (1998)**[45] n=108	
Pretest risk		Very low (<5%): 8% (239) Low (6-9%): 28% (823) Intermediate (10-90%): 61% (1825) High (>90%): 3% (90)		Low-to-intermediate		Low: 8% Intermediate: 46% High: 3%		Low-moderate risk (mean 2.4 ± 1.3 risk factors)	
Followup		Median 3.34 years (IQR 2.33 to 4.55)		Mean 2.6 years		Mean 566 ± 142 days		12 months	
Test result **Sample size**		**Positive** (n=358)	**Negative** (n=2489)	**Positive** (n=85)	**Negative** (n=172)	**Positive** (n=587)	**Negative** (n=974)	**Positive** (n=10)	**Negative** (n=98)
Outcomes	Mortality % (n)	0.5% (2)	0.04% (1)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	MI % (n)	0.8% (3)	0.1% (3)	1% (1)	0.6% (1)	0% (0)	0% (0)	0% (0)	0% (0)
	Any Cardiac Event*	9.7% (35)§	2.0% (50)§	5% (4)	4% (7)	2.0% (12)**	0.9% (9)**	30% (3)†	3% (3)†

CAD = coronary artery disease; CI = confidence interval; IQR = interquartile range; MI = myocardial infarction; NR = not reported; SD = standard deviation

* 12% (8/68) of patients with significant ST segment changes on exercise underwent primary revascularization or died of noncardiac causes and were excluded from analysis.† Originally stated they enrolled 2268, have data on 2200 patients, but table 1 demos only report on 2113 patients, as they censored 89 patients for undergoing early revascularization (<60 days after testing).

‡ Also includes equivocal/indeterminate outcome, see Table 3.

§ Also includes equivocal and nondiagnostic outcomes, see Table 4.

** Includes cardiac deaths (n=13) and nonfatal myocardial infarctions (n=26).

Table F9. Demographics and study characteristics for single arm coronary artery calcium scoring studies with patients at low to intermediate risk

Author (year) **Sample size**		**Kim (2012)**[49] n=2088		**Dedic (2011)**[47] n=422*	**Laudon (2010)**[50] n=263
Test result		**Positive** (n=974)	**Negative** (n=1114)	**Total population**	**Total population**
Patient demographics	Female, % (n)	42.8 (417)	58 (643)	49 (205)	40% (104)
	Age (years); mean ± SD	NR	55.3 ± 10.1	56 ± 9.9	47.3 ± 7
	Race, % (n)	NR	NR	NR	NR
	Pretest risk	Very low: 2% Low: 12% Intermediate: 75% High: 11%	Very low: 4% Low: 18% Intermediate: 72% High: 7%	Low-to-intermediate	Low to moderate
	Subgroup	None	None	None	NR
Cardiac risk factors, % (n)	Chest pain	100% (974)	100% (1114)	100% (422)	100% (263)
	Typical angina	20% (195)	12% (130)	32% (136)	NR
	Atypical angina	44% (424)	45% (499)	52% (220)	NR
	Unstable angina	NR	NR	NR	100% (263)
	Noncardiac angina	36% (355)	44% (485)	16% (66)	NR
	Dyspnea	NR	NR	NR	NR
	Prior MI	0% (0)	0% (0)	NR	NR
	Prior revascularization	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR
	Known CAD	NR	NR	0% (0)	0% (0)
	Hypertension	64% (620)	41% (454)	50% (213)	32% (84)
	Diabetes	24% (238)	9% (102)	14% (58)	6% (16)
	Hyperlipidemia	52% (503)	44% (485)	59% (249)	NR
	Smoker	15% (145)	11% (126)	27% (116)	53% (140)
Test details	Type of stressor	Contrast (70 mL of iopamidol)	Contrast (70 mL of iopamidol)	Exercise (bicycle)	NR
Study characteristics	Followup period % completed followup (n)	Mean 2.8 years ± 4.5 months; 99.3% (2073)	Mean 2.8 years ± 4.5 months; 99.3% (2073)	Mean 2.6 years, 90% (424)	5 years, 81% (212/263)
	Setting	Hospital	Hospital	Outpatient	Emergency Department

CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation

* Also includes groups who underwent calcium scoring or computed tomography angiography included for other comparisons; demographics based on overall population, calculated using weighted means; demographics only reported for patients with followup.

Table F10. Summary outcomes for single arm coronary artery calcium scoring studies with patients at low to intermediate risk

Author (year) **Sample size**		**Kim (2012)**[49] n=2088		**Dedic (2011)**[47] n=422		**Laudon (2010)**[50] n=263	
Pretest risk		Very low: 2% Low: 12% Intermediate: 75% High: 11%	Very low: 4% Low: 18% Intermediate: 72% High: 7%	Low-to-intermediate	Low-to-intermediate	Low to moderate	Low to moderate
Followup		Mean 2.8 years ± 4.5 months		Mean 2.6 years		5 years	
Test result		**Positive** (n=974)	**Negative** (n=1114)	**Positive** (n=266)	**Negative** (n=151)	**Positive** (n=130)	**Negative** (n=133)
Outcomes	Mortality % (n)	1.6 (16)	0.7 (8)	2 (4)	0 (0)	NR	NR
	MI % (n)	0.4 (4)	0.1 (1)	2 (6)	0 (0)	11.5% (15)	0%
	Any Cardiac Event	4.7 (46)	1.3 (14)	11 (28)	1 (2)	0%*	0%*

CAD=coronary artery disease; CI=confidence interval; IQR=interquartile range; MI=myocardial infarction; NR=not reported; SD=standard deviation.
*Have cardiogenic chest pain as an outcome, not included

Table F11. Demographics and study characteristics for single arm stress echocardiography studies with patients at intermediate to high risk

	Pharmacologic	
Author (year) **Sample size**		**Dodi (2001)**[28] n=244
Patient demographics	Female, % (n)	100% (244)
	Age (years); mean ± SD	60 ± 10
	Race, % (n)	NR
	Pretest risk	Pretest risk, mean: 56 ± 27 <70%: 60% (146) patients ≥70%: 40% (98) patients
	Subgroup	Women
Cardiac risk factors, % (n)	Chest pain	100%
	Typical angina	36% (89)
	Atypical angina	63% (155)
	Unstable angina	0%
	Noncardiac angina	NR
	Atypical chest pain or dyspnea	NR
	Dyspnea	NR
	Prior MI	0% (0)
	Prior revascularization	0% (0)
	Prior CABG/PCI)	0% (0)
	Known CAD	0% (0)
	Hypertension	39.7% (97)
	Diabetes	3.6% (9)
	Hyperlipidemia/ hypercholesterolemia	28.2% (69)
	Smoker	16.3% (40)
Test details	Type of stressor	Dobutamine (73) or dipyridamole (171) ECHO
Study characteristics	Followup period % completed followup (n)	36 ± 18 months, %NR
	Setting	NR

CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation

Table F12. Summary outcomes for single arm stress echocardiography studies with patients at intermediate to high risk

Author (year) **Sample size**		**Dodi (2001)**[28] N=244	
Pretest risk		Pretest risk, mean (SD): 56 ± 27 <70%: 60% (146) patients ≥70%: 40% (98) patients	
Followup		Mean 3yrs	
Test result **Sample size**		**Positive** (n=33)	**Negative** (n=211)
Outcomes	Mortality % (n)	NR	NR
	MI % (n)	NR	NR
	Any Cardiac Event	33% (11)	1.4% (3)

MI = myocardial infarction; NR = not reported; SD = standard deviation

Table F13. Demographics and study characteristics for single arm stress echocardiography studies with patients not stratified by risk

	Exercise	
Author (year) **Sample size**		**Krivokapich (1993)**[51] n=360
Patient demographics	Female, % (n)	34.1% (123)
	Age (years); mean ± SD	62 ±13
	Race, % (n)	NR
	Pretest risk	Known high pretest incidence of CAD
	Subgroup	NR
Cardiac risk factors, % (n)	Chest pain	NR
	Typical angina	NR
	Atypical angina	NR
	Unstable angina	NR
	Noncardiac angina	NR
	Atypical chest pain or dyspnea	NR
	Dyspnea	NR
	Prior MI	35.2% (127)
	Prior revascularization	NR (see below)
	Prior CABG/PCI)	17.7% (64)
	Known CAD	NR
	Hypertension	NR
	Diabetes	NR
	Hyperlipidemia/ hypercholesterolemia	46% (750)
	Smoker	44% (704)
Test details	Type of stressor	Treadmill exercise ECHO
Study characteristics	Followup period % completed followup (n)	12 months 100% (360/360) followup
	Setting	NR

CABG = coronary artery bypass graft; CAD = coronary artery disease; ECHO = echocardiography; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation

Table F14. Summary results for single arm stress echocardiography studies with patients not stratified by risk

		Exercise	
Author (year) **Sample size**		**Krivokapich (1993)**[51] N=211	
Pretest risk		Known high pretest incidence of CAD	Known high pretest incidence of CAD
Followup		1st year	
Test result **Sample size**		**Positive** (n=22)	**Negative** (n=189)
Outcomes	Mortality % (n)	0% (0)	0% (0)
	MI % (n)	9% (2)	1% (2)
	Any Cardiac Event	32% (7)*	7% (13)*

CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention
*Death, MI, CABG or PCI

Table F15. Demographics and study characteristics for single arm stress electrocardiography (ECG) studies with patients not stratified by risk

		Exercise or Pharmacologic	Exercise
Author (year) **Sample size**		**Gentile (2001)*** n=132	**Heupler (1997)**† n=405
Patient demographics	Female, % (n)	31.2% (42)	100% (405)
	Age (years); mean ± SD	70.8	56 ± 11
	Race, % (n)	NR	NR
	Pretest risk	NR	8 ± 5% (range, 0% to 38%)‡
	Subgroup	Elderly (>65 years)	Women only
Cardiac risk factors, % (n)	Chest pain	63% (83)	NR
	Typical angina	27% (36)	NR
	Atypical angina	15% (20)	NR
	Unstable angina	14% (19)	NR
	Noncardiac angina	NR	NR
	Dyspnea	19% (25)	NR
	Prior MI	0% (0)	7% (36)
	Prior revascularization	0% (0)	0% (0)
	Prior CABG/PCI	NR	NR
	Known CAD	NR	18% (92)
	Hypertension	NR	39% (197)
	Diabetes	NR	10% (53)
	Hyperlipidemia	NR	NR
	Smoker	NR	16% (81)
Test details	Type of stressor	Exercise (bicycle, modified Balke protocol) or pharmacologic (dipyridamole)	Exercise (treadmill)
Study characteristics	Followup period % completed followup (n)	Mean 27.8 months (range 24-48), 94% (124)	Mean 41 ± 10 months, 94% (508)
	Setting	NR	Tertiary referral center

ED = emergency department; IM = intermediate risk; IQR = interquartile range; NA = not applicable; NR = not reported

* Demographics based on overall population; results are only reported for patients with followup.

† Demographics based on patients with complete followup.

‡ 10 year cardiac risk based on Framingham in patients without known CAD.

Table F16. Summary results for single arm stress electrocardiography (ECG) studies with patients not stratified by risk

		Exercise or Pharmacologic		Exercise	
Author (year) **Sample size**		**Gentile (2001)**[52] n=132		**Heupler (1997)**[53] n=405	
Pretest risk		NR		8 ± 5% (range, 0% to 38%)*	
Followup		Mean 27.8 months		Mean 41 months	
Test result Sample size		**Positive** (n=95)	**Negative** (n=29)	**Positive** (n=68)†	**Negative** (n=337)
Outcomes	Mortality % (n)	7% (7)	7% (2)	NR	NR
	MI % (n)	3% (3)	10% (3)	NR	NR
	Any Cardiac Event	NR	NR	15% (9)	5% (8), OR 3.1, p=0.01

MI = myocardial infarction; NR = not reported; OR = odds ratio; SD = standard deviation

* 10 year cardiac risk based on Framingham in patients without known CAD

†12% (8/68) of patients with significant ST segment changes on exercise underwent primary revascularization or died of noncardiac causes and were excluded from analysis

Table F17. Demographics and study characteristics for single arm coronary artery calcium scoring studies with patients not stratified by risk

Author (year) **Sample size**		**Schmermund (2004)**[54*] n=255
Test result		
Patient demographics	Female, % (n)	29% (74)
	Age (years); mean ± SD	58 ± 11 years
	Race, % (n)	NR
	Pretest risk	NR
	Subgroup	NR
Cardiac risk factors, % (n)	Chest pain	NR
	Typical angina	NR
	Atypical angina	NR
	Unstable angina	0% (0)
	Noncardiac angina	NR
	Dyspnea	NR
	Prior MI	0% (0)
	Prior revascularization	0% (0)
	Prior CABG/PCI	NR
	Known CAD	NR
	Hypertension	40.8% (104)
	Diabetes	7.1% (18)
	Hyperlipidemia/ hypercholesterolemia	NR
	Smoker	NR
Test details	Type of stressor	
Study characteristics	Followup period % completed followup (n)	3.5 years, 85% (255/300)
	Setting	Outpatient

CABG = coronary artery bypass graft; CAD = coronary artery disease; ECHO = echocardiography; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation

*authors only report on patients with complete followup, though they do note that patients lost to followup were younger and had lower cholesterol than patients followed.

Table F18. Summary results for single arm coronary artery calcium scoring studies with patients not stratified by risk

Author (year) **Sample size**		**Schmermund (2004)[54]** n=255	
Pretest risk		NR	
Followup		Mean 38 months	
Test result **Sample size**		**Positive*** (n=193)	**Negative** (n=62)
Outcomes	Mortality % (n)	1.6% (3)†	NR
	MI % (n)	1.0% (2)	NR
	Any Cardiac Event	20.2% (39)	1.6% (1)

MI = myocardial infarction; NR = not reported; SD = standard deviation

*Patients with a positive result are reported as having a calcium score of 1.4 – 4041 (categorized in text into 4 quartiles, Q1 is 0-1.4 and Q2-4 are combined as positive)

†1 patient was excluded from analysis because of death for unknown cause (unclear which group this patient was in).

Appendix G. Safety Information in Included Comparative Studies and Studies Included for Safety Information Only

Safety Results for Studies Included for Safety Information Only

Table G1. Demographics for observational studies where patients received both stress echo and a second test and are included for safety information only[**]

Author (year)		**Ferrara (1991)[29]**		**Severi (1994)[30]**		**Takeuchi (1996)[*31]**	
Test Sample size		Stress Echo (n=130)	Ex ECG (n=130)	Stress Echo (n=429)	Ex ECG (n=429)	Stress Echo (n=70)	SPECT (n=61)
Patient demographics	Female, % (n)	38% (49)	38% (49)	28.4% (122)	28.4% (122)	100% (70)	100% (61)
	Age (years); mean ± SD	>65 years: 48% ≤65 years: 52%	>65 years: 48% ≤65 years: 52%	55 ± 4.1	55 ± 4.1	65 range (37 – 82)	NR
	Race, % (n)	NR	NR	NR	NR	NR	NR
	Pretest risk, % (n)[†]	NR	NR	NR	NR	High: 41% IM: 26% Low 33%	NR
	Subgroup	NR	NR	NR	NR	Women only	Women only
Cardiac risk factors, % (n)	Chest pain	100% (130)	100% (130)	100% (429)	100% (429)	NR	NR
	Typical angina	63.1% (82)	63.1% (82)	30.7% (132)	30.7% (132)	NR	NR
	Atypical angina	29.2% (38)	29.2% (38)	NR	NR	NR	NR
	Silent ischemia	13% (10)	13% (10)	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR
	Prior MI	5.4% (6)	5.4% (6)	NR	NR	NR	NR
	Prior revascularization	NR	NR	NR	NR	10% (7)	NR
	Prior CABG/PCI	NR	NR	NR	NR	NR	NR
	Known CAD	NR	NR	NR	NR	NR	NR
	Chest pain frequency	NR	NR	NR	NR	NR	NR
	Hypertension	NR	NR	28% (124)	28% (124)	NR	NR
	Diabetes	NR	NR	10% (44)	10% (44)	NR	NR
	Hyperlipidemia	NR	NR	15% (66)	15% (66)	NR	NR
	Current smoker	NR	NR	55% (238)	55% (238)	NR	NR
Test details	Type of stressor	Dobutamine	Bicycle	Dobutamine	Bicycle	Pharmacologic (dobutamine)	Exercise or pharmacologic (bicycle ergometer or dipyridamole)
	Contrast (dose)	NR	NA	NR	NA	NR	Thallium-201 tracer
Study characteristics	Setting	Outpatient	Outpatient[‡]	Outpatient	Outpatient	NR	NR
	Followup period % completed followup (n)	Median 9.7 months (range 5.4-15.4)[§] %NR	Median 9.7 months (range 5.4-15.4)[§] %NR	mean 37.8 ± 14 (range 1 to 73) months 100% (429)	mean 37.8 ± 14 (range 1 to 73) months 100% (429)	NR 97.2% (70/72)	NR %NR

Author (year)		Ferrara (1991)[29]		Severi (1994)[30]		Takeuchi (1996)*[31]	
	Study Design	Prospective cohort	Prospective cohort	Prospective cohort	Prospective cohort	Retrospective	Retrospective

CAD = coronary artery disease; CABG = coronary artery bypass graft; ECG = electrocardiogram; Echo = echocardiogram; Ex = exercise; IM = intermediate risk; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation; SPECT = single photon emission computed tomography

*Results reported only for patients with complete followup.

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Table E41 for details.

‡ Performed in a thermostatically controlled room.

§ Reported as days, converted to months by dividing by 30.

**Demographics for included comparative studies are included in Appendix E.

Table G2. Demographics for observational studies where patients received both computed tomography and CACS tests and are included for safety information only

Author (year)		**Nabi (2010)[56]**		**Nance (2012)[57]**	
Test **Sample size**		SPECT (n=1031)	CACS (n=1031)	CCTA (n=458)	CACS (n=458)
Patient demographics	Female, % (n)	60% (623)	60% (623)	64% (293)	64% (293)
	Age (years); mean ± SD	54 ± 13.5	54 ± 13.5	55 ± 11	55 ± 11
	Race, % (n)	NR	NR	NR	NR
	Pretest risk, % (n)*	Low: 35.6% Moderate: 29.6% Moderately high: 15.1% High: 19.7%	Low: 35.6% Moderate: 29.6% Moderately high: 15.1% High: 19.7%	Low: 76% IN: 18% High: 6%	Low: 76% IN: 18% High: 6%
	Subgroup	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	100% (1031)	100% (1031)	100% (458)	100% (458)
	Typical angina	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR
	Unstabe angina	NR	NR	NR	NR
	Noncardiac angina	0% (0)	0% (0)	NR	NR
	Silent ischemia	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR
	Prior MI	NR	NR	NR	NR
	Prior revascularization	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR
	Known CAD	0% (0)	0% (0)	NR	NR
	Chest pain frequency	NR	NR	NR	NR
	Hypertension	57.2% (590)	57.2% (590)	69% (314)	69% (314)
	Diabetes	14.7% (152)	14.7% (152)	21% (96)	21% (96)
	Hyperlipidemia	34.1% (352)	34.1% (352)	45% (205)	45% (205)
	Current smoker	18.6% (192)	18.6% (192)	30% (138)	30% (138)
Test details	CT images (slice)	NA	16 multidetector	NR	NA
	CACS performed	Yes	Yes	Yes	Yes
	Type of stressor	Exercise (treadmill) or pharmacologic (adenosine or dobutamine) Technetium-99m	NR	NR	NR
	Contrast (dose)	None	None	Sublingual nitroglycerine (0.4mg)	NR
Study characteristics	Setting	ED	ED	ED	ED
	Followup period % completed followup (n)	Mean 7.4 ± 3.3 months 99% (1018)`	Mean 7.4 ± 3.3 months, 99% (1018)	Median 13 months	Median 13 months
	Study Design	Prospective cohort	Prospective cohort	Retrospective cohort	Retrospective cohort

CACS = coronary artery calcium scoring; CAD = coronary artery disease; CABG = coronary artery bypass graft; ECG = electrocardiogram; Echo = echocardiogram; Ex = exercise; IM = intermediate risk; MI = myocardial infarction; NA = not

applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation; SPECT = single photon emission computed tomography
*As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Table E41 for details.
†Patients were randomized as to the order in which tests were performed

Safety Results for Included Comparative Studies

Table G3. Safety outcomes reported in included comparative studies

Pretest CAD Risk	Type of Test Comparison	Author, Year Study Design	Intervention	Comparator	Adverse Events/Side Effects/Harms (intervention vs. comparator)
Low	Functional vs. functional	Sabharwal, 2007[2] RCT	SPECT	Exercise ECG	NR
Intermediate	Anatomic vs. usual care	Hoffman, 2012[13] RCT	CCTA (+ Usual Care)	Usual Care	• Perioprocedural complications: 0.4% (2/501) vs. 0% (0/499)* • Undetected ACS: 0% (0/501) vs. 0% (0/499)
		Gruettner/Henzler, 2013[17, 18] Pro observational	CCTA	Usual Care	NR
	Functional vs. functional	Shaw 2011[14] RCT	SPECT	Exercise ECG	NR
		Sabharwal 2007[2] RCT	SPECT	Exercise ECG	NR

Pretest CAD Risk	Type of Test Comparison	Author, Year Study Design	Intervention	Comparator	Adverse Events/Side Effects/Harms (intervention vs. comparator)
	Anatomic vs. functional	Douglas, 2015[15] RCT	CCTA	"Functional testing" (primarily nuclear stress testing)	• Major procedural complication (includes stroke, major bleeding, anaphylaxis, and renal failure requiring dialysis): o 12 months followup: 0.1% (4/4996) vs. 0.1% (5/5007); RR 0.80† (95% CI 0.22 to 2.98); p=0.7413† o Mean 35 months followup: 0.1% (4/4996) vs. 0.1% (5/5007); RR 0.80† (95% CI 0.22 to 2.98); p=0.7413† • Stroke (procedural): 0.02% (1/4996) vs. 0.4% (2/5007); RR 0.50† (95% CI 0.05 to 5.52); p=0.5649† • Major bleeding (procedural): 0.1% (3/4996) vs. 0.1% (3/5007); RR 1.00† (95% CI 0.20 to 4.96); p=0.9978† • Anaphylaxis (procedural): 0% (0/4996) vs. 0% (0/5007) (RR, p-value NC) † • Renal failure requiring dialysis (from procedure): 0% (0/4996) vs. 0% (0/5007) (RR, p-value NC) † • Exercise-induced hypotension (BP fall >20 mmHg): 0% (0/4996) vs. 0.1% (6/5007) (RR 0† (95% CI NC); p=0.0144† • Stress-induced symptoms (not resolved <20 minutes): 0% (0/4996) vs. 0.1% (4/5007) (RR 0† 95% CI NC); p=0.0457† • Rapid atrial fibriallation that does not slow or convert: 0% (0/4996) vs. 0% (0/5007) (RR, p-value NC) † • Ventricular tachycardia: 0% (0/4996) vs. 0.1% (4/5007); RR 0† (95% CI NC); p=0.0457† • Hemodynamic instability (systolic BP < 80 mmHg): 0% (0/4996) vs. 0.04% (2/5007); RR 0† (95% CI NC); p=0.1577† • Any events potentially related to vasodilators: 0% (0/4996) vs. 0.1%

Pretest CAD Risk	Type of Test Comparison	Author, Year Study Design	Intervention	Comparator	Adverse Events/Side Effects/Harms (intervention vs. comparator)
	Anatomic vs. functional	Levsky, 2015[16]	CCTA	SPECT	• Periprocedural chest pain, shortness of breath, or palpitations: 0.5% vs. 15.9% (RD -15.4, 95% CI -20.8 to -10.1 per 100 persons) • "General" adverse reactions (including headache, nausea, dizziness, or feeling of warmth) (24.2% vs. 24.5%, p=0.25) • Rash or pruritus (1.6% vs. 0%, p=0.25). • No cases of posttest renal dysfunction.
Low to intermediate	Anatomic vs. usual care	Litt, 2012[19] RCT	CCTA	Usual Care ‡	• Bradycardia (presumed to be related to the medication to control heart rate): 0.1% (1/908) vs. 0.2% (1/462)
		Miller, 2011[20] RCT	CCTA+ Usual Care	Usual Care alone	NR
		Poon, 2013[24] Retro observational	CCTA	Usual Care	NR
	Anatomic vs. functional	Goldstein, 2011[21] RCT	CCTA	SPECT	NR
		Goldstein, 2007[23] RCT	CCTA	SPECT	"no complication as a results of either test: 0% (0/99) vs. 0% (0/98)
		Cheezum, 2011[25] Retro observational	CCTA	SPECT	• Incidental findings requiring further investigation§: 7.1% (18/252) vs. 0% (0/241); p=0.0001
		Hamilton-Craig, 2014[22] RCT	CCTA	Exercise ECG	NR
		Nielsen, 2011/2013[26, 27] Retro observational	CCTA	Exercise ECG	NR
Intermediate to high	Functional vs. functional	Hachamovitch, 2012/Hlatky, 2014[11, 12] Pro observational	PET	SPECT	NR
	Anatomic vs. functional	Min, 2012[10] RCT	CCTA	SPECT (exercise or pharm)	NR
	Functional vs. functional	Sabharwal, 2007[2] RCT	SPECT	Exercise ECG	NR

Pretest CAD Risk	Type of Test Comparison	Author, Year Study Design	Intervention	Comparator	Adverse Events/Side Effects/Harms (intervention vs. comparator)
Mixed population (risk NR or not stratified by risk)	Anatomic vs. usual care	Chang, 2008[1] RCT	CCTA	Usual Care	• Clinical or laboratory evidence of contrast-induced nephropathy: 0% (0/133) vs. 0% (0/133) • Diffusing irritating skin rash after imaging, (resolved spontaneously): 1.5% (2/133) vs. NR
	Functional vs. functional	Sabharwal, 2007[2] RCT	SPECT	Exercise ECG	NR
		Shreibati, 2011[6] Retro Admin Database	SPECT	Exercise ECG	NR
		Sanfilippo, 2005[3] RCT	Stress echo	Exercise ECG	NR
		Marwick, 2003[5] Pro observational	Stress echo	Exercise ECG	NR
		Shreibati, 2011[6] Retro Admin Database	Stress Echo	Exercise ECG	NR
		Ferrera, 1991[29**] Pro observational	Stress echo (dipyridamole)	Exercise ECG	• Chest pain: 36.7% (40/109) vs. NR • Flushing: 22% (24/109) vs. NR • Headache: 30% (33/109) vs. NR • Dyspnea: 11% (13/109) vs. NR • Hypotension: 6.4% (7/109) vs. NR • Nausea: 5.5% (6/109) vs. NR • Dizziness: 4.5% (5/109) vs. NR • ST depression: 49.5% (54/109) vs. NR
		Severi, 1994[30**] Pro observational	Stress echo (dipyridamole)	Exercise ECG	• Major periprocedural side effects: 0% (0/429) vs. 0% (0/429) • Excessive tachycardia with palpitations: 0.2% (1/429) vs. NR • Hypotension and symptomatic bradycardia: 0.5% (2/429) vs. NR
		Dodi, 2001[28**] Retro observational	Stress echo (dipyradimole or dobutamine)	Exercise ECG	"No major complication as a result of either test" (details NR): 0% (0/244) vs. 0% (0/244)

Pretest CAD Risk	Type of Test Comparison	Author, Year Study Design	Intervention	Comparator	Adverse Events/Side Effects/Harms (intervention vs. comparator)
		Takeuchi, 1996[31] Retro observational	Stress Echo (dobutamine)	SPECT	• No serious side effects vs. NR • Sustained arrhythmia: 0% (0/70) vs. NR • Severe hypotension: 0% (0/70) vs. NR • MI: 0% (0/70) vs. NR • Test terminated for severe chest pain: 11% (8/70) vs. NR • Extracardiac side effects (e.g., dyspnea and nausea): 5.7% (4/70) vs. NR • Increased BP: 2.9% (2/70) vs. NR • Multiple ventricular ectopy: 1.4% (1/70) vs. NR
		Shreibati, 2011[6] Retro Admin Database	Stress Echo (exercise or pharmacologic)	SPECT	NR
	Anatomic vs. functional	McKavanagh, 2014 RCT[4]	CCTA	Exercise ECG	"No complications after any investigation": 0% (0/243) vs. 0% (0/245)
		Shreibati, 2011[6] Retro Admin Database	CCTA	Exercise ECG	NR
		Tandon, 2012[8] Pro Registry	CCTA	SPECT	NR
		Min, 2008[9] Retro Admin Database	CCTA	SPECT	NR
		Yamauchi, 2012[7] Pro observational	CCTA	MPI (Nuclear)	"adverse events during initial test" (details NR) ††: 0.5% (3/625) vs. 0.9% (11/1205)
		Shreibati, 2011[6] Retro Admin Database	CCTA	MPI (Nuclear)	NR
		Shreibati, 2011[6] Retro Admin Database	CCTA	Stress Echo	NR

CCTA = coronary computer tomography angiography; CI = confidence interval; ECG = electrocardiogram; ECHO = echocardiogram; ICA = invasive coronary angiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; NA = not applicable; NC = not calculable; NR = not reported; RCT = randomized controlled trial; PET = positron emission tomography; pro = prospective; retro = retrospective; RR = risk ratio; SPECT = single photon-emission computed tomography

*One patient suffered from perioperative bleeding after cardiothoracic surgery for an identified anomalous coronary artery and the second had a transient increase in the creatinine level after CCTA w/o need for dialysis.

† RR and *p values calculated using Rothman Episheet.

‡total of 60% of patients received stress testing: 58% had stress test w/ imaging, 2% stress test w/o imaging.

§Incidental findings included (not reported by test group): pulmonary nodule ≥4 mm (n=5), hepatic cyst (n=3), liver hemangioma (n=2), fatty liver (n=2), mediastinal lymphadenopathy (n=2), pulmonary embolism (n=1), thoracic aortic aneurysm (n=1), esophageal thickening (n=1), and pleural thickening (n=1)

**All patients received both tests. Ferrera and Severi: tests performed-on different days and in random order-within 1 week of coronary angiography; Dodi: test performed in random order and on different days within 3 weeks of each other. All 3 studies included for safety only.
††Cases calculated from % given.

Table G4. Radiation exposure in included comparative studies

Tests	Author, Year Study Design	Index Visit	Additional Testing
CCTA vs. Usual Care	Hoffman, 2013[13] RCT	CCTA: 13.9 ± 10.4 Usual Care 4.7 ± 8.4 p<0.001	Cumulative radiation exposure, index visit plus followup (mSv) CCTA: 14.3 ± 10.9 Usual Care: 5.3 ± 9.6 p<0.001
	Litt, 2012[19] RCT	Bradycardia (presumed to be related to the medication to control heart rate) CCTA: 0.1% (1/908) Usual Care: 0.2% (1/462)	NR
	Miller, 2011[20] RCT	NR	Cumulative median radiation dose 5.88 mSv (95% CI: 5.2 to 6.4) (n=1037); Retrospective scans: 16.22 mSv (95% CI: 15.0 to 17.4) (n=432 [42%]); Prospective scans: 3.61 mSv (95% CI: 3.4 to 3.8) for (n=605 [58%]).
	Poon, 2013[24]	Median effective dose (mSv): CCTA: 5.88 (95% CI, 5.2 to 6.4) retrospective scans: 16.22 (95% CI, 15.0 to 17.4) prospective scans: 3.61 (95% CI, 3.4 to 3.8) Usual Care: NR	NR
	Gruettner, 2013/ Henzler, 2013[17, 18] Pro observational	Mean effective dose (mSv): CCTA: 8.7 Usual Care: NR	NR
CCTA vs. SPECT	Goldstein, 2011[21] RCT (CT-STAT)	Median effective radiation dose at index visit (mSv) CCTA: 11.5 (6.8-16.8) SPECT: 12.8 (11.6-13.9 p=0.02	NR
	Goldstein, 2007[23] RCT	Test complications CCTA: 0% (0/99) SPECT: 0% (0/99)	NR
	Min, 2012[10] RCT	Estimated median (IQR) effective dose at index visit: CCTA: 6.5 mSv (5.1–13.3) SPECT: 13.3 mSv (13.1–38.0) p<0.0001	Cumulative radiation (estimated median (IQR) effective dose): CCTA: 7.3 mSv (5.1–13.7) SPECT: 13.3 mSv (13.1–38.0) p<0.0001

Tests	Author, Year Study Design	Index Visit	Additional Testing
	Cheezum, 2011[25]	Incidental findings requiring further investigation* CCTA: 7.1% (18/252) SPECT: 0% (0/241) P=0.0001 * included pulmonary nodule ≥4 mm (n=5), hepatic cyst (n=3), liver hemangioma (n=2), fatty liver (n=2), mediastinal lymphadenopathy (n=2), pulmonary embolism (n=1), thoracic aortic aneurysm (n=1), esophageal thickening (n=1), and pleural thickening (n=1)	NR
	Min, 2008[9]	NR	NR
	Tandon, 2012[8]	Radiation exposure (mSv, median (IQR)) CCTA: 14.9 (13.1, 17.1) SPECT: 10.5 (10.1, 11.4) p<0.001	Radiation exposure from ICA (mSv, median (IQR)) CCTA (n=129): 15.2 (12.7, 17.1) SPECT (n=125): 10.8 (10.2, 11.7) p<0.001
CCTA vs. MPI (nuclear)	Shreibati, 2011[6]	NR	NR
	Yamauchi, 2012[7]	"adverse events during initial test" (details NR) CCTA: 0.5% MPI: 0.9%	NR
CCTA vs. functional (various)	Douglas, 2015[15]	NR	cumulative through 90 days: mean 12.0 ± 8.5 vs. 10.1 ± 9.0 mSv (mean difference, 3.0, 95% CI 2.7 to 3.3)
CCTA vs. SPECT	Levsky, 2015[16]	initial test : CCTA: 9.6 mSv (IQR, 6.2 to 23) SPECT: 27 mSv (IQR, 19 to 27) (mean difference, -17.4, 95% NR, p<0.001).	Cumulative through 12 months: CCTA: 12 mSv (IQR 6.4 to 26) SPECT: 27 mSv (IQR 19 to 27) (mean difference -15, 95% CI NR, p<0.001); cumulative through the entire follow-up period (median of 40.4 months): CCTA: 13 mSv (IQR, 6.9 to 27) SPECT: 27 mSv (IQR 19 to 27) (mean difference, -14, 95% NR, p<0.001)
CCTA vs. Exercise ECG	Hamilton-Craig, 2014[22] RCT	Mean radiation exposure CCTA: 3.8 mSv (95% CI: 3.5, 4.1) (range: 0.63–16.9) ECG: NA	NR
	McKavanagh, 2014 RCT[4]	NR	NR
	Nielse,n 2011/2013[26, 27] Retrospective cohort	NR	Cumulative radiation exposure by test results

Tests	Author, Year Study Design	Index Visit	Additional Testing
	Shreibati, 2011[6]	NR	NR
Stress Echocardiography vs. Exercise ECG	Sanfilippo, 2005[3] RCT	NR	NR
	Ferrara, 1991[29]	Dipyridamole stress echo: Chest pain 36.7% (40/109) Flushing 22% (24/109) Headache 30% (33/109) Dyspnea 11% (13/109) Hypotension 6.4% (7/109) Nausea 5.5% (6/109) Dizziness 4.5% (5/109) ST depression 49.5% (54/109) ECG: NR	NR
	Marwick, 2003[5]	NR	NR
	Takeuchi, 1996[31]	Dobutamine stress echo: No serious side effects defined as sustained arrhythmia, severe hypotension or MI Test terminated for severe chest pain: 11% (8/70) Extracardiac side effects: 5.7% (4/70) Increased BP: 2.9% (2/70) multiple ventricular ectopy: 1.4% (1/70) ECG: NR	NR
	Dodi, 2001[28] Retrospective cohort	Dipyradimole or dobutamine stress echo NR “There was no major complication as a result of either test” (details NR)	NR
	Severi, 1994[30] Prospective cohort	Dipyradimole stress echo “No major side effects from either test” Echo: excessive tachycardia with palpitations: 0.2% (1/429) hypotension and symptomatic bradycardia: 0.5% (2/429)	NR
	Shreibati, 2011[6]	NR	NR

Tests	Author, Year Study Design	Index Visit	Additional Testing
Stress Echocardiography vs. SPECT	Takeuchi, 1996[31]	Dobutamine stress echo: No serious side effects defined as sustained arrhythmia, severe hypotension or MI Test terminated for severe chest pain: 11% (8/70) Extracardiac side effects: 5.7% (4/70) Increased BP: 2.9% (2/70) multiple ventricular ectopy: 1.4% (1/70) ECG: NR	NR
	Shreibati, 2011[6]	NR	NR

BP = blood pressure; CCTA = coronary computer tomography angiography; CI = confidence interval; ECG = electrocardiogram; ECHO = echocardiogram; ICA = invasive coronary angiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; RCT = randomized controlled trial; SPECT = single photon-emission computed tomography

Appendix H. Diagnostic Accuracy of Noninvasive Tests in Included Studies

Table H1. Diagnostic accuracy: Exercise ECG compared with coronary angiography as reference standard for diagnosis of CAD

Author, Year	Search Dates	Number (type) of Studies	Study Quality	Reference Standard (threshold)	Population	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes*	Risk of Bias
Dolor, 2012[58†]	01/2000-09/2011	29†	Assessed with QUADAS; assigned summary score Good: 34% Fair: 52% Poor: 14%	Coronary angiography (≥ 50 - 75% stenosis)	• N=3392 • % male: 0% • Age: NR • Condition: symptomatic for CAD • Subgroup: women	No known CAD	• Prevalence (mean): 41% (range, 18-67%) • Sensitivity: 62% (95% CI, 55-68%) • Specificity: 68% (95% CI, 63-73%) • PPV: 57% • NPV: 72% • LR+: 1.94 • LR-: 0.56 • DOR: NR	Low
		10†	Assessed with QUADAS; assigned summary score Good: 100%	Coronary angiography (≥ 50 - 75% stenosis)	• N=1410 • % male: 0% • Age: NR • Condition: symptomatic for CAD • Subgroup: women	No known CAD	• Prevalence (mean): 38% (range, 18-67%) • Sensitivity: 70% (95% CI, 58-79%) • Specificity: 62% (95% CI, 53-69%) • PPV: 53% • NPV: 77% • LR+: 1.84 • LR-: 0.48 • DOR: NR	Low
Nielsen, 2014[26]	01/2002-02/2013	7	Assessed with QUADAS-2 and Newcastle Ottawa Scale; assigned summary score. Fair to good (% NR)	Coronary angiography (≥ 50 stenosis)	• N=911 • % male: 50-74% (range) • Age: 54-63 yrs. (range of means) • Condition: stable with suspected CAD	With or without known CAD (details NR)	• Prevalence: NR • Sensitivity: 67% (95% CI, 54-78%) • Specificity: 46% (95% CI, 30-64%) • PPV: 41% (95% CI, 30-55%) • NPV: 72% (95% CI, 54-84%) • LR+: NR • LR-: NR • DOR: 2 (95% CI, 1-4)	Low

CAD = coronary artery disease; CI = confidence interval; DOR = Diagnostic odds ratio; ECG = electrocardiogram; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; NR = not reported; PPV = positive predictive value; QUADAS = quality assessment of diagnostic accuracy studies

*Results pooled unless otherwise indicated.

†For inclusion, data for women must have been presented separately from that of men. Results for men were reported but for mixed populations (i.e., with and without known CAD) only and thus were not included here.

Table H2. Diagnostic accuracy: Stress echocardiography compared with coronary angiography as reference standard for diagnosis of CAD

Author, Year	Search Dates	Number of Studies	Study Quality	Reference Standard (threshold)	Population	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes*	Risk of Bias
de Jong, 2012[59]	01/2000-05/2011	10	Assessed with QUADAS. Number of items "yes": 13/16: 40% 12/16: 10% 11/16: 40% 10/16: 10%	Coronary angiography (≥ 50 - 75% stenosis)	• N=795 • % male: 61-82% (range) • Age: 56-67 yrs. (range of means) • Condition: known or suspected CAD	Known (previously diagnosed) or suspected CAD	• Prevalence (mean): 66% • Sensitivity: 87% (95% CI, 81-91%) • Specificity: 72% (95% CI, 56-83%) • PPV: 85%§ • NPV: 73%§ • LR+: 3.08 (95% CI, 1.65-4.50) • LR-: 0.18 (95% CI, 0.13-0.24) • DOR: 16.94 (95% CI, 9.84-29.15)	Mod.
		1	Assessed with QUADAS. Number of items "yes": 11/16	Coronary angiography (≥ 50 stenosis)	• N=50 • % male: 68% • Age: 67 yrs. (mean) • Condition: suspected CAD (and no history of MI, PCI or CABG)	Suspected CAD, without known CAD (no history of MI, PCI or CABG)	• Prevalence: 64% • Sensitivity: 88% (95% CI, 60-97%) • Specificity: 89% (95% CI, 58-98%) • PPV: 93%§ • NPV: 80%§ • LR+: 8.35 (95% CI, 6.67-21.76) • LR-: 0.13 (95% CI, -0.05-0.32) • DOR: 62.76 (95% CI, 7.37-534.54)	Mod.
Lapado, 2013[60]	01/1990-11/2012	4	NR	Coronary angiography (≥ 50 - 75% stenosis)	• N=5216 • % male: 46-100% (range) • Age: 53-62 yrs. (range of means) • Condition: stable with suspected CAD	With or without known CAD (Excluded studies with ≥ 15% history of MI or revascularization)	• Prevalence: 60-100%** • Prevalence, (estimated mean): 68%† • Sensitivity: 84% (95% CI, 80-89%) • Specificity: 77% (95% CI, 69-86%) • PPV: 89%§§ • NPV: 69%§§ • LR+: 3.65 (95% CI, 3.33-4.00 §§ • LR-: 0.21 (95% CI, 0.19-0.23)§§	Mod.

CAD = coronary artery disease; CABG = coronary artery bypass graft; CI = confidence interval; DOR = diagnostic odds ratio; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = quality assessment of diagnostic accuracy studies

*Results pooled unless otherwise indicated.

§Calculated.

** A single study had 100%, but reported only on patients with abnormal exercise test result.

†Estimated from 2 studies (n=4966); excluded one study with no reported prevalence (n=50) and one study that only reported prevalence for patients with abnormal exercise test result (n=200).
§§ Calculated based on estimated mean prevalence and reported sensitivity and specificity.

Table H3. Diagnostic accuracy: Single photon emission computed tomography compared with coronary angiography as reference standard for diagnosis of CAD

Author, Year	Search Dates	Number of Studies	Study Quality	Reference Standard (threshold)	Population	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes*	Risk of Bias
de Jong, 2012[59]	01/2000-05/2011	13	Assessed with QUADAS. Number of items "yes": 13/16: 15.4% 12/16: 7.7% 11/16: 38.5% 10/16: 15.4% 9/16: 15.4% 8/16: 7.7%	Coronary angiography (> 50 to ≥ 75% stenosis)	• N=1323 • % male: 0-95% (range) • Age: 51-67 yrs. (range of means) • Condition: known or suspected CAD	Known (previously diagnosed) or suspected CAD	• Prevalence (mean): 50% • Sensitivity: 83% (95% CI, 73-89%) • Specificity: 77% (95% CI, 64-86%) • PPV: 79%† • NPV: 79%† • LR+: 3.56 (95% CI, 2.07-5.04) • LR-: 0.22 (95% CI, 0.14-0.31) • DOR: 15.84 (95% CI, 9.74-25.77)	Mod.
		4	Assessed with QUADAS. Number of items "yes": 13/16: 25% 12/16: 25% 11/16: 50%	Coronary angiography (≥ 50 stenosis)	• N=535 • % male: 54-68% (range) • Age: 57-67 yrs. (range of means) • Condition: suspected CAD (and no history of MI, PCI or CABG)	Suspected CAD, without known CAD (no history of MI, PCI or CABG)	• Prevalence: 41% • Sensitivity: 83% (95% CI, 70-91%) • Specificity: 79% (95% CI, 66-87%) • PPV: 72%† • NPV: 84%† • LR+: 3.88 (95% CI, 2.03-5.73) • LR-: 0.21 (95% CI, 0.09-0.34) • DOR: 18.15 (95% CI, 8.34-39.52)	Mod.
McArdle, 2012[61]	01/2008-03/2012	8	Assessed with QUADAS. Unclear if ICA results blinded to SPECT results (75% of studies)	Coronary angiography (> 50 to > 70% stenosis)	• N=1755 • % male: 55% • Age (mean): 61.1 yrs. (range: 59.1-63.2) • Condition: known or suspected CAD (previous MI: 3.4%; PCI/CABG: 3.2%)	Known or suspected CAD	• Prevalence: 50% • Sensitivity: 85% (95% CI, 82-87%) • Specificity: 85% (95% CI, 82-87%) • PPV: 85%† • NPV: 85%† • LR+: 5.13 (95% CI, 4.01-6.56) • LR-: 0.18 (95% CI, 0.15-0.21)§ • DOR: 28.29 (95% CI, 17.66-45.30)	Low

Author, Year	Search Dates	Number of Studies	Study Quality	Reference Standard (threshold)	Population	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes*	Risk of Bias
		NR	See above	NR	• N=1320 • % male: NR • Age (mean): NR • Condition: No known CAD	Suspected CAD only (known CAD excluded)	• Prevalence: NR • Sensitivity: 84% (95% CI, 81-87%) • Specificity: 85% (95% CI, 82-88%) • PPV: 85%‡ • NPV: 84%‡ • LR+: 5.01 (95% CI, 3.36-7.47) • LR-: 0.19 (95% CI, 0.16-0.22)‡ • DOR: 23.83 (95% CI, 11.77-48.2)	Low

CAD = coronary artery disease; CABG = coronary artery bypass graft; CI = confidence interval; DOR = Diagnostic odds ratio; ECG = electrocardiogram; ICA = invasive coronary angiography; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = quality assessment of diagnostic accuracy studies; SPECT = single photon emission computerized tomography

*Results pooled unless otherwise indicated.

†Calculated.

‡Calculated assuming prevalence of 50%.

Table H4. Diagnostic accuracy: Positron emission tomography compared with coronary angiography as reference standard for diagnosis of CAD

Author, Year	Search Dates	Number of Studies	Study Quality	Reference Standard (threshold)	Population	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes*	Risk of Bias
Jaarsma, 2012[62]	01/1990-02/2010	8	Assessed for likelihood of verification bias. Yes: 12.5% Likely: 12.5% No: 75%	Coronary angiography (≥ 50 to ≥ 70% stenosis)	• N=677 • % male: 49-86% (range) • Age: 56-67 yrs. (range of means) • Condition: known or suspected CAD	Known or suspected CAD	• Prevalence (mean): 80%† • Sensitivity: 82% (95% CI, 78-85%) • Specificity: 86% (95% CI, 78-92%) • PPV: 96%† • NPV: 53%† • LR+: 5.88 (95% CI, 3.72-9.28) † • LR-: 0.21 (95% CI, 0.17-0.26)† • DOR: 44.31 (95% CI, 23.93-82.06)	Mod.
		2	Assessed for likelihood of verification bias. No: 100%	Coronary angiography (≥ 50 stenosis)	• N=290 • % male: 64% (reported for one study only) • Age: 57 yrs. (reported for one study only) • Condition: suspected CAD	Suspected CAD only	• Prevalence: 75%† • Sensitivity: 91% (95% CI, 86-95%)† • Specificity: 82% (95% CI, 71-90%)† • PPV: 94%† • NPV: 75%† • LR+: 4.97 (95% CI, 3.04-8.14)† • LR-: 0.11 (95% CI, 0.07-0.17)†	Mod.
McArdle, 2012[61]	01/2008-03/2012	15	Assessed with QUADAS. Unclear if ICA results blinded to PET results in 27% of studies	Coronary angiography (> 50 to > 70% stenosis)	• N=1344 • % male: 63.5% • Age (mean): 61.2 yrs. (range: 59.0-64.4) • Condition: known or suspected CAD (previous MI: 30%; PCI/CABG: 32%)	Known or suspected CAD	• Prevalence: 63% • Sensitivity: 90% (95% CI, 88-92%) • Specificity: 88% (95% CI, 85-91%) • PPV: 93%† • NPV: 84%† • LR+: 5.57 (95% CI, 4.02-7.72) • LR-: 0.11 (95% CI, 0.09-0.14)† • DOR: 56.73 (95% CI, 37.99-84.71)	Low

Author, Year	Search Dates	Number of Studies	Study Quality	Reference Standard (threshold)	Population	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes*	Risk of Bias
		NR	See above	NR	• N=297 • % male: NR • Age (mean): NR • Condition: No known CAD	Suspected CAD only (known CAD excluded)	• Prevalence: NR • Sensitivity: 90% (95% CI, 84-94%) • Specificity: 91% (95% CI, 84-95%) • PPV: 94%‡ • NPV: 84%‡ • LR+: 8.89 (95% CI, 2.46-32.09) • LR-: 0.11 (95% CI, 0.07-0.17)‡ • DOR: 92.05 (95% CI, 18.54-456.98)	

CAD = coronary artery disease; CABG = coronary artery bypass graft; CI = confidence interval; DOR = diagnostic odds ratio; ECG = electrocardiogram; ICA = invasive coronary angiography; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; PET = positron emission tomography; PPV = positive predictive value; QUADAS = quality assessment of diagnostic accuracy studies
*Results pooled unless otherwise indicated.
†Calculated.
‡Calculated assuming prevalence of 63%.

Table H5. Diagnostic accuracy: Stress cardiac magnetic resonance imaging compared with coronary angiography as reference standard for diagnosis of CAD

Author, Year	Search Dates	Number of Studies	Study Quality	Reference Standard (threshold)	Population	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes*	Risk of Bias
Nandalur, 2007[63]	01/1990-01/2007	13	Assessed with QUADAS. Number of items "yes": 10/10: 15.4% 9/10: 7.7% 8/10: 30.8% 7/10: 38.5% 6/10: 7.7%	Coronary angiography (≥ 50 - 75% stenosis)	• N=735 • % male: 56-96% (range) • Age: 52-63 yrs. (range of means) • Condition: known or suspected CAD	Known or suspected CAD	• Prevalence (mean): 70.5% • Sensitivity: 83% (95% CI, 79-88%) • Specificity: 86% (95% CI, 81-91%) • PPV: 94%† • NPV: 68%† • LR+: 5.93 (95% CI, 4.25-8.26)† • LR-: 0.20 (95% CI, 0.16-0.24)†	Mod.
		8	Assessed with QUADAS. Number of items "yes": 10/10: 12.5% 9/10: 12.5% 8/10: 12.5% 7/10: 50% 6/10: 12.5%	Coronary angiography (≥ 50 - 75% stenosis)	• N=520 • % male: 71-88% (range) • Age: 52-62 yrs. (range of means) • Condition: suspected CAD	Suspected CAD only	• Prevalence: 67%§ • Sensitivity: 81% (95% CI, 77-85%)† • Specificity: 87% (95% CI, 81-92%)† • PPV: 93%† • NPV: 70%† • LR+: 6.39 (95% CI, 4.31-9.47)† • LR-: 0.21 (95% CI, 0.17-0.27)†	Mod.

CAD = coronary artery disease; CI = confidence interval; DOR = Diagnostic odds ratio; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; MRI = magnetic resonance imaging; NR = not reported; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = quality assessment of diagnostic accuracy studies

*Results pooled unless otherwise indicated.

†Calculated.

Table H6. Diagnostic accuracy: Coronary artery calcification (CAC score >0) compared with coronary angiography as reference standard for diagnosis of CAD

Author, Year	Search Dates	Number of Studies	Study Quality	Reference Standard (threshold)	Population	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes*	Risk of Bias
Skelly, 2009[64]	Through 07/2009	7	Good to Moderate (LoE I/II)†	NR	• N=7354 • % male: 60-80% (range) • Age: 56-62 yrs. (range of means) • Condition: Symptomatic and suspected CAD	Symptomatic with suspected CAD and no history of revascularization (PCI or CABG)	• Prevalence (mean): 55.4% • Sensitivity: 99% (95% CI, 98-99%) • Specificity: 35% (95% CI, 33-36%) • PPV: 65%‡ • NPV: 95%‡ • LR+: 1.51 (95% CI, 1.47-1.54)‡ • LR-: 0.04 (95% CI, 0.03-0.06)‡	Mod.
Sarwar, 2009[65]	01/1990-03/2008	18	Formal quality assessment not reported; in all studies CT readers blinded to ICA results	Coronary angiography (> 50% stenosis)	• N=10, 355 • % male: NR for diagnostic accuracy studies • Age: NR for diagnostic accuracy studies • Condition: Symptomatic and suspected CAD	Symptomatic with suspected CAD	• Prevalence (mean): 56% • Sensitivity: 98% • Specificity: 40% • PPV: 68% • NPV: 93%	Mod.

CABG = coronary artery bypass graft; CAC = coronary artery calcification; CAD = coronary artery disease; CI = confidence interval; DOR = Diagnostic odds ratio; ICA = invasive coronary angiography; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; MRI = magnetic resonance imaging; NR = not reported; PCI = percutaneous coronary intervention; PPV = positive predictive value

*Results pooled unless otherwise indicated.

† LoE stands for level of evidence; studies rated as LoE I or II were at least risk of bias (broad spectrum of relevant patient populuation, blinded interpretation of test and referent, adequate description of test and referent).

‡Calculated.

Table H7. Diagnostic accuracy: Coronary computed tomography angiography compared with coronary angiography as reference standard for diagnosis of CAD

Author, Year	Search Dates	Number of Studies	Study Quality	Reference Standard (threshold)	Population	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes*	Risk of Bias
von Ballmoos, 2011[66] (Lose-dose-radiation CT: prospective ECG gating technique)	Through 10/2010	13 (Review was of 16 studies, 13 of which assessed at patient level)	Assessed with QUADAS; not reported by study. Of 16 studies (including 3 additional that assessed at vessel level), 8 of 12 QUADAS criteria were met by 75% or more of the studies. In all studies, readers of CT were blinded to ICA results, and vice versa.	Coronary angiography (>50% stenosis)	• N=789 • % male: NR • Age: 63 yrs. (mean of 16 studies) • Condition: Symptomatic and suspected CAD	Symptomatic with suspected CAD	• Prevalence (mean): 58%† • Sensitivity: 100% (95% CI, 98-100%) • Specificity: 89% (95% CI, 85-92%) • PPV: 93%† • NPV: 99%† • LR+: 9.2 (95% CI, 6.7-12.5) • LR-: 0.00 (95% CI, 0.00-0.02)	Low
Paech, 2011[67] (Radiation dose and technique NR)	12/2006 to 3/2009	18 (review was of 28 studies, 18 of which assessed at patient level)	Assessed with QUADAS (ratings not reported) and were assigned a level of evidence in accordance with the NHMRC of Australia (6 level II, 11 level III-1, and 1 level III-2 diagnostic studies)	Coronary angiography (>50% stenosis)	• N=2441 • % male: 67% • Age: mean 61.2 years • Condition: suspected CAD because of a range of symptoms (e.g., angina)	Symptomatic with suspected CAD (patients with previous PCI or CABG were excluded)	• Prevalence (mean): 59.9% (range, 28-85%) • Sensitivity: 98.2% (95% CI 97.4-98.8%) • Specificity: 81.6% (95% CI 79.0-84.0%) • PPV (median): 90.5% (range, 76-100%) • NPV: 99.0% (range, 83-100%) • LR+: NR • LR-: NR	

CABG = coronary artery bypass graft; CAD = coronary artery disease; CCTA = coronary computer tomography angiography; CI = confidence interval; DOR = Diagnostic odds ratio; ECG: electrocardiography; ICA = invasive coronary angiography; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; MI = myocardial infarction; MRI = magnetic resonance

imaging; NHMRC = National Health and Medical Research Council; NPV = negative predictive value; NR = not reported; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = quality assessment of diagnostic accuracy studies
*Results pooled unless otherwise indicated.
†Calculated.

Appendix I. Quality Ratings for Included Studies

Quality Ratings

Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes. Good quality studies are considered to have the least risk of bias and their results are considered valid.

Fair-quality studies may not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating will vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid. Fair-quality studies are susceptible to some bias, though not enough to invalidate the results.

Poor-quality studies have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies are at least as likely to reflect flaws in the study design as the true difference between the compared interventions. Poor quality studies have significant flaws that imply biases of various types that may invalidate the results.

Table I1. Individual study quality ratings in patients with mixed pretest risk for CAD

Methodological Principle		Chang 2008[1]*	Sabharwal 2007[2]*	Sanfilippo 2005[3]	Marwick 2003[5]	Shreibati 2011 (Stress Echo vs. Ex ECG)[6]	Shreibati 2011 (Stress Echo vs. Ex ECG)[6]	Shreibati 2011 (Stress Echo vs. MPI)[6]	Shreibati 2011 (MPI vs. Ex ECG)[6]
Study design	Randomized controlled trial	✓	✓	✓					
	Prospective cohort study				✓				
	Retrospective cohort study								
	Administrative database study					✓	✓	✓	✓
	Registry study								
	Case-control								
	Case-series								
Random sequence generation†		Unclear	Yes	Unclear	NA	NA	NA	NA	NA
Statement of Concealed allocation†		No	No	Unclear	NA	NA	NA	NA	NA

Methodological Principle		Chang 2008[1]*	Sabharwal 2007[2]*	Sanfilippo 2005[3]	Marwick 2003[5]	Shreibati 2011 (Stress Echo vs. Ex ECG)[6]	Shreibati 2011 (Stress Echo vs. Ex ECG)[6]	Shreibati 2011 (Stress Echo vs. MPI)[6]	Shreibati 2011 (MPI vs. Ex ECG)[6]
Analysis according to random assignment†		Yes	Yes	No	NA	NA	NA	NA	NA
Independent or blinded outcome assessment		Unclear	Unclear	Yes	Unclear	Clinical outcomes: Unclear Management: NA	Clinical outcomes: Unclear Management: NA	Clinical outcomes: Unclear Management: NA	Clinical outcomes: Unclear Management: NA
Patients comparable at baseline on key CAD risk factors		Yes	Yes	No	No	Yes	Yes	No	No
Prespecified threshold or definition for a positive test		Yes	Yes	Yes	Yes	No	No	No	No
Attrition (≤ 20% overall; ≤ 10% difference between groups)		Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Comparable followup time or accounting for time at risk		Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Controlling for possible confounding‡		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Full reporting on pre-specified outcomes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall Quality Rating		Fair	Fair	Poor	Poor	Fair	Fair	Fair	Fair

CAD = coronary artery disease; NA = not applicable

* These studies stratified patients by low, intermediate, and high risk but study quality was assessed for the study as a whole.

†Applies only to randomized controlled trials

‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods)

Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Table I1. continued

Methodological Principle		McKavanaugh 2014[4]	Tandon 2012[8]	Min 2008[9]	Yamauchi 2012[7]	Shreibati 2011 (CCTA vs. Ex ECG)[6]	Shreibati 2011 (CCTA vs. MPI)[6]	Shreibati 2011 (CCTA vs. Stress echo)[6]
Study design	Randomized controlled trial	✓						
	Prospective cohort study				✓			
	Retrospective cohort study							
	Administrative database study			✓		✓	✓	✓
	Registry study		✓					
	Case-control							
	Case-series							
Random sequence generation*		Yes	NA	NA	NA	NA	NA	NA
Statement of Concealed allocation*		No	NA	NA	NA	NA	NA	NA
Analysis according to random assignment*		Yes	NA	NA	NA	NA	NA	NA
Independent or blinded outcome assessment		Unclear	Unclear	Unclear	Unclear	Clinical outcomes: Unclear Management: NA	Clinical outcomes: Unclear Management: NA	Clinical outcomes: Unclear Management: NA
Patients comparable at baseline on key CAD risk factors		Yes	No	Yes	No	No	No	No
Prespecified threshold or definition for a positive test		Yes	Yes	No	No	No	No	No
Attrition (≤ 20% overall; ≤ 10% difference between groups)		Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Comparable followup time or accounting for time at risk		Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controlling for possible confounding†		Yes	No	Yes	Yes	Yes	Yes	Yes
Full reporting on pre-specified outcomes		Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall Quality Rating		Fair	Poor	Fair	Fair	Fair	Fair	Fair

CAD = coronary artery disease; NA = not applicable
*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods)
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Table I2. Individual study quality ratings in patients considered to have intermediate to high pretest risk for CAD

Methodological Principle		Hachamovitch 2012/ Hlatky 2014[11, 12]	Min 2012[10]
Study design	Randomized controlled trial		✓
	Prospective cohort study		
	Retrospective cohort study		
	Administrative database study		
	Registry study	✓ (prospective)	
	Case-control		
	Case-series		
Random sequence generation*		NA	Unclear
Statement of Concealed allocation*		NA	Unclear
Analysis according to random assignment*		NA	Yes
Independent or blinded outcome assessment		Unclear	No
Patients comparable at baseline on key CAD risk factors		No	No
Prespecified threshold or definition for a positive test		Yes	Yes
Attrition (≤ 20% overall; ≤ 10% difference between groups)		Yes	Yes
Comparable followup time or accounting for time at risk		Yes	Unclear
Controlling for possible confounding†		Yes	Yes
Full reporting on pre-specified outcomes		Yes	Yes
Overall Quality Rating		Fair	Poor

CAD = coronary artery disease; NA = not applicable
*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods)
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Table I3. Individual study quality ratings in patients considered to have low to intermediate pretest risk for CAD

Methodological Principle		Litt 2012[19]	Miller 2011[20]	Poon 2013[24]	Goldstein 2011[21]	Goldstein 2007[23]	Cheezum 2011[25]	Hamilton-Craig 2014[22]	Nielsen 2011/2013[26, 27]
Study design	Randomized controlled trial	✓	✓		✓	✓		✓	
	Prospective cohort study								✓
	Retrospective cohort study			✓			✓		
	Administrative database study								
	Registry study								
	Case-control								
	Case-series								
Random sequence generation*		Yes	Yes	NA	Yes	Yes	NA	Unclear	NA
Statement of concealed allocation*		No	No	NA	Yes	Unclear	NA	No	NA
Analysis according to random assignment*		Yes	Yes	NA	Yes	Unclear	NA	Yes	NA
Independent or blinded outcome assessment		Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear	Unclear
Patients comparable at baseline on key CAD risk factors		Yes	Unclear	Yes	Yes	No	Yes	Yes	Yes
Prespecified threshold or definition for a positive test		Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Attrition (≤ 20% overall; ≤ 10% difference between groups)		Yes	Yes	Yes	Yes	Yes	Yes	Overall, Yes Differential, Unclear	Yes
Comparable followup time or accounting for time at risk		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear

Methodological Principle		Litt 2012[19]	Miller 2011[20]	Poon 2013[24]	Goldstein 2011[21]	Goldstein 2007[23]	Cheezum 2011[25]	Hamilton-Craig 2014[22]	Nielsen 2011/2013[26, 27]
Controlling for possible confounding†		Yes	No	Yes	Yes	No	Yes	Yes	No
Full reporting on pre-specified outcomes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Overall Quality Rating		Fair	Poor	Fair	Good	Fair	Fair	Fair	Fair

CAD = coronary artery disease; NA = not applicable
*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods)
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Table I4. Individual study quality ratings in patients considered to have intermediate pretest risk for CAD

	Methodological Principle	Hoffman 2012/Truong 2013[13, 68]	Gruettner/Henzler 2013[17, 18]	Shaw 2011[14]	Douglas 2015[15]	Levksy 2015[16]
Study design	Randomized controlled trial	✓		✓	✓	✓
	Prospective cohort study		✓			
	Retrospective cohort study					
	Administrative database study					
	Registry study					
	Case-control					
	Case-series					
Random sequence generation*		Yes	NA	Yes	Yes	Yes
Statement of concealed allocation*		No	NA	No	Yes	Yes
Analysis according to random assignment*		Yes	NA	Yes	Yes	Yes
Independent or blinded outcome assessment		Unclear	Unclear	Yes	Yes	ICA not leading to revascularization, yes Otherwise no
Patients comparable at baseline on key CAD risk factors		Yes	No	Yes	Yes	Yes

	Methodological Principle	Hoffman 2012/Truong 2013[13, 68]	Gruettner/Henzler 2013[17, 18]	Shaw 2011[14]	Douglas 2015[15]	Levksy 2015[16]
Prespecified threshold or definition for a positive test		Unclear	Yes	Yes	Yes	No
Attrition (≤ 20% overall; ≤ 10% difference between groups)		Yes	Yes	Yes	Yes	Yes
Comparable followup time or accounting for time at risk		Yes	Yes	Yes	Yes	Yes
Controlling for possible confounding†		Yes	No	Yes	Yes	Yes
Full reporting on pre-specified outcomes		Yes	Yes	Yes	Yes	Yes
		Fair	Poor	Fair	Good	Fair

CAD = coronary artery disease; NA = not applicable
*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods)
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Appendix J. Strength of Evidence Tables

Strength of Evidence Grades:

"High" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect;

"Moderate" grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate;

"Low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate;

"Insufficient" grade indicates evidence either is unavailable or is too limited to permit any conclusion, due to the availability of only poor-quality studies, extreme inconsistency, or extreme imprecision.

Final Strength of Evidence Note: Outcomes for which data from randomized controlled trials (RCTs) and observational studies were available, if the strength of evidence for the observational studies was deemed insufficient, the final strength of evidence was based on RCT.

Table J1. Strength of evidence for included studies with patients considered to be at low risk for coronary artery disease

Outcomes	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause)	CCTA vs. Usual Care (ED setting)	1 RCT (n=99 in low-risk subgroup)	Medium	Direct	Unknown	Imprecise (downgraded by 2; subanalysis)	Undetected	Insufficient
Invasive Coronary Angiography Referral	CCTA vs. Usual Care (ED setting)	1 RCT (n=99 in low-risk subgroup)	Medium	Direct	Unknown	Imprecise (downgraded by 2; subanalysis)	Undetected	Insufficient
	SPECT vs. Exercise ECG (Outpatient)	1 RCT (n=68 in low risk subgroup)	Medium	Direct	Unknown	Imprecise (downgraded by 2; subanalysis)	Undetected	Insufficient
Revascularization	CCTA vs. Usual Care (ED setting)	1 RCT (n=99 in low-risk subgroup)	Medium	Direct	Unknown	Imprecise (downgraded by 2; subanalysis)	Undetected	Insufficient
Additional Testing	SPECT vs. Exercise ECG (Outpatient)	1 RCT (n=68 in low risk subgroup)	Medium	Direct	Unknown	Imprecise (downgraded by 2; subanalysis)	Undetected	Insufficient
Hospitalization (Cardiac related)	CCTA vs. Usual Care (ED Index visit)	1 RCT (n=99 in low-risk subgroup)	Medium	Direct	Unknown	Imprecise (downgraded by 2; subanalysis)	Undetected	Insufficient

CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; ED = emergency department; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography

Table J2. Strength of evidence for included studies with patients considered to be at low to intermediate risk for coronary artery disease

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause)	CCTA vs. Usual Care (ED setting)	1 RCT (N=1392)	Medium	Direct	Unknown	Imprecise	Undetected	Low
		1 observational (N=1,788)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
		Overall SOE	Medium	Direct	Consistent	Imprecise	Undetected	FINAL: Low
	CCTA vs. SPECT (ED setting for RCTs	2 RCTS (N=952)	Low	Direct	Consistent	Imprecise	Undetected	Moderate
	CCTA vs. SPECT (inpatient or outpatient for observational study)	1 Observational (N=252)	Low	Direct	Unknown	Imprecise	Undetected	Insufficient
	CCTA vs. Exercise ECG (ED)	1 RCT (N=562)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Exercise ECG (Outpatient)	1 Observational (N=468)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
Myocardial Infarction	CCTA vs. Usual Care (ED setting)	1 RCT (N=1392)	Medium	Direct	Unknown	Imprecise	Undetected	Low
		1 observational (N=1,788)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
		Overall SOE	Medium	Direct	Consistent	Imprecise	Undetected	FINAL: Low
	CCTA vs. SPECT (ED setting)	2 RCTS (N=952)	Low	Direct	Consistent	Imprecise	Undetected	Low
	CCTA vs. Exercise ECG (ED)	1 RCT (N=562)	Medium	Direct	Consistent	Imprecise	Undetected	Low

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	CCTA vs. Exercise ECG (0utpatient)	1 Observational (N=498)	Medium	Direct	Consistent	Imprecise	Undetected	Insufficient
Invasive Coronary Angiography Referral	CCTA vs. Usual Care (ED setting) Index ED visit	1 RCT (N=1392)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Usual Care (ED setting) Through 1-3 months (RCTS) Within 1 month (observational)	2 RCTs (N=1452) 1 observational (N=1,788) Overall SOE	Medium Medium Medium	Direct Direct Direct	Consistent Unknown Inconsistent	Imprecise Imprecise Imprecise	Undetected Undetected Undetected	Low Insufficient FINAL: Low
	CCTA vs. SPECT (ED setting for RCTs)	2 RCTS (N=952)	Low	Direct	Inconsistent	Imprecise	Undetected	Low
	CCTA vs. SPECT inpatient or outpatient for observational study	1 Observational (N=252)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
	CCTA vs. Exercise ECG (ED setting)	1 RCT (N=562)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Exercise ECG (Outpatient)	1 Observational (n=468)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
Revascularization	CCTA vs. Usual Care (ED setting) Index ED visit	1 RCT (N=1392)	Medium	Direct	Unknown	Imprecise	Undetected	Low

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	CCTA vs. Usual Care (ED setting) Through 1-3 months	2 RCTs (N=1452)	Medium	Direct	Consistent	Imprecise	Undetected	Low
		1 observational (N=1,788)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
		Overall SOE	Medium	Direct	Consistent	Imprecise	Undetected	FINAL: Low
	CCTA vs. SPECT (ED setting)	2 RCTS (N=952)	Low	Direct	Consistent	Imprecise	Undetected	Moderate
	CCTA vs. Exercise ECG (ED Setting)	1 RCT (N=562)	Medium	Direct	Consistent	Precise	Undetected	Low
	CCTA vs. Exercise ECG (Outpatient)	1 Observational (n=96 subset of test-positive patients)	Medium	Direct	Consistent	Precise	Undetected	Insufficient
Percutaneous Coronary Intervention	CCTA vs. Usual Care (ED setting)	1 RCT (N=60)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. SPECT (ED setting)	2 RCTS (N=952)	Low	Direct	Consistent	Imprecise	Undetected	Moderate
	CCTA vs. Exercise ECG (Outpatient)	1 Observational (n=96 subset of test-positive patients)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
Coronary Artery Bypass Graft	CCTA vs. Usual Care (ED setting)	1 RCT (N=60)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. SPECT (ED setting)	2 RCTS (N=952)	Low	Direct	Consistent	Imprecise	Undetected	Moderate
	CCTA vs. Exercise ECG	1 Observational (n=96 subset of test-positive patients)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
Additional Testing	CCTA vs. Usual Care (ED setting) Index ED visit	1 RCT (N=1392)	Medium	Direct	Unknown	Precise	Undetected	Moderate

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	CCTA vs. Usual Care (ED setting) Through 1 month post ED visit	1 RCT (N=1392) 1 observational (N=1,788) Overall SOE	Medium Medium Medium	Direct Direct Direct	Unknown Unknown Consistent	Precise Imprecise Precise	Undetected Undetected Undetected	Moderate Insufficient FINAL: Moderate
	CCTA vs. Usual Care (ED setting) Through 3 months	1 RCT (N=60)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. SPECT (ED setting for RCTs	2 RCTS (N=952)	Low	Direct	Consistent	Precise	Undetected	High
	CCTA vs. SPECT (ED setting)	1 RCT (N=197)	Medium	Direct	Consistent	Imprecise	Undetected	Low
	CCTA vs. SPECT (inpatient or outpatient for observational study)	1 Observational (N=252)	Medium	Direct	Consistent	Imprecise	Undetected	Insufficient
	CCTA vs. Exercise ECG	1 Observational (n=468)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
Hospitalization (Cardiac related)	CCTA vs. Usual Care (ED setting) Index ED visit	1 RCT (N=1392)	Medium	Direct	Unknown	Precise	Undetected	Moderate
	CCTA vs. Usual Care (ED setting) Through 1 month post ED visit	1 RCT (N=1392)	Medium	Direct	Unknown	Precise	Undetected	Moderate
	CCTA vs. SPECT (ED setting)	1 RCT (N=749)	Low	Direct	Unknown	Imprecise	Undetected	Moderate

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	CCTA vs. SPECT (inpatient or outpatient for observational study)	1 Observational (N=252)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
Harms	CCTA vs. Usual Care (ED setting)	1 RCT (N=1392)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. SPECT (inpatient or outpatient for observational study)	1 Observational (N=252)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient

CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; ED = emergency department; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography

Table J3. Strength of evidence for included studies with patients considered to be at intermediate risk for coronary artery disease

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause)	CCTA vs. Usual Care (ED setting)	2 RCTs (N=1098*)	Medium	Direct	Consistent	Imprecise	Undetected	Low
		1 Observational (N=200)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
		Overall SOE	Medium	Direct	Consistent	Imprecise	Undetected	FINAL: Low
	SPECT vs. Exercise ECG (Women; Setting not reported)	1 RCT (N=824)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Functional (Outpatient)	1 RCT (N=10,003)	low	Direct	Unknown	Imprecise	Undetected	Moderate
	CCTA vs. SPECT (Telemetry)	1 RCT (N=400)	Medium	Direct	Unknown	Imprecise	Undetected	Low
Myocardial Infarction	CCTA vs. Usual Care (ED setting)	2 RCTs (N=1098*)	Medium	Direct	Consistent	Imprecise	Undetected	Low
		1 Observational (N=200)	Low	Direct	Unknown	Imprecise	Undetected	Insufficient
		Overall SOE	Medium	Direct	Consistent	Imprecise	Undetected	FINAL: Low
	CCTA vs. Functional (Outpatient)	1 RCT (N=10,003)	Low	Direct	Unknown	Imprecise	Undetected	Moderate
Heart Failure	CCTA vs. Usual Care (ED setting)	1 Observational (N=200)	Low	Direct	Consistent	Imprecise	Undetected	Insufficient
Invasive Coronary Angiography Referral	CCTA vs. Usual Care (ED setting) Index visit	2 RCTs (N=1098*)	Medium	Direct	Consistent	Imprecise	Undetected	Low
	CCTA vs. Usual Care (ED setting) (28 days followup)	1 RCT (N=987)	Medium	Direct	Consistent	Imprecise	Undetected	Low

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	SPECT vs. Exercise ECG (Women; setting not reported)	1 RCT (N=824)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	SPECT vs. Exercise ECG (Outpatient)	1 RCT (n=280 in intermediate risk subgroup)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Functional (Outpatient)	1 RCT (N=10,003)	Low	Direct	Unknown	Precise	Undetected	High
	CCTA vs. SPECT	1 RCT (N=400)	Medium	Direct	Unknown	Imprecise	Undetected	Low
Revascularization	CCTA vs. Usual Care (ED setting)	2 RCTs (N=1098*)	Medium	Direct	Consistent	Imprecise	Undetected	Low
	SPECT vs. Exercise ECG (Women; setting not reported)	1 RCT (N=824)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Functional (Outpatient)	1 RCT (N=10,003)	Low	Direct	Unknown	Precise	Undetected	High
	CCTA vs. SPECT (Telemetry)	1 RCT (N=400)	Medium	Direct	Unknown	Imprecise	Undetected	Low
Percutaneous Coronary Intervention	CCTA vs. Usual Care (ED setting)	1 RCT (N=987)	Medium	Direct	Unknown	Imprecise	Undetected	Low
		1 Observational (N=200)	Low	Direct	Unknown	Imprecise	Undetected	Insufficient
		Overall SOE	Medium	Direct	Consistent	Imprecise	Undetected	FINAL: Low
	CCTA vs. Functional (Outpatient)	1 RCT (N=10,003)	Low	Direct	Unknown	Precise	Undetected	High
	CCTA vs. SPECT (Telemetry)	1 RCT (N=400)	Medium	Direct	Unknown	Imprecise	Undetected	Low

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Coronary Artery Bypass Graft	CCTA vs. Usual Care (ED setting)	1 RCT (N=987)	Medium	Direct	Unknown	Imprecise	Undetected	Low
		1 Observational (N=200)	Low	Direct	Unknown	Imprecise	Undetected	Insufficient
		Overall SOE	Medium	Direct	Consistent	Imprecise	Undetected	FINAL: Low
	CCTA vs. Functional (Outpatient)	1 RCT (N=10,003)	Low	Direct	Unknown	Precise	Undetected	High
	CCTA vs. SPECT (Telemetry)	1 RCT (N=400)	Medium	Direct	Unknown	Imprecise	Undetected	Low
Additional Testing	CCTA vs. Usual Care (ED setting)	1 RCT (N=987)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	SPECT vs. Exercise ECG (Women; setting not reported)	1 RCT (N=824)	Medium	Direct	Unknown	Precise	Undetected	Moderate
	SPECT vs. Exercise ECG (Outpatient)	1 RCT (n=280 in intermediate risk subgroup)	Medium	Direct	Unknown	Imprecise (subgroup)	Undetected	Low
	CCTA vs. SPECT (Telemetry)	1 RCT (N=400)	Medium	Direct	Unknown	Imprecise	Undetected	Low
Hospitalization (Cardiac related)	CCTA vs. Usual Care (ED setting)	2 RCTs (N=1098*)	Medium	Direct	Inconsistent	Precise	Undetected	Low
		1 Observational (N=200)	Low	Direct	Unknown	Imprecise	Undetected	Insufficient
		Overall SOE	Medium	Direct	inconsistent	Precise	Undetected	FINAL: Low
	SPECT vs. Exercise ECG (Women; setting not reported)	1 RCTs (N=824)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Functional (Outpatient)	1 RCT (N=10,003)	Low	Direct	Unknown	Imprecise	Undetected	Moderate

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	CCTA vs. SPECT (Telemetry)	1 RCT (N=400)	Medium	Direct	Unknown	Imprecise	Undetected	Low
Harms	CCTA vs. Functional (Outpatient)	1 RCT (N=10,003)	Low	Direct	Unknown	Imprecise	Undetected	Moderate
	CCTA vs. SPECT (Telemetry)	1 RCT (N=400)	Medium	Direct	Unknown	Imprecise	Undetected	Low

CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; ECHO = echocardiogram; ED = emergency department; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography

*Number of patients includes the 987 patients in the Hoffman trial and the subset of 111 patients who were at intermediate pre-test risk in the Chang trial.

Table J4. Strength of evidence for included studies with patients considered to be at intermediate to high risk for coronary artery disease

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause)	PET vs. SPECT (hospital and outpatient centers)	1 Observational (N=1113)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
	CCTA vs. SPECT (Outpatient)	1 RCT (N=180)	Medium	Direct	Unknown	Imprecise (downgrade 2)	Undetected	Insufficient
Myocardial Infarction	PET vs. SPECT (hospital and outpatient centers)	1 Observational (N=1113)	Medium	Indirect	Unknown	Imprecise	Undetected	Insufficient
	CCTA vs. SPECT (Outpatient)	1 RCT (N=180)	Medium	Direct	Unknown	Imprecise (downgrade 2)	Undetected	Insufficient
Invasive Coronary Angiography Referral	PET vs. SPECT (hospital and outpatient centers)	1 Observational (N=1113)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	CCTA vs. SPECT (Outpatient)	1 RCT (N=180)	Medium	Direct	Unknown	Imprecise	Undetected	Low
Revascularization	PET vs. SPECT (hospital and outpatient centers)	1 Observational (N=1113)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	CCTA vs. SPECT (Outpatient)	1 RCT (N=180)	Medium	Direct	Unknown	Imprecise	Undetected	Low
Percutaneous Coronary Intervention	PET vs. SPECT (hospital and outpatient centers)	1 Observational (N=1113)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
Coronary Artery Bypass Graft	PET vs. SPECT (hospital and outpatient centers)	1 Observational (N=1113)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
Additional Testing	CCTA vs. SPECT (Outpatient)	1 RCT (N=180)	Medium	Direct	Unknown	Imprecise	Undetected	Low
Hospitalization (Cardiac related)	CCTA vs. SPECT (Outpatient)	1 RCT (N=180)	Medium	Direct	Unknown	Imprecise	Undetected	Low

CCTA = coronary computed tomography angiogram; PET = positron emission tomography; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography

Table J5. Strength of evidence for included studies with patients considered to be at high risk for coronary artery disease

Outcomes	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause)	CCTA vs. Usual Care (ED setting)	1 RCT (n=56 in high-risk subgroup)	Medium	Direct	Unknown	Imprecise (downgraded by 2; subanalysis)	Undetected	Low
Invasive Coronary Angiography Referral	CCTA vs. Usual Care (ED setting)	1 RCT (n=56 in high-risk subgroup)	Medium	Direct	Unknown	Imprecise (downgraded by 2; subanalysis)	Undetected	Low
	SPECT vs. Exercise ECG (Outpatient)	1 RCT (n=106 in high-risk subgroup)	Medium	Direct	Unknown	Imprecise (downgraded by 2; subanalysis)	Undetected	Low
Revascularization	CCTA vs. Usual Care (ED setting)	1 RCT (n=56 in high-risk subgroup)	Medium	Direct	Unknown	Imprecise (downgraded by 2; subanalysis)	Undetected	Low
Additional Testing	SPECT vs. Exercise ECG (Outpatient)	1 RCT (n=106 in high-risk subgroup)	Medium	Direct	Unknown	Imprecise (downgraded by 2; subanalysis)	Undetected	Low
Hospitalization (Cardiac related)	CCTA vs. Usual Care (ED Index visit)	1 RCT (n=56 in high-risk subgroup)	Medium	Direct	Unknown	Imprecise (downgraded by 2; subanalysis)	Undetected	Low

CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; ED = emergency department; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography

Table J6. Strength of evidence for comparative studies with patients of mixed risk

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause)	SPECT vs. Exercise ECG (Outpatient)	1 RCT (N=457)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	Nuclear MPI vs. Exercise ECG (Medicare Population)	1 Observational (N=193,406)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	Stress Echo vs. Stress ECG (outpatient)	1 Observational (n=5894 with no known CAD)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	Stress Echo vs. Exercise ECG (Medicare Population)	1 Observational (N=141,667)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	Stress Echo vs. MPI (Medicare Population)	1 Observational (N=212,947)	Low	Direct	Unknown	Precise	Undetected	Low
	Exercise ECG vs. MPI (Medicare Population)	1 Observational (N=193,406)	Low	Direct	Unknown	Precise	Undetected	Low
	CCTA vs. Exercise ECG (ED setting)	1 RCT (N=500)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Exercise ECG (Medicare Population)	1 Observational (N=69,883)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	CCTA vs. MPI (nuclear) (Medicare Population)	1 Observational (N=141,163)	Low	Direct	Unknown	Precise	Undetected	Low
	CCTA vs. Stress Echo (Medicare Population)	1 Observational (N=89,424)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
Myocardial Infarction	CCTA vs. Usual Care (ED setting through 1 month)	1 RCT (N=266)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	SPECT vs. Exercise ECG (Outpatient)	1 RCT (N=457)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Exercise ECG (ED setting, through 12 months)	1 RCT (N=500)	Medium	Direct	inconsistent	Imprecise	Undetected	Low
Invasive Coronary Angioplasty Referral	Nuclear MPI vs. Exercise ECG (Medicare population)	1 Observational (N=193,406)	Low	Direct	Unknown	Precise	Undetected	Low
	Stress Echo vs. Exercise ECG (Outpatient)	1 Observational (N=5894)	Medium	Direct	Unknown	Precise	Undetected	Insufficient

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	Stress Echo vs. Exercise ECG (Medicare population)	1 Observational (N=141,667)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	Stress Echo vs. MPI (Medicare Population)	1 Observational (N=212,947)	Low	Direct	Unknown	Precise	Undetected	Low
	CCTA vs. Exercise ECG (ED setting; 12 months)	1 RCT (N=500)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Exercise ECG (Medicare Population)	1 Observational (N=69,883)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	CCTA vs. SPECT (Setting not reported)	2 observational (N=12,132)	Medium	Direct	inconsistent	Precise	Undetected	Insufficient
	CCTA vs. MPI (nuclear) (Setting not reported)	1 Observational (N=1856)	Low	Direct	Unknown	Precise	Undetected	Insufficient
	CCTA vs. MPI (nuclear) (Medicare Population)	1 Observational (N=141,163)	Low	Direct	Unknown	Precise	Undetected	Low
	CCTA vs. Stress Echo (Medicare population)	1 Observational (N=89,424)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
Revascularization	SPECT vs. Exercise ECG (Outpatient)	1 RCT (N=457)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	Nuclear MPI vs. Exercise ECG (Medicare)	1 Observational (N=193,406)	Low	Direct	Unknown	Precise	suspected	Low
	Stress Echo vs. Exercise ECG (Outpatient)	1 Observational (N=5894)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	Stress Echo vs. Exercise ECG (Medicare Population)	1 Observational (N=141,667)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	Stress Echo vs. MPI (Medicare Population)	1 Observational (N=212,947)	Low	Direct	Unknown	Precise	suspected	Low
	CCTA vs. Exercise ECG (ED setting)	1 RCT (N=500)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Exercise ECG (Medicare Population)	1 Observational (N=69,883)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	CCTA vs. SPECT (Setting not reported)	2 observational (N=12,132)	Medium	Direct	Consistent	Precise	Undetected	Insufficient
	CCTA vs. MPI (nuclear) (Setting not reported	1 observational (N=1856)	Low	Direct	Consistent	Precise	Undetected	Low
	CCTA vs. MPI (nuclear) (Medicare Population)	1 observational (N=141,163)	Low	Direct	Consistent	Precise	Undetected	Low

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	CCTA vs. Stress Echo (Medicare)	1 Observational (N=89,424))	Medium	Direct	Unknown	Precise	Undetected	Insufficient
Percutaneous Coronary Intervention	Nuclear MPI vs. Exercise ECG (Medicare)	1 Observational (N=193,406)	Low	Direct	Unknown	Precise	Undetected	Low
	Stress Echo vs. Exercise ECG (Outpatient)	1 Observational (N=5894)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	Stress Echo vs. Exercise ECG (Medicare)	1 Observational (N=141,667)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	Stress Echo vs. MPI (Medicare)	1 Observational (N=212,947)	Low	Direct	Unknown	Precise	Undetected	Low
	CCTA vs. Exercise ECG (ED setting)	1 RCT (N=500)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Exercise ECG (Medicare Population)	1 Observational (N=69,883)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	CCTA vs. SPECT (Setting not reported)	2 Observational (N=12,132)	Medium	Direct	Consistent	Precise	Undetected	Insufficient
	CCTA vs. MPI (nuclear) (Medicare Population)	1 Observational (N=141,163)	Low	Direct	Unknown	Precise	Undetected	Low
	CCTA vs. Stress Echo (Medicare Population)	1 Observational (N=89,424)	Low	Direct	Unknown	Precise	Undetected	Insufficient
Coronary Artery Bypass Graft	Nuclear MPI vs. Exercise ECG (Medicare)	1 Observational (N=193,406)	Low	Direct	Unknown	Precise	Undetected	Low
	Stress Echo vs. Exercise ECG (Outpatient)	1 Observational (N=5894)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	Stress Echo vs. Exercise ECG (Medicare Population)	1 Observational (N=141,667)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	Stress Echo vs. MPI (Medicare Population)	1 Observational (N=212,947)	Low	Direct	Unknown	Precise	Undetected	Low
	CCTA vs. Exercise ECG (ED setting, up to 12 months)	1 RCT (N=500)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Exercise ECG (Medicare)	1 Observational (N=69,883)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	CCTA vs. SPECT(setting not reported)	2 observational (N=12,132)	Medium	Direct	Consistent	Precise	Undetected	Insufficient
	CCTA vs. MPI (nuclear) (Medicare Population)	1 Observational (N=141,163)	Low	Direct	Unknown	Precise	Undetected	Low
	CCTA vs. Stress Echo (Medicare Population)	1 Observational (N=89,424)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
Additional Testing	Exercise Echo vs. Exercise ECG (various settings)	1 RCT (N=111)	high	Direct	Unknown	Imprecise	Undetected	Insufficient
	Stress Echo vs. Exercise ECG (Medicare)	1 Observational (N=141,667)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	Stress Echo vs. MPI (Medicare Population)	1 Observational (N=212, 947)	Low	Direct	Unknown	Precise	Undetected	Low
	CCTA vs. Exercise ECG (ED setting, 12 months)	1 RCT (N=500)	Medium	Direct	Unknown	Precise	Undetected	Moderate
	CCTA vs. Exercise ECG (Medicare)	1 Observational (N=69,883)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	CCTA vs. SPECT (Setting not reported)	1 Observational (N=9960)	Medium	Direct	inconsistent	Imprecise	Undetected	Insufficient
	CCTA vs. MPI (nuclear) (Medicare)	1 Observational (N=141,163)	Low	Direct	Unknown	Precise	Undetected	Low
	CCTA vs. Stress Echo (Medicare)	1 Observational (N=89, 424)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
Hospitalization (cardiac related)	Nuclear MPI vs. Exercise ECG (Medicare)	1 Observational (N=193,406)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
	Stress Echo vs. Exercise ECG (Medicare)	1 Observational (N=141,667)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	Stress Echo vs. MPI (Medicare)	1 Observational (N=212,947)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	CCTA vs. Exercise ECG (ED setting)	1 RCT (N=500)	Medium	Direct	Unknown	Precise	Undetected	Moderate
	CCTA vs. Exercise ECG (Medicare)	1 Observational (N=69,883)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	CCTA vs. SPECT (Setting not reported)	1 observational (N=9690)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
	CCTA vs. MPI (nuclear) (Medicare)	1 Observational (N=141,163)	Medium	Direct	Unknown	Precise	Undetected	Insufficient

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	CCTA vs. Stress Echo (Medicare Population)	1 Observational (N=89,424)	Medium	Direct	Unknown	Precise	Undetected	Insufficient
Harms	CCTA vs. Usual Care (ED setting)	1 RCT (N=266)	Medium	Direct	Unknown	Imprecise	Undetected	Low
	CCTA vs. Exercise ECG (ED setting)	1 RCT (N=500)	Medium	Direct	Unknown	Imprecise	Undetected	Insufficient
	CCTA vs. MPI (nuclear) (Setting not reported)	1 Observational (N=1856)	Medium	Direct	Unknown	Precise	Undetected	Insufficient

CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; Echo = echocardiogram; ED = emergency department; MPI = myocardial perfusion imaging; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography

Appendix K. Clinical Trials in Patients With Suspected Coronary Artery Disease

Table K1. Clinical trials in patients with suspected coronary artery disease listed on the Clinical Trials Web Site (ClinicalTrials.gov)

Trial Name (Number)	Intervention	Condition (Estimated N)	Outcomes	Status (Estimated Completion) Related Publications
Stress Testing Compared to Coronary Computed Tomographic Angiography in Patients With Suspected Coronary Artery Disease (NCT01368770)	Stress MPI, SPECT, CCTA	Patients with chest pain or suspected CAD N=303	• Angiography • Revascularization • MACE	Completed, June 2014 Publications: not provided
Computed Tomography Versus Exercise Testing in Suspected Coronary Artery Disease (NCT01393028)	CCTA, CCS, Usual Care	Patients with chest pain N=350	• Chest pain • Revascularization • Overall medical expenses • Cost-effectiveness • Radiation dose • MACE • QOL	Terminated, Estimated completion July 2011 Publications: not provided
Coronary CT Angiography as the Primary Initial Method of Evaluating Patients With Subacute Chest Pain (CT PRIME) (NCT00584337)	CCTA, Usual Care	Patients with chest pain N=300	• Diagnostic accuracy	Withdrawn prior to enrollment, estimated completion June 2009 Publications: not provided
PROspective Multicenter Imaging Study for Evaluation of Chest Pain - The PROMISE Trial (NCT01174550)	Coronary angiography, stress echocardiography, nuclear stress test, exercise ECG	Patients with chest pain N=10,003	• Death • MI • Unstable angina hospitalization • Major complications from CV procedures • Cumulative radiation exposure • Medical costs • QOL	Completed, October 2014 Publications: Douglas (2015)[15]; Douglas (2014)[69] *included in present report*
Usefulness of Coronary CTA for the Diagnosis of Acute Coronary Syndrome in the Emergency Room. (NCT01682096)	CCTA, Exercise echocardiography	Patients with chest pain N=150	• Diagnosis of acute coronary syndrome • MACE • Costs during admission	Completed, October 2013 Publications: not provided
Utility of 2D Strain Echocardiography in Triage of Patients With Chest Pain in the Emergency Department (NCT01163019)	Echocardiography, ECG, nuclear imaging	Patients with chest pain N=700	• Diagnosis of acute coronary syndrome • Significant CAD • MACE	Completed, February 2014 Publications: not provided

Trial Name (Number)	Intervention	Condition (Estimated N)	Outcomes	Status (Estimated Completion) Related Publications
Myocardial Perfusion Assessment With Multidetector Computed Tomography (NCT00846079)	Multi-detector CT	Patients with suspected CAD N=100	• Diagnostic accuracy • Radiation dosimetry	Unknown, Estimated completion September 2009 Publications: not provided
Association of Endothelial Function and Clinical Outcomes in Subjects Admitted to Chest Pain Unit (NCT01618123)	ECG, EndoPAT, stress nuclear imaging, stress echo	Patients with chest pain N=300	• Long-term outcomes • Short-term outcomes (no further details provided)	Recruiting, July 2015 Publications: not provided
A Study of Stress Heart Imaging in Patients With Diabetes at Risk for Coronary Disease. (NCT00162344)	MPI, Exercise ECG	Diabetic patients with atypical chest pain N=205	• Diagnosis of ischemic heart disease • Diagnostic accuracy • Relative value for identifying risk	Completed, December 2005 Publications: not provided
Role of Cardiac CT in Rapid Access Chest Pain Clinics (RADICAL) (NCT01464203)	CCTA, Usual Care	Patients with chest pain N=600	• Diagnostic accuracy • QOL • Number of invasive angiograms • Revascularization • Prognostic value	Unknown, Estimated completion December 2011 Publications: Yerramasu (2010)*; Yerramasu (2014)†
Combined Use of Coronary MDCTA, Coronary Doppler Ultrasonography and PET Perfusion in Diagnosing Coronary Artery Disease (PECTUS) (NCT00627172)	CCTA, PET, ICA, FFR	Patients with chest pain N=107	• Diagnosis of coronary artery lesions • QOL	Completed, January 2007 Publications: Kajander (2011)*; Bucci (2011)*; Kajander (2010)*
Stress Testing Versus Non-Stress Testing Based Strategy in Patients Hospitalized With Low-Risk Acute Coronary Syndromes: A Randomized, Single-Center Pilot Study (NCT01703156)	Stress test, no stress test	Patients with chest pain N=70	• All-cause mortality • Hospitalization for STEMI • Revascularization • Angiography • Further testing • Medication adjustments • Medication side effects	Completed, July 2012 Publications: not provided

CAD = coronary artery disease; CACS = coronary artery calcium scan; CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; FFR = fractional flow reserve; ICA = invasive coronary angiography; MACE = major adverse cardiovascular events; MPI = myocardial perfusion imaging; QOL = quality of life; SPECT = single photon-emission computed tomography

*Excluded from present report at title/abstract.

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Appendix L. Appendix References

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