Noninvasive Cardiac Imaging for Coronary Artery Disease – Re-review

FINAL Evidence Report

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This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

Aggregate Analytics, Inc. is a contract research organization whose team has over fifteen years of experience in performing health technology assessments, comparative effectiveness reviews and systematic reviews for a variety of clients based on accepted methodologic standards for such research. AAI's mission is to assist healthcare professionals and organizations in the objective synthesis and generation of evidence for the purpose of improving future healthcare delivery by providing timely, methodologically rigorous, transparent services and quality evidence synthesis products.

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Introduction

Clinical

Coronary artery disease (CAD), also referred to as coronary heart disease (CHD) or ischemic heart disease (IHD), is a leading cause of death for both men and women in the United States and is the most common form of cardiovascular disease. The public health and economic burdens of CAD are substantial. Atherosclerosis is the most common underlying cause of CAD and is the result of plaque buildup on artery walls. The buildup of plaque may partially or completely block blood flow (and hence oxygen and nutrient flow) in the coronary arteries via two primary mechanisms: 1) progressive narrowing of the vessel lumen and (2) thrombotic occlusion of the artery wherein the hard surface of the plaque tears away exposing inner fatty prothrombotic and platelet activating components at the site creating enlargement of the obstruction. The resulting decrease in blood flow may be chronic or acute. It may restrict blood supply to the myocardium and impair ability to supply oxygenated blood either at rest or during exertion. Atherosclerotic plaque occurs commonly and is asymptomatic for years and most people with plaque will never develop clinical coronary artery disease. Chest pain (angina) is the most common symptom of obstructive CAD and is the first presenting symptom in most patients. Plaque distribution, presence of collateral circulation and degree of vessel narrowing are factors which may influence symptom development and clinical impact of CAD, however, symptoms do **not** always correlate with lesion severity. Ischemia and impaired function may be present in the absence of observed obstruction.[57]

Diagnosis of CAD

Accurate and early assessment of patients with symptomatic CAD is important for risk stratification and initiation of appropriate treatments to reduce morbidity and mortality. Noninvasive techniques used to diagnose CAD fall into two general categories, those that evaluate the anatomical aspects of vessel occlusion and those that evaluate the functional impact of occlusion on cardiac function. Each has strengths and limitations. Noninvasive anatomic tests provide information on location and extent of blockage and include coronary CT angiography (CCTA) and cardiac magnetic resonance imaging (CMRI). Functional tests allow assessment of whether symptoms are correlated with narrowing leading to ischemic areas and generally include exercise (treadmill) electrocardiography (ECG), exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single-photon emission computed tomography (SPECT) or pharmacologic stress with positron emission tomography (PET). There has been recent interest in use of pharmacologic stress as part of computed tomography (CT) and magnetic resonance imaging (MRI) and in determining fractional flow reserve (FFR) with CT. The choice of testing is dependent on a variety of patient and other factors, particularly in patients with stable CAD. The patient's pre-test probability of CAD, test accuracy and the likelihood that test results would change management and lead to better outcomes important considerations. The effectiveness of non-invasive imaging tests is influenced by patient pretest probability/underlying disease prevalence which impacts test performance for measures that are influenced by disease prevalence. For any test, in patients with low pre-test probability of CAD, the number of potential false positive results necessitating further follow-up needs to be weighed against the potential for accurate

detection of CAD. In some included RCTs, the frequency of MI and death was low, reflecting the low pre-test probability in these trials. In these instances, the benefit of testing may be unclear. Clinical decision-making regarding choice of test(s) needs to also include consideration of the potential for additional/downstream testing, availability of other tests, cumulative radiation exposure and how results will inform appropriate management strategies and lead to improved outcomes while avoiding risks of testing such as additional radiation, false positives, and incidental findings.

Exercise electrocardiogram treadmill testing (ETT) and the imaging tests CTTA, stress nuclear imaging and stress echocardiography have become established as diagnostic tests for CAD. The focus of this HTA will be on the imaging tests and will not include ETT as an intervention. This review does not include evaluation of MRI (including stress MRI). As established testing modalities, the focus will be on evaluating their impact on clinical decision making for directing management that leads to improved patient outcomes.

Policy context/Reason for selection

CCTA and stress nuclear imaging were reviewed in 2008 and 2013 respectively. They are being re-reviewed in 2021 due to newly available published evidence. Stress echocardiography was not previously reviewed.

Objectives

The aim of this report is to evaluate the clinical impact, safety and cost-effectiveness of the three primary noninvasive imaging methods of diagnosing CAD, namely CCTA, stress nuclear imaging and stress echocardiography. In addition, adjuncts to CCTA including FFR and CT perfusion imaging were included. This review updates the 2008 CCTA HTA and 2013 nuclear imaging HTA and adds evaluation of stress echocardiography.

Contextual Questions

Three cardiac imaging modalities for diagnosis of CAD in symptomatic patients will be evaluated: CCTA, stress nuclear imaging, and stress echocardiography. Prior to addressing research questions related to the impact of cardiac imaging on clinical outcomes ***the diagnostic accuracy (validity)*** of these modalities compared with invasive coronary angiography (the usual reference standard) will be briefly summarized for context. Diagnostic accuracy parameters include sensitivity and specificity and prognostic value (positive and negative predictive values). Inter- and intra-rater reliability (reproducibility) will be described. Information for the contextual questions will be summarized using citations captured in the formal search for this HTA.

Key Questions and Scope

The following Key Questions focus on ***the impact on clinical outcomes*** for the use of CCTA, stress nuclear imaging, and stress echocardiography to diagnose CAD **in patients with known or suspected CAD who are *symptomatic.***

1. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) in leading to improved clinical outcomes (e.g., MI, mortality)?
2. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with respect to clinical decision-making including additional testing and treatments?
3. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with regard to harms or adverse events which may result directly from testing or additional, downstream testing?
4. Does effectiveness (in terms of clinical outcomes) or safety differ in special populations (e.g., women, those with comorbidities, the elderly) from noninvasive cardiac anatomic or functional imaging (CCTA, stress nuclear imaging, stress echocardiography)?
5. What is the cost-effectiveness of CCTA, stress nuclear imaging and stress echocardiography for clinical outcomes?

PICOTS/Scope:

Study Component	Inclusion	Exclusion
Patients	Adult patients (≥18 years of age) with symptoms of suspected (previously undiagnosed) 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 non-chest pain symptoms, such as dyspnea or worsening effort tolerance) • Suspected acute coronary syndrome (ACS) in emergency departments. Symptomatic adults with known/established CAD including those who have had prior MI and/or revascularization. For all questions, data on special populations and circumstances including the following will be evaluated: • Women • Patients with atypical symptoms • Elderly patients • Patients with comorbidities (including renal insufficiency, DM), LBBB)	• Asymptomatic patients • Patients presenting for evaluation of cardiac pathologies other than CAD (e.g., congenital abnormalities, valvular disease, evaluation of cardiomyopathy etiology, CHF) • Patients with STEMI
Intervention	• Coronary CT Angiography (including use of FFR) and CT perfusion imaging (pharmacologic stress) with 64 slice or higher CT • Stress nuclear imaging (including PET, SPECT) • Stress echocardiography	• CACS • Screening • Novel uses of any of these tests • MRI/MRA • Comparisons of technical performance parameters or variations of a testing modality (e.g., comparison different CT techniques) • Outdated equipment or

Study Component	Inclusion	Exclusion
		methods
Comparator(s)	• No testing • Usual care* • Comparison of the above interventions with each other • Invasive coronary angiography	
Outcomes	Clinical health outcomes (PRIMARY) • MI, cardiac death, all-cause mortality Clinical decision making • Referral for treatment • Referral for additional testing Harms, risks and consequences of testing (initial testing and subsequent testing) • Harms of testing (e.g., adverse events related to contrast agents, medication for pharmacologic stress testing), vascular complications (e.g. stroke) • Risks and consequences of testing (radiation exposure, psychological consequences of diagnosis, ramifications of additional testing, other†) Economic: Incremental cost-effectiveness or similar outcome	• Intermediate outcomes
Timing	• Emergent or non-emergent • Any point in the diagnostic workup	• None
Setting(s)	• Emergency department • Non-emergent settings	• None
Studies	• Focus will be on studies with the least potential for bias. Focus will start with RCT evidence; in the absence of RCTs, high quality comparative observational studies that control for potential confounding will be considered. Observational studies will primarily be considered for test-related harms. • Studies published in English in peer-reviewed journals, technology assessments or publicly available FDA reports. • Full (comparative) economic studies • Studies published after 2000 (except for stress echocardiography)	• Non-comparative studies • Modeling studies for prediction • Prognostic studies • Costing studies • Studies evaluating the incremental benefit of adding a test to another. • Studies published prior to 2000 (except for stress echocardiography)

CACS = coronary artery calcium scoring; CAD = coronary artery disease; CHF = congestive heart failure; CT = computed tomography; DM = diabetes mellitus; FFR = fractional flow reserve; LBBB = left bundle branch block; RCT = randomized controlled trials; MI = myocardial infarction; PET = positron emission tomography; SPECT = single photon emission computed tomography; STEMI = ST-segment elevation myocardial infarction.

*Usual care typically includes no treatment/nothing if low pretest probability, "watchful waiting", or medical treatment if high pretest probability.

†Other may include impact on patients such as days lost from work, procedures cancelled (waiting for tests), vacations cancelled, etc.

Methods

The scope of this report and final key questions were refined based on input from clinical experts. Clinical expert input was sought to confirm critical outcomes on which to focus. Draft Key Questions and PICOTS scope were published on the HCA website for public comment. None were received. Public

comments as well as those from clinical experts and peer-reviewers were considered for finalization of this report.

The 2008 review of CCTA focused on diagnostic accuracy and only one RCT measured the impact of CCTA on patient outcomes. Since 2008, many RCTs comparing CCTA with functional testing have been published and use of CCTA clinically has become more mature. In recent years, the technologies and their application have evolved and matured. Therefore, this HTA focuses on the clinical impact of CCTA. The key questions for 2013 review of cardiac nuclear imaging differed from this review evaluation and the prior review included screening of asymptomatic patients. This HTA focuses on the clinical impact of stress nuclear imaging (SPECT and PET). Given that stress echocardiography is an established modality for evaluating cardiac function, based on clinical input it is included in this HTA.

A formal, structured systematic search of the peer-reviewed literature was performed across multiple databases including PubMed to identify relevant peer reviewed literature as well as other sources (e.g., ECRI Guideline Trust) to identify pertinent clinical guidelines and previously performed assessments (Appendix B). For the systematic review portion of the report, studies were selected for inclusion based on pre-specified criteria detailed in the full report. All records were screened by two independent reviewers. Selection criteria included a focus on studies with the least potential for bias that were written in English and published in the peer-reviewed literature. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria. Assessment of RCTs followed appropriate criteria based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions* [19,58] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[5] In keeping with the AHRQ methods and the 2016 report on non-invasive imaging for CAD,[129] each study was given a final rating of "good", "fair", or "poor" quality based on the degree to which valid methods for patient selection, inclusion, allocation to treatment were used as well as the comparability of intervention groups, attrition and use of appropriate means for controlling bias. These are more described in detail in the full report. Systematic reviews were evaluated using AMSTAR-2 and economic studies Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et. al.[104]

An overall Strength of Evidence (SOE) combines the appraisal of study limitations with consideration of the number of studies and the consistency across them, directness and precision of the findings to describe an overall confidence regarding the stability of estimates as further research is available. The SOE was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[48,51,52] as outlined by the Agency for Healthcare Research and Quality (AHRQ).[5] The strength of evidence was based on the highest quality evidence available for the primary outcomes. Briefly, bodies of evidence consisting of RCTs were initially considered as High strength of evidence. The strength of evidence could be downgraded based on the limitations (i.e., risk of bias, consistency of effect, directness of outcome, precision of effect estimate, and reporting/publication bias). When assessing the SOE for studies performing subgroup analysis, we also considered whether the subgroup analysis was preplanned (*a priori*) and whether a test for homogeneity or interaction was done. The final strength of evidence was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome or the body of evidence has unacceptable efficiencies precluding judgment. If no evidence was identified, this was stated as such.

Methods for quantitative analysis are described in the full report. Briefly, meta-analyses were conducted using profile likelihood methods to get more precise effect estimates and focused on the primary outcomes. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. Sensitivity analyses were conducted excluding poor-quality studies, outlying data and related to clinical heterogeneity.

Results

To answer the key questions, from 15,443 unique citations retrieved from systematic searches, 295 were reviewed at full text and 81 studies across 112 publications were retained. The bulk of the new trials evaluated CCTA. A total of 36 studies (in 66 publications) (35 RCTs and 1 prospective comparative cohort)[3,9,17,18,23-25,27,28,42-44,50,54,59,60,62,68,73,76-79,81-84,86-89,92,94,99-102,107,108,111,117,121,123-125,131,132,135-137,139,140,142] comprised the primary evidence base for Key Questions 1–4 and an additional 31 studies (2 SRs and 29 nonrandomized observational studies)[2,7,8,10-12,16,22,30-32,34,37,38,40,46,63,64,66,67,72,90,91,95-97,103,110,112,116,128] provided supplemental data on safety (Key Question 3; see Appendix Tables O23-O25 for details). For cost-effectiveness (Key Question 5), 14 studies across 15 publications (3 systematic reviews and 11 formal economic analyses) were included.[6,13,14,41,50,61,65,74,85,93,114,115,134,138,143] Most trials were considered fair (17 RCTs) with 11 considered good and seven considered poor quality. In addition, 14 studies/reports that provided data for the contextual questions are described below.

Although we sought studies in the three symptomatic populations of interest (i.e., patients with unknown but suspected CAD, those with known/established CAD and those with suspected ACS), only 1 trial was specifically in patients with known CAD.[109] Populations in 13 trials[17,25,28,47,68,89,94,119,121,123,127,132,142] and one prospective comparative cohort[29] were predominately (≥80%) those with unknown/suspected CAD presenting to in an outpatient setting and are described as stable outpatients in the results. Five trials enrolled a mixed population of known and suspected CAD.[24,62,98,120,126] Sixteen trials were in patients presenting acutely to the ED or similar setting with suspected ACS (unstable angina or NSTEMI).[18,23,43,44,54,59,76,78,80,82,83,92,99,102,111,137] Studies in patients with STEMI were excluded. There was heterogeneity across trials regarding how pre-test risk was determined and reported. As described by authors, most populations were low to intermediate risk of CAD. Table 24 of the full report provides additional information on the pretest risk for included studies. Given this heterogeneity it was not possible to stratify results by this variable. Appendix M provides information as reported by trial authors, and patient and study characteristics can be found in Appendix Q.

Below is a summary of the key findings for this report.

An overview of results from the contextual question will be presented first followed by results for the key questions.

Contextual questions

Overall, evidence on diagnostic accuracy was available from 5 government related reports[1,55,105,106,129] and 9 systematic reviews [4,45,53,71,113,130,144] published in the peer review literature. The quality of systematic reviews was assessed; they varied with regard to whether and how individual accuracy studies were evaluated for risk of bias. Additional detail is found in the full report and Appendix L. Most studies focused on patients with stable symptoms with either suspect (not diagnosed) CAD or known CAD. The following tables summarize the general range for diagnostic accuracy parameters for each of the tests across populations and from government sources (see full report) using ICA as a referent and assuming 50% stenosis on ICA. Notes on risk of bias are included in the table. In addition, tables across populations and all sources identified are presented. Although ICA is commonly considered the gold standard for identifying CAD, there are well known limitations regarding variability, reliability, and image distortion in its use.[69,122] There have been many technological advances to ICA in the past decades that have addressed many of the limitations. Some limitations related to interpretation of ICA remain as is true of all tests included in this HTA.

ICA is an anatomic test, so accuracy for anatomic tests such as CCTA may differ from functional tests such as stress nuclear imaging or stress echocardiography when compared with ICA; a strict correspondence between ICA and functional tests is not expected.

The full report contains additional detail for accuracy parameters by population. No studies focusing on specific subpopulations were identified. Differential accuracy based on specific populations was not assessed in any of the studies identified.

Summaries from government systematic reviews including the 2008 and 2013 ICER HTAs: **diagnostic accuracy of imaging tests compared with invasive coronary angiography (ICA threshold ≥50% stenosis unless otherwise noted)**

Author, year	Risk of Bias	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Coronary Computed Tomography Angiography								
2016 AHRQ (Low radiation) *	ROB assessment varied by SR	100%	89%	93%	99%	9.2	0.00	58%
NICE 2016	25 studies; no serious ROB	96%	79%	84%†	97%†	4.57†	0.05†	NR
ICER 2008	34 studies; 9 rated good, rest as fair	98%	82%	89%†	97%†	5.44†	0.02†	59%
Nuclear Stress Testing (SPECT)								
2016 AHRQ REPORT	ROB assessment varied by SR	83% to 85%	77% to 85%	79% to 85%	79% to 85%	3.56 to 5.13	0.18 to 0.22	50%

Author, year	Risk of Bias	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
NICE 2016	11 studies, ROB serious or very serious in 55%	81%	78%	88%	65%	3.68	0.24	NR
ICER 2013 (SPECT vs. FFR via ICA)	4 studies; ROB high in 25% of QUADAS domains	66% to 90%	50% to 100%	73% to 81%	58% to 91%	1.32 to 9.00*	0.10 to 0.68*	NR
Nuclear Stress Testing (PET)								
2016 AHRQ REPORT	ROB assessment varied by SR	82% to 90%	86% to 88%	93% to 96%	53% to 84%	5.57 to 5.88	0.11 to 0.21	63% to 80%
NICE 2016	1 study, no serious ROB	91%	86%	87%*	90%*	6.50*	0.10*	NR
ICER 2013 (SPECT vs. FFR via ICA)	2 studies; ROB high in 30% of QUADAS domains;	76% to 95%	83% to 91%	76% to 86%	83% to 97%	4.47 to 10.56*	0.05 to 0.29*	NR
Stress Echocardiography								
2016 AHRQ REPORT	ROB assessment varied by SR	84% to 87%	72% to 77%	85% to 89%	69% to 73%	3.08 to 3.65	0.18 to 0.21	66% to 68%
NICE 2016 Wall motion, vasodilators	5 studies, no serious ROB	77%	76%	93%*	97%*	3.21*	0.30*	NR
NICE 2016 Wall motion, HR modifiers	8 studies, no serious ROB	76%	80%	88%	62%	3.80	0.30	NR

AHRQ = Agency for Healthcare Research and Quality; CAD = coronary artery disease; ICER = Institute for Clinical and Economic Review; HR = heart rate; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NICE = National Institute for Health and Care Excellence; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; SR= systematic review.
* All included studies used prospective electrocardiography gating for CT; uses much lower radiation doses than other techniques.
† Calculated from other values the authors provide.

Summary of diagnostic accuracy across all sources (see full report)

	CCTA	SPECT	PET	Stress Echo
Sensitivity	93.4% to 100%	76% to 87%	90% to 91%	64% to 90%
Specificity	72% to 92%	70% to 92%	82% to 91%	72% to 96%
PPV	47% to 93%	32% to 95%	78% to 96%	72% to 98%
NPV	89% to 100%	47% to 97%	53% to 94%	36% to 97%
LR+	3.43 to 12.50	2.88 to 10.48	4.97 to 8.89	3.08 to 18.67
LR-	0.00 to 2.64	0.18 to 2.33	0.10 to 0.21	0.13 to 2.95
CAD prevalence ranges	24.2% to 75.5%	14.1% to 86%	36.5% to 80%	35.1% to 90.8%

CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; PET = positron emission tomography; PPV = positive predictive value; SPECT = single-photon emission computed tomography; Stress Echo = stress echocardiography.

Summary of diagnostic accuracy across all sources (see full report), continued.

	FFRct	CT perfusion
Sensitivity	84% to 91%	54% to 66%
Specificity	55% to 84%	98% to 100%
PPV	58% to 100%	96% to 100%
NPV	0% to 90%	66% to 100%
LR+	2.02 to 3.70	33.00 to 54.00
LR-	0.16 to 0.23	0.45 to 0.47
CAD prevalence ranges	32% to 100%	NR

CAD = coronary artery disease; CT = computed tomography; FFRct = CT with fraction flow reserve; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

Intraobserver reliability for CCTA was reported in three studies.[75,118,141] Between observer reliability was investigated in six studies.[15,49,59,75,118,141] Intraobserver reliability was investigated in two studies[20,39] for FFRct but no studies were found on interobserver agreement. CT perfusion was only investigated in one study.[21] Risk of bias for reliability studies is described in the full report.

For SPECT one intraobserver[33] and two interobserver[21,33] studies were identified ((k=0.96 and k=0.91 to 0.95) and one study[141] investigating PET was identified. Reliability studies on stress echocardiography included both exercise and dobutamine for inducing stress and included, three intraobserver[33,36,56] studies and five studies[33,35,36,45,56,70] in inter-rater reliability. Findings from these studies are summarized below.

- Intraobserver reliability in CCTA ranged from substantial agreement to almost perfect agreement (k=0.72 to 0.96), while interobserver reliability ranged from moderate to almost perfect agreement (k=0.58 to 0.94). In FFRct, intraobserver reliability ranged from fair to almost perfect agreement (k=0.40 to 0.94), but no studies were found for interobserver reliability. Likewise, only interobserver reliability was studied in CT perfusion and found substantial to almost perfect agreement (k=0.72 to 0.86).
- SPECT studies found almost perfect agreement for both intra- and interobserver agreement (k=0.96, k=0.91 to 0.95). Likewise, PET studies also saw almost perfect agreement for bother intra- and interobserver reliability (k=0.94, k=0.82).
- Intraobserver agreement studies in stress echocardiography found almost perfect agreement (k=0.81 to 0.90), while studies on interobserver agreement found moderate to almost perfect agreement (k=0.56 to 0.87).

Key Questions Results

Key Questions results are organized by testing modality for Key Questions 1 through 4 on the efficacy and safety of CCTA, stress nuclear testing (SPECT, PET) and stress echocardiography respectively. Key Question 5 is summarized separately.

The Key findings are summarized here. The bulk of the evidence identified for this report compared CCTA with functional testing. Therefore, results for will be summarized separately for Key Questions 1 through 4. Key findings for CCTA compared with ICA, and for CCTA plus FFRct, SPECT, PET and stress

echo will then be presented by outcomes for KQ 1 through 3. No studies of differential effectiveness or safety were identified for these tests. No studies of CT perfusion meeting the inclusion criteria were identified.

Please note that the Strength of Evidence (SOE) tables for KQ 1 through 4 are found section 10 and are not repeated here. Formal SOE across economic studies is not assessed.

CCTA versus functional testing

Figure A provides a summary of findings for key questions 1 and 2.

Key Question 1: Comparative effectiveness on clinical outcomes

There were 17 RCTs comparing CCTA with functional testing, six RCTs[28,68,89,94,123,132] in stable patients with suspected CAD and 11 RCTs (12 publications)[18,23,43,44,54,59,60,76,81,83,111,137] in patients with suspected ACS that reported primary clinical outcomes. Functional testing included imaging tests (stress nuclear, stress echocardiography and ETT. Given the limitations of ETT as a functional test, sensitivity analyses comparing CCTA with functional imaging tests only were conducted. There was no statistical interaction between the patient populations for any outcome.

Across studies that include stable patients with suspected CAD and patients with suspected ACS presenting to an emergency department or similar setting:

- There is no clear difference in the frequency of MI between CCTA and functional imaging tests (SOE Moderate).
    - Three smaller RCTs, one in stable patients and two in those with suspected ACS, reported no MI in either testing arm.
    - CCTA was associated with lower MI risk compared with functional testing based on pooled estimates across the 14 remaining RCTs (pooled RR 0.70, 95% CI 0.56 to 0.89, I^2=0%),[18,23,28,43,54,59,60,81,83,89,111,123,132,137], however, the RD (0.4, 95% CI 0.1 to 0.8 per 100 patients) was small. The association was no longer clearly significant following exclusion of one RCT (SCOT-HEART) in stable patients with suspected CAD in which 85% of all patients had ETT in addition to CCTA (13 RCTs, pooled RR 0.75, 95% CI 0.57 to 0.99, I^2=0) or when CCTA was compared with functional *imaging* only (11 RCTs, pooled RR 0.74, 95% CI 0.55 to 0.98) This pattern was seen across RCTs of stable patients when the one trial was excluded. Across 10 RCTs in patients with suspected ACS, there was no difference in the frequency of MI between CCTA and functional testing at any time.
- There was no association between CCTA and reduction in all-cause mortality compared with functional testing (SOE Moderate).
    - Six RCTs reported no mortality in either testing arm (one RCT in stable patients, five RCTs in suspected ACS patients).
    - There was no difference in all-cause mortality between CCTA and functional testing across the remaining 11 RCTs (pooled RR 0.99, 95% CI 0.40 to 2.68, I^2=0%). There was also no difference in all-cause mortality when the populations were considered separately.
- Cardiac death was rare in both patient populations, with six total cardiac deaths reported in patients receiving CCTA and 13 reported in patients receiving functional testing (SOE Insufficient).

- It is possible that smaller trials in particular may have been underpowered to detect differences in MI, all-cause mortality, and cardiac death between CCTA and functional testing given that many trials enrolled patients with low or low to intermediate pre-test risk.

Key Question 2: Clinical decision making

The majority of RCTs comparing CCTA with functional testing which reported one or more of the following outcomes in either stable patients with suspected CAD or patients presenting emergently with suspected ACS: Referral for ICA (19 RCTs, N=22,335), any additional noninvasive testing (17 RCTs, N=11,595), referral for any revascularization (19 RCTs, N=23,124) and referral for PCI specifically (12 RCTs, N=18,960). There was no statistical interaction between the patient populations for any outcome.

Summary of results across populations

Across studies that include stable patients with suspected CAD and patients with suspected ACS presenting to an emergency department or similar setting:

- **ICA referral:** CCTA was associated with more frequent ICA referral compared with functional testing (19 RCTs, 14.4 vs. 12 per 100 patients, pooled RR 1.25, 95% CI 1.09 to 1.47, I^2=67%, RD 2.7, 95% CI 1 to 4 per 100, I^2=59%) (SOE Moderate).
    - **In stable outpatients**, ICA referral was more frequent following CCTA, but the association bordered the null and there was substantial heterogeneity. However, exclusion of SCOT-HEART increased the effect size and strengthen the association between CCTA and ICA referral compared with functional testing and substantially reduced the heterogeneity (4 RCTS pooled, RR 1.57, 95% CI 1.21 to 1.65, I^2=0%, RD 4.1, 95% CI 3.0 to 5.2 per 100 patients).
    - **In patients with suspected ACS**, ICA referral (cumulative) was also more frequent following CCTA compared with functional testing but was less than the frequency seen in stable outpatients. Referral for ICA was highest at the index evaluation.
- **Referral for any additional noninvasive testing** was not different between CCTA and functional testing groups across populations (17 RCTs, 7.2 versus 7.6 per 100, pooled RR 0.82, 95% CI 0.53 to 1.28, I^2=83%) (SOE Low) or when populations were considered individually. Type of additional testing was inconsistently reported but appears to be primarily stress imaging.
- **Revascularization:** CCTA was associated with more frequent revascularization (9.5 per 100 patients) compared with functional testing (7.1 per 100 patients): 19 RCTs, pooled RR 1.52, 95% CI 1.26 to 1.90, I^2=66%, RD 2.4, 95% CI 1.4 to 3.3 per 100) (SOE Moderate). Again, this was also true when the populations were considered individually.
- **PCI for revascularization:** CCTA was associate with higher frequency of PCI as a revascularization procedure compared with functional testing (12 RCTs, 8.2 vs. 6.0 per 100 patients, pooled RR 1.63, 95% CI 1.22 to 2.35, I^2=74%, RD 2.4, 95% CI 1.3 to 3.6 per 100 patients) across populations (SOE Moderate).
    - In stable outpatients with suspected CAD, PCI was more common with CCTA, but the association failed to reach statistical significance (pooler RR 1.16, 95% CI 0.96 to 2.99).
    - In patients with suspected ACS the association between CCTA and PCI was seen at index testing but there was no difference between CCTA and functional testing at 1 to 6.5 months or ≥12 months.
- **Hospitalization**:

- **In stable outpatients t**here was no difference in hospitalization between CCTA and functional testing across four RCTs (SOE Moderate).
- **In patients with suspected ACS**,
  - At index testing, across comparators with CCTA there is substantial heterogeneity and results are mixed. While four RCTs comparing CCTA with any functional test suggest that hospitalization is less common with CCTA, large studies of CCTA vs echo and SPECT suggest that hospitalization may be more with CCTA (SOE Insufficient).
  - There was no difference in hospitalization between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months after index testing (9 RCTs, 3.0 vs. 3.9 per 100 patients, pooled RR 0.76, 95% CI 0.49 to 1.1, I^2=18%)[18,23,43,44,59,81,83,92,99] (SOE High). Similarly, there was no difference between testing arms at ≥12 months (6 RCTs 14.9 vs. 17.4 per 100 patients, pooled RR 0.90, 95% CI 0.77 to 1.03, I^2=0%).[54,60,76,78,81,137] (SOE High).

- **Subsequent ED visits:** In patients with suspected ACS there was no difference in emergency department visits after index testing between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months (7 RCTs, pooled RR 0.84, 95% CI 0.66 to 1.06, I^2=0%)[23,43,44,59,83,92,99] or at ≥12 months (5 RCTs, pooled RR 1.06, 95% CI 0.93 to 1.56, I^2=16%)[54,60,76,78,111] (SOE High for both time frames).
- **Medication**: CCTA was not consistently associated with initiation of, discontinuation of or changes in medications and results for many mediations were mixed. Evidence is insufficient to draw firm conclusions about the impact of testing on medication use (SOE Insufficient).

Figure A. Summary of CCTA vs. any functional test, KQ 1 and 2 results

Outcome	All patients	ED/similar setting	Stable outpatients
Key Question 1: Clinical outcomes			
MI	**ϴ*** Moderate SOE (14; N=21,661)	**ϴ** (10; N=5,977)	**ϴ*** (4; N=15,684)
All-cause death	**ϴ Moderate** SOE (11; N=18,935)	**ϴ** (7; N=4,001)	**ϴ** (4; N=14,934)
Cardiac death	Insufficient evidence	Insufficient evidence	Insufficient evidence
Key Question 2: Decision-making			
ICA	**↑†** Moderate SOE (19; N=22,335)	**↑** (14; N=7,227)	**ϴ†** (4; N=15,107)
Any additional NIT	**ϴ Low** SOE (17; N=11,595)	**ϴ** (13; N=6,491)	**ϴ** (4; N=5,104)

Any revascularization	↑ Moderate SOE (19; N=23,124)	↑ (13; N=7,014)	↑ (19; N=16,110)
Hospitalization	Data not pooled	Index visit: Insufficient evidence Θ High SOE 1–6.5 mos. (9; N=5,144) ≥12 mos. (6; N=3,624)	Any timepoint: Θ Moderate SOE (4; N=14,810)
Subsequent ED visit	NR	Θ High SOE 1–6.5 mos. (7; N=4,294) ≥12 mos. (5; N=2,855)	NR
Medication change	Insufficient evidence	Insufficient evidence	Insufficient evidence

Θ = no difference between groups, ↓ = decreased risk with CCTA, ↑ = increased risk with CCTA
ED = emergency department; ICA = invasive coronary angiography; MI = myocardial infarction; mos. = months; NIT = noninvasive testing; NR = not reported; SOE = strength of evidence
*Excluding SCOT-HEART results not clearly statistically significant; similar results when studies comparing to ETT were excluded
†Exclusion of SCOT-HEART increased the effect size and strengthened the association between CCTA and ICA referral compared with functional testing and substantially reduced the heterogeneity

Key Question 3: Safety

Adverse events

- Major or serious test-related adverse events/harms are rare for all modalities. Complications reported across studies were minor. For stress testing most reported symptoms are expected responses to the pharmacologic agents used.
- No major complications were observed across 3 RCTS at time of index test or within 24 hours. (SOE Low) The largest RCT in stable outpatients also reported no test-related hospitalization in the CCTA arm and 0.1% (5/4837) in the functional testing arm[28] (SOE low).
- Minor complications at time of index test or within 24 hours was <4% across treatment arms across five RCTs in stable outpatients and five RCTs in patients with suspected ACS. Two other trials in patients with suspected ACS reported on a broader range of minor complications, one finding that 24% of patients in each testing arm[78] experienced them and the other that 14% of CCTA patients and 6.4% experienced minor complications (1 RCT, RR 2.16, 95% CI 1.12 to 4.14)[76] (SOE Low).
    - Contrast-related events related to CCTA occurred in ≤3% of patients at time of index testing as reported in six RCTs[18,23,28,59,68,87,123,140] and one case series. Transient creatinine elevation not requiring dialysis were reported in two trials as 0.2%[59] and 1%[23] (SOE Low) and a third RCT[18] reported that no contrast-induced nephropathy occurred (SOE Insufficient). Mild contrast reaction occurred in 0.5% to 2.1% of patients across six RCTs (SOE Low).
    - CCTA was associated with lower risk of chest pain, shortness of breath, or palpitations at the time of index testing compared with stress SPECT (1 RCT, 0.5% vs. 16% RR 0.03, 95%

CI 0.004 to 0.24, p<0.001) and stress echo (1 RCT, 0% vs. 3%, p=0.03)[76] in patients with suspected ACS (SOE Low). The symptoms are likely consistent with inducing cardiac stress with pharmacologic agents. One large RCT in stable outpatients reported much lower risk of symptoms related to nuclear stress testing (0.1%) and events related to dipyridamole or adenosine (0.2%) (SOE Low).

- Arrythmias occurred in ≤ 0.2% in all testing arm across testing arms (SOE Insufficient).

Radiation exposure

- **Radiation from index tests**: Across six RCTs comparing CCTA specifically with SPECT radiation exposure at index tended to be lower with CCTA (SOE Low). Five RCTs reported that CCTA was associated with a lower effective radiation dose for the index test; the sixth trial reported that CCTA was associated with slightly higher radiation (estimated difference 1.8 mSv). Rough estimates of difference between tests ranged from approximately 1.30 mSv to 11.9mSv. Stress echocardiography and ETT do not involve ionizing radiation (SOE Low).
- **Cumulative radiation**: Across nine RCTs, results are somewhat mixed, but suggest that cumulative radiation may be higher when CCTA is the initial test (SOE Low). Good- or fair-quality RCTs[23,28,59,76,82,99] found that CCTA was associated with higher cumulative radiation compared with functional testing with rough estimates of differences ranging from 1.9 mSv to 9.0 mSv in these trials. It is unclear from included RCTs what tests (e.g., SPECT, ICA) or procedures (e.g., PCI) were included in the estimates. Stress echocardiography does not involve ionizing radiation. It is unclear if some of the differences between arms would impact clinical decision making. CCTA was associated with lower cumulative radiation versus SPECT in two RCTs (estimated range 6 mSv to 15 mSv)[68,78] and no statistical difference between CCTA and SPECT was reported in a third smaller poor-quality RCT.[94]

Incidental Findings

Incidental findings are common with CCTA (28% to 44%) across included RCTs, systematic reviews and nonrandomized studies with pulmonary findings being most common. The proportions that were considered "potentially significant" "clinically significant" or "required follow-up" ranged from 4.9% to 16% (SOE Low).

Key Question 4. Differential effectiveness and safety

To evaluate differential efficacy and safety (heterogeneity of effect, interaction), we focused on RCTs as they have the least potential for bias and confounding thus allowing for causal inference. Further, only RCTs that formally tested for interaction between subgroups were reported for Key Question 4.

Three large RCTs comparing CCTA with functional testing reported tests for interaction between subgroups on efficacy and/or safety outcomes.[3,84,86,100,107,108,117,124,125,135,136] Only one of these pre-specified subgroup analyses and consider this in sample size determinations.[28,84,86,107,108,124,125] All performed multiple analyses for multiple outcomes, including multiple composite outcomes. None of the RCTs specified all outcomes evaluated. None specified hypotheses to be tested or expected direction.

- **Clinical outcomes**: Only one RCT[3,123] reported on the primary clinical outcomes of interest for this HTA. At a median of 3.2 years, the effect of CCTA did not appear to vary based on anginal classification (non-anginal chest pain, possible anginal chest pain) for MI (SOE Low), all-cause mortality (SOE Insufficient) or death due to CAD (SOE Insufficient). As many of these outcomes

appear to be rare, it is possible that this trial was not sufficiently powered to effectively evaluate interaction. The factors, outcomes and hypothesized direction do not appear to have been specified a priori.

- **Downstream testing:** One RCT in patients with suspected ACS found no significant variation in use of downstream testing with CCTA based on sex or race at either the index visit, or 28 day follow up. Downstream testing did vary by diabetes status; more downstream testing occurred with CCTA in patients with diabetes at index visit and by 28-day follow-up (interaction p-values 0.001 and 0.002 respectively). The factors, outcomes and hypothesized direction do not appear to have been specified a priori in this fair-quality trial (SOE Low).
- **ICA referral:** Across two RCTs, one in stable outpatients[124,125] and the other in patients with suspected ACS[136] the effect of CCTA versus functional testing on ICA referral did not vary by diabetes status. (SOE Low) Similarly, there was no effect modification in the trial in patients with suspected ACS by sex or race at index visit or by 28-day follow-up (SOE Low).
- **Revascularization**: Across two RCTs, one in stable outpatients[124,125] and the other in patients with suspected ACS[136] the effect of CCTA versus functional testing on revascularization did not vary by diabetes status (SOE Low). The effect of CCTA versus functional testing on revascularization was not modified by either sex (1 RCT) [136] or angina classification (1 RCT)[3] (SOE Insufficient).
- **Radiation exposure:** In stable outpatients, CTTA cumulative radiation may vary based on baseline heart rate. Patients with ≥75 beats-per-minute may have higher cumulative radiation with CCTA compared with functional testing. Tests for interaction by age, sex and BMI were not significant (SOE Insufficient). In patients with suspected ACS, there was insufficient evidence to confidently make conclusions about how radiation dose may vary by sex, diabetes status or race for CCTA versus functional testing index testing or within 28 days (SOE Insufficient).

CCTA versus ICA

Two RCTs (N=1,971 randomized), compared CCTA as an index diagnostic test versus direct referral to ICA in patients with suspected CAD (known CAD was an exclusion criteria). One good-quality trial included patients with atypical chest pain who had a mix of stable/chronic (treated on an outpatient basis) and acute (hospitalized) presentation.[25] One fair-quality trial included stable patients at primarily intermediate pre-test risk who were treated on an outpatient basis.[17]

- There was no difference in the risk of all-cause mortality or MI in CCTA versus ICA group at 12 and a median 40 months across one good- and one fair-quality RCT (SOE Low for both). Cardiac mortality was rare (SOE Insufficient).
- Compared with direct referral to ICA, CCTA was associated with a reduced risk of ICA without obstructive CAD (2 RCTs, N=1,019; 22 versus 65 per 100 patients; pooled RR 0.32, 95% CI 0.18 to 0.51, I^2=0%; pooled RD –48.0%, 95% CI –67.0% to –29.2%, I^2=73%) (SOE Moderate) and any revascularization (2 RCTs, N=1,832; 13 vs. 18 per 100 patients; pooled RR 0.71, 95% CI 0.55 to 0.96, I^2=0%; pooled RD –5.0%, 95% CI –8.0% to –2.0%, I^2=0%) (SOE Moderate) to include PCI but not CABG procedures, but an increased risk of additional downstream noninvasive testing (1 fair-quality RCT, N=1,503; 53 vs. 27 per 100 patients; RR 1.96, 95% CI 1.71 to 2.25; RD 26.0%, 95% CI 21.1% to 30.7%) (SOE Moderate). This latter trial found no difference between tests in the risk of cardiac hospitalization (4 vs. 4 per 100 patients) over 12 months (SOE Moderate).

- No major complications were reported in one good-quality trial and only one major complication was reported in the second fair-quality trial, major bleeding, which occurred in two patients (0.4%) in the ICA group; one patient (0.1%) required transfusion (SOE Low).

CCTA with FFR versus any noninvasive testing and versus ICA

One prospective comparative observational study was identified that enrolled patients into two simultaneous cohorts based on the planned test (per their physician) prior to enrollment: noninvasive test cohort (CCTA with FFR vs. any NIT; N=204) and (CCTA with FFR vs. direct referral to ICA; N=380).[26,29] The decision to send patients for noninvasive or invasive testing prior to enrollment was made by the patients' physicians; it is unclear what criteria were used to make this decision, though it is assumed that those patients who were being sent directly to ICA were higher risk than those being sent for noninvasive testing resulting is some selection bias.

Key Questions 1 and 2

CCTA with FFR vs. any NIT (planned NIT cohort)

- There was no difference between groups in any outcome over 12 months (SOE Insufficient for all outcomes).
- One MI occurred in the any noninvasive test group (0 vs. 1 per 100 patients). There were no deaths or hospitalizations with urgent revascularization in either group. Given that these are rare events, the study may not have been sufficiently powered to detect a difference.
- Risk of ICA was 21 vs. 16 per 100 patients; of ICA without obstructive CAD was 13 vs. 6 per 100 patients (at 3 months); and of any revascularization was 10 vs. 7 per 100 patients, respectively.

CCTA with FFR vs. ICA (planned ICA cohort)

- There were no differences between groups over 12 months in the risk of MI (1 vs. 1 per 100 patients), all-cause death (0 vs. 1 per 100 patients) or hospitalization with urgent revascularization (1 vs. 0 per 100 patients). Given that these are rare events, the study may not have been sufficiently powered to detect a difference (SOE Insufficient).
- Compared with direct referral to ICA, patients who underwent CCTA with FFR were referred to ICA significantly less often (51 vs. 100 per 100 patients; RR 0.51, 95% CI 0.45 to 0.59) and importantly, there were no events in the 61% of CCTA with FFR patients in whom ICA was cancelled in the planned ICA cohort. The risk of ICA without obstructive CAD was also significantly reduced following CCTA with FFR (39 vs. 100 per 100 patients; RR 0.39, 95% CI 0.33 to 0.47) (SOE Insufficient).
- There was no difference between groups in the risk of any revascularization (SOE Insufficient).

Key Question 3, Safety

- There was one mild contrast reaction from CCTA testing; no other information was provided (SOE Insufficient).
- Patients who received CCTA with FFR had significantly greater cumulative radiation exposure over 12 months compared to those who received any noninvasive test (planned noninvasive test cohort): 9.6 vs. 6.4 mSv, MD 3.1 (95% CI, 0.6 to 5.7); there was no difference for CCTA with FFR versus direct referral to ICA (planned ICA cohort) (SOE Low).

SPECT versus Stress Echocardiography and versus Exercise ECG

Key Questions 1 and 2, Efficacy

Four trials (1 good- and 3 fair-quality, N=1960) comparing SPECT with stress echocardiography (2 RCTs; 1 in stable, 1 in acute patients with suspected or known CAD)[120,126,133] and with exercise ECG (2 RCTs in stable, suspected CAD patients)[119,127] were identified. Given that the results across the four trials comparing SPECT with stress echocardiography and exercise ECG showed similar results in general, they are summarized together in the bullet points below.

- There was no difference in the risk of MI (SOE Insufficient), all-cause mortality (SOE low) or cardiac mortality (SOE Insufficient) between SPECT and stress echocardiography (2 trials) or exercise ECG (2 trials) across four trials (N=1,908) with varying populations and follow-up periods. The absolute risk was <2 per 100 patients across all testing arms for all outcomes over follow-up periods ranging from 1 to 24 months. Given that these are rare events, trials may not have been sufficiently powered to detect a difference.
- There was no difference in the risk of ICA (4 trials, N=1,908) (SOE Low) or additional noninvasive testing (N=3 trials, N=1,679) (SOE Insufficient) for SPECT versus stress echocardiography or exercise ECG across all four trials over follow-up periods ranging from 1 to 24 months, however, there was substantial heterogeneity. Individually, only the trials comparing SPECT versus exercise ECG reported statistically significant differences which favored SPECT for both ICA (1 trial) and additional noninvasive testing (2 trials); however, for the latter, the estimates across trials were inconsistent and imprecise. Differences in testing protocols, patient populations and/or pretest risk, and follow-up periods may have played a role in these findings.
- There was no difference in the risk of revascularization (4 trials, N=1,908) (SOE Moderate) or hospitalization (3 RCTs, N=1,451) (SOE Low) between SPECT and stress echocardiography or exercise ECG, or ED visits in 1 trial (N=229) of SPECT vs. echocardiography through 24 months of follow-up (SOE Low).

SPECT versus Clinical Assessment Alone and versus NICE Guideline-Directed Care

Key Questions 1 and 2, Efficacy

Two trials, one fair-quality trial (N=1,508)[80] comparing SPECT versus clinical assessment alone in acute patients with suspected ACS presenting to the ED and one good-quality trial (N=721)[47] comparing SPECT with NICE guideline-directed care in stable outpatients with suspected CAD, were identified. Given that the results across the two trials comparing SPECT with clinical assessment alone and with NICE guideline-directed care showed similar results in general, they are summarized together in the bullet points below.

- There was insufficient evidence to draw conclusions regarding the risk of MI and all-cause mortality in one RCT (SPECT vs. NICE guideline-directed care) with a median follow-up of 16 months and cardiac death across both RCTs (follow-up range, 1 to median 16 months). The absolute risk was ≤1.3 per 100 patients across both test arms in both trials for all outcomes. Given that these are rare events, the trials may not have been sufficiently powered to detect a difference (SOE Insufficient for all).
- SPECT was associated with a decreased risk of ICA across both trials (10.2 vs. 21.1 per 100, pooled RR 0.49, 95% CI 0.26 to 0.95, I^2=85%; pooled RD –11.1%, 95% CI –14.4% to –7.8%) (SOE

Low); the association was stronger in the trial comparing SPECT versus NICE guideline-directed care, likely due the direct referral to ICA of patients with high pretest risk per the NICE guideline algorithm, and could account for much of the heterogeneity in the pooled estimate. SPECT was also associated with a decreased risk of ICA showing no obstructive CAD (1 RCT, SPECT vs. clinical assessment alone: 21.9 vs. 39.3 per 100 patients; RR 0.56, 95% CI 0.32 to 0.96; RD –17.4%, 95% CI –33.3% to –1.4%) and unnecessary ICA (1 RCT, SPECT vs. NICE guideline-directed care: 7.1 vs. 28.8 per 100 patients; RR 0.25, 95% CI 0.17 to 0.36; RD –21.7%, 95% CI –27.9% to –15.5%) (SOE: Low for both).

- There was no difference between SPECT and clinical assessment alone or NICE guideline-directed care in the risk of any revascularization (2 RCTs, 5.9 vs. 7.0 per 100 patients; RR 0.85, 95% CI 0.57 to 1.28, I^2=0%) (SOE Low).
- SPECT was associated with decreased risk of additional downstream NIT over 12 months (12.1 vs. 68.3 per 100 patients; RR 0.18, 95% CI 0.15 to 0.21; RD –56.2%, 95% CI –60.7% to –51.7%) and hospitalization at the index visit (10.2 vs. 18.5 per 100 patients; RR 0.55, 95% CI 0.42 to 0.71; RD –8.3%, 95% CI –12.2% to –4.4%) compared with clinical assessment alone in one trial (SOE Low for both).

SPECT versus ICA

Key Questions 1 and 2, Efficacy

One good-quality trial (N=446)[126,133] comparing SPECT with ICA in stable outpatients with a mix of known and suspected CAD referred for outpatient angiography was identified.

- There was insufficient evidence to draw conclusions regarding the risk of MI, all-cause mortality and cardiac mortality between groups. Over 18 months, the absolute risk was ≤2 per 100 patients across both test arms for all outcomes; at 72 months, the absolute risk of all-cause mortality was 3 per 100 patients. Given that these are rare events, the trial may not have been sufficiently powered to detect a difference (SOE Insufficient).
- Compared with ICA, SPECT was associated with a decreased risk of additional downstream NIT (0.4 vs. 3.6 per 100 patients; RR 0.12, 95% CI 0.02 to 0.98; RD –3.2%, 95% CI –5.8% to –0.6%; timing unclear) and any revascularization after the index visit through 36 months (43.8 vs. 53.2 per 100 patients; RR 0.82, 95% CI 0.68 to 0.99; RD –9.4%, 95% CI –18.6% to –0.2%). There was no difference in the risk of any hospitalization for chest pain (SOE: Low for all).

Safety of SPECT (Key Question 3)

- Test-related complications appear to be rare following SPECT in one good-quality trial[47] (SOE Low).
- Data from one fair-quality trial was insufficient to draw conclusions regarding radiation exposure.[127] Mean exposure following SPECT was 14 mSv; exercise ECG does not use radiation.
- Adverse events from stress agents are relatively common and ranged from 2% to 13% of patients (5% to 37% of events) for dipyridamole and from 4% to 53% for regadenoson; the most common events included headache, dyspnea, GI upset/nausea and dizziness or lightheadedness (SOE Low). Most were minor and transient and are likely expected with use of pharmacologic cardiac stress.

Stress Echocardiography versus Exercise ECG

Key Questions 1 and 2, Efficacy

Five trials (1 good-, 1 fair- and 3 poor-quality) comparing stress echocardiography with exercise ECG, two (N=543) in stable patients with suspected CAD treated on an outpatient basis[50,121,142] and three (N=854) in patients with acute symptoms presenting to the ED or hospital.[24,62,102]

- There was insufficient evidence to draw conclusions regarding the risk of MI, all-cause mortality and cardiac mortality following stress echocardiography versus exercise ECG across the five trials. The absolute risks of MI and all-cause mortality across four trials were 1.3 vs. 0.9 and 0.6 vs. 0.9 per 100 patients, respectively, across follow-up periods ranging from 2 to 36 months. The absolute risk of cardiac mortality in one RCT was 0.5 vs. 0 at 36 months. Given that these are rare events, the trial may not have been sufficiently powered to detect a difference (SOE Insufficient for all).
- In stable patients with suspected CAD, stress echocardiography was associated with a reduced risk of ICA (1 good-quality RCT; 6.3 vs. 13.4 per 100 patients; RR 0.47, 95% CI 0.24 to 0.90; RD –7.1%, 95% CI –13.0 to –1.2%) (SOE Low) and additional downstream NIT (2 RCTs, 1 good and 1 poor quality; 5.8 vs. 42.7 per 100 patients; pooled RR 0.15, 95% CI 0.06 to 0.28, I^2=0%; pooled RD –31.6 (95% CI –49.3% to –14.0%, I^2=84%) (SOE Low) compared with exercise ECG over 28 to 36 months. Across the three trials in acute patients with a mix of known or suspected CAD, there was no difference between groups in either outcome, though one fair-quality trial tended to favor echocardiography for ICA (lower risk); heterogeneity was high possibly due to differences in populations, pretest risk and follow-up times (SOE Low for ICA; SOE Insufficient for additional NIT).
- Across trials in both stable (1 RCT) and acute patients (3 RCTs) with varying pretest risks of CAD, there were no differences between testing arms in the risk of revascularization (4 RCTs, 1 good, 2 fair and 1 poor quality) or (re)hospitalization (3 RCTs, 1 good, 1 fair and 1 poor quality) over follow-up periods ranging from 2 to 36 months (SOE Moderate for both).

Stress Echocardiography versus Standard Care

Key Questions 1 and 2, Efficacy

Data from one small, poor-quality trial (N=201)[102] in acute patients with suspected ACS are insufficient to draw conclusions regarding the risk of MI, all-cause or cardiac mortality, ICA, additional downstream NIT, any revascularization and rehospitalization for acute chest pain following stress echocardiography versus standard care.

- No MIs and no deaths were reported in either test arm. Stress echocardiography resulted in fewer referrals for ICA and additional NITs, and fewer rehospitalizations for acute chest pain, but no difference in revascularization rates (SOE Insufficient).

Stress Echocardiography versus ICA

Key Questions 1 and 2, Efficacy

One good-quality trial (N=448)[126,133] comparing stress echocardiography with ICA in stable outpatients with a mix of known and suspected CAD was identified.

- There was insufficient evidence to draw conclusions regarding the risk of MI, all-cause mortality and cardiac mortality between groups. Over 18 months, the absolute risk was <3 per 100 patients across both test arms for all outcomes; at 72 months, the absolute risk of all-cause mortality was 4.9 vs. 3.2 per 100 patients. Given that these are rare events, the trial may not have been sufficiently powered to detect a difference (SOE Insufficient).
- There were no differences between stress echocardiography and ICA in the risk of additional downstream NIT (SOE Insufficient), any revascularization and hospitalization for chest pain (SOE: Low for both).

Safety of Stress Echocardiography (Key Question 3)

- Data from one poor-quality trial is insufficient to draw conclusions regarding test-related complications.[102]
- Across 11 case-series,[10,22,38,46,64,90,95,103,110,112,128] the risk of major or life-threatening adverse events (e.g., death, MI, unstable angina, cerebrovascular accident, acute pulmonary edema) as a result of pharmacologic stress agents appears to be low: for dobutamine, ≤0.1% across all outcomes, and for dipyridamole and adenosine no major adverse events were reported. Minor transient events (e.g., arrhythmias, chest pain, headache, dyspnea, nausea/vomiting) were not uncommon (SOE low for all); most reported symptoms are expected responses to the pharmacologic agents used.
- Definite or suspected contrast related adverse events and allergic reactions appear to be rare (≤2% across all studies/outcomes) (SOE Low).

PET vs. SPECT

Two trials comparing PET versus SPECT, one in stable patients with a mixed of suspected or known CAD (N=210)[98] and one in stable patients with known CAD presenting with new or worsening symptoms (N=322),[109] were identified. Across both trials, there were no difference between test groups in any of the reported outcomes.

- There was insufficient evidence from one good-quality trial in patients with known CAD and new or worsening symptoms to draw firm conclusions regarding MI and all-cause mortality. The absolute risks of MI and all-cause mortality were ≤1 per 100 patients across both the PET and SPECT arms over 12 months (SOE Insufficient). There was no difference in the risk of ICA (29 vs. 28 per 100 patients); of diagnostic failure, defined as unnecessary ICA or additional confirmatory noninvasive testing within 2 months (2.0 vs. 2.5 per 100 patients); of any revascularization (16 vs. 15 per 100 patients); and of escalation in antianginal therapy (26 vs. 23 per 100 patients) (SOE Low for all).
- The only outcome reported by the older, poor-quality trial evaluating a mixed population of suspected and known CAD was cardiac mortality (absolute risk 3 vs. 4 in 100 patients over a mean 9 months) (SOE Insufficient).
- Neither trial reported on test safety or on differential effectiveness or safety.

Key Question 5: Cost-effectiveness of testing

Economic studies identified for inclusion primarily compared combinations of testing strategies involving CCTA, stress nuclear imaging (primarily SPECT), stress echocardiography, exercise ECG treadmill testing and invasive coronary angiography, with only few directly comparing one specific test to another. Only

full economic studies that compared a test with one or more tests or strategy of no testing and evaluated cost-effectiveness based on hard clinical outcomes and reporting on cost per QALY (ICER) or cost per correct diagnosis or cost per life saved, were included. A total of three systematic reviews[134,138,143] and 11 primary studies were included. Eight of the studies (in nine publications) were in stable outpatients with suspected CAD,[6,13,14,50,61,65,74,85,93] and three were in patients with suspected ACS.[41,114,115] Of these, two studies in stable outpatients[65,93] and three studies in patients with suspected ACS were conducted in the United States.[41,114,115] Industry funding was noted and/or author ties to related industries were described in three studies.[41,65,93] Full economic studies of diagnostic testing are complex, challenging to perform and challenging to interpret. A variety of assumptions and estimates from diverse sources (which may vary in quality) provide input into any economic model and impact the results of that model. These are discussed in the full report.

Most economic models described in the systematic reviews and the primary studies compared testing strategies (i.e., different scenarios for index test and subsequent sequential tests) not individual tests, making it difficult to draw definitive conclusions for specific tests. The results below attempt to focus on findings for specific tests. Variation across studies in data sources, estimation of model parameters, clinical pathways for test sequencing and decision making leading to additional testing and/or treatment make comparison across studies challenging. Evidence was mixed for demonstrating a definitive cost-effective diagnostic approach.

- Results across studies (including systematic reviews) were somewhat mixed.
- Cost-effectiveness and ICERs varied based on testing sequencing, pre-test likelihood of CAD, assumed accuracy of tests across populations. These key drivers were also identified in the prior HTAs.
- In stable outpatients with suspected CAD
    - The U.S. studies generally found CCTA to be the dominant initial testing strategy against comparators/other strategies, which included ICA and functional tests. FFRct in addition to CCTA was consider cost-effective in one industry-funded study.
    - Stress echocardiography and SPECT were found to be cost-effective compared to ICA.
    - Two systematic reviews suggest that stress echo or nuclear stress testing may be more cost effective than comparators in some settings depending on patient prior probability of CAD and prevalence of CAD. Stress echo may be more cost-effective than SPECT in patients with low to intermediate probability.
- In patients presenting with suspected ACS in an emergency setting
    - CCTA was compared with standard of care (variably defined), ETT, expert consensus based on ACC/AHA guidelines and “do nothing” strategies. CCTA was the dominant or cost-effective approach in most all comparisons.
    - In one poor-quality review of seven studies in patients with acute chest pain, stress nuclear testing was cost-effective versus traditional strategies involving ECG. However, authors note that stress nuclear testing in the acute setting may not often used in ‘real life’, due to logistical challenges.
- Common limitations across studies include
    - The assumption that ICA has 100% sensitivity and specificity.
    - Extrapolation of data to lifetime time horizon particularly when RCT data is only

available for approximately 2 years for many of the studies. Results from short-term time horizons may differ from those seen at longer term.
- Lack of or insufficient modeling of indeterminate tests, false positive and false negative results, test accuracy based on sequencing of tests, potential adverse events and follow-up of incidental findings.
- Some modeled strategies (e.g., some "do nothing" strategies) may not be consistent with clinical practice. Modeling of appropriate "no test" strategies was not done.
- Models assume the availability of all tests and competence in performing and interpreting them across clinical settings.
- Lack of information on the potential impact of radiation exposure for index and downstream testing.

Discussion

Regarding the pathophysiology of CAD and ischemia, several factors are important to consider. First, identification and degree of obstruction do not always correlate to patient symptoms, the presence or degree of ischemia or the functional impact. In addition, ischemia may be present in the absence of obstruction and would not be identified by anatomic testing.

The bulk of new evidence for this report is from RCTs comparing CCTA with functional tests.

- There is no clear difference between CCTA and functional imaging tests (i.e., stress nuclear testing, stress echocardiography) regarding impact on improving clinical outcomes (MI, all-cause mortality) in stable outpatients with suspected CAD or in patients with suspected ACS presenting to the ED or similar settings. It should be remembered that evidence of the impact of testing on clinical outcomes is indirect.
- CCTA was associated with higher frequency of ICA referral and use of PCI for revascularization compared with functional imaging. From the evidence available, it is not clear to what extent patients referred for these were considered at high risk for MI requiring revascularization. While increased ICA/PCI use may lead to fewer symptoms, related increased resource utilization and radiation exposure should be considered. No differences in the use of additional noninvasive testing between CCTA and functional tests were identified.
- Risk of serious test-related adverse events was very low across all imaging tests.
- While radiation exposure at time of index testing tended to be lower in CCTA recipients compared with SPECT (stress echo does not involve ionizing radiation), the evidence suggests that cumulative radiation may be higher with CCTA as an initial test. The extent to which this is influenced by additional non-invasive testing and/or ICA and PCI referral is unclear across included RCTs.
- Incidental findings requiring follow-up in patients receiving CCTA are common and require additional resources.
- Definitive conclusions regarding cost-effectiveness of any of the noninvasive imaging tests are not possible in large part due to substantial heterogeneity across economic studies regarding testing strategies and test sequencing.
- There was insufficient evidence for the use of FFRct in conjunction with CTTA.

The applicability of the evidence and findings reported here may be limited by the following factors.

- There was substantial heterogeneity across studies regarding patients, their pre-test risks of CAD (and how this was determined) and CAD risk factors, equipment used, testing protocols and study methods.
- Pretest CAD risk described in this HTA was as reported by study authors and included a variety of methods. Stratification by pre-test risk was not considered to be feasible given this heterogeneity.
- Stress echocardiography and SPECT are established modalities for diagnosis of CAD.
    - Fewer trials of these modalities were identified; most were older than CCTA trials and reflect older research methods and reporting standards. Included RCTs do not reflect state of the art equipment or techniques, whereas studies of CCTA involve more state-of the-equipment and methods.
    - Given that these are more established modalities, there has been less impetus and funding for RCTs and high-quality prospective observational studies than for evaluation of CCTA.
    - It is possible that more advanced techniques related to stress echocardiography using contrast for left ventricular opacification or myocardial perfusion imaging or quantitative methods for PET may have been used in included RCTs but were not assessed as separate advances.
- Substantial expertise is required to perform and interpret all diagnostic imaging tests for CAD. Across included studies, the level of expertise for all imaging tests was high. This level of expertise may not translate to all clinical settings. Similarly, the availability of updated equipment may also vary across settings. These factors need to be considered when weighing options for the “best test” for a given patient.

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1 Appraisal

1.1 Background and Rationale

1.1.1 Policy Context

CCTA and stress nuclear imaging were originally reviewed in 2008 and 2013 respectively. They are being re-reviewed in 2021 due to newly available published evidence. In addition, stress echocardiography is being reviewed (not previously reviewed by HTAP).

1.1.2 Objectives

The aim of this report is to evaluate the clinical impact (i.e., patient outcomes and patient management), safety and cost-effectiveness of the three primary noninvasive diagnostic tests for CAD, namely CCTA , stress nuclear imaging and stress echocardiography as well as FFR based on CT and CT perfusion (CTP) imaging. This review updates the 2008 CCTA HTA and 2013 nuclear imaging HTA and adds evaluation of stress echocardiography. Information on diagnostic accuracy (validity) for these modalities was summarized for context only given the clinical maturity of these imaging modalities. Coronary artery calcium scoring (CACS) as a diagnostic test was excluded as it is not a standalone diagnostic test; further, it was not chosen for re-review by the Health Care Authority. Use of CT (including CACS), CCTA, nuclear imaging and stress echocardiography for ***screening*** for CAD in ***asymptomatic*** individuals was excluded.

1.2 Contextual Questions

Prior to addressing research questions related to the impact of cardiac imaging on clinical outcomes ***the diagnostic accuracy (validity)*** of these modalities compared with invasive coronary angiography (the usual reference standard) will be briefly summarized for context, given the clinical maturity of these imaging modalities.

In patients with **known or suspected CAD who are *symptomatic*:**

1. What is the diagnostic accuracy of *CCTA* for anatomical confirmation of obstructive CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

2. What is the diagnostic accuracy of *CCTA with determination of fractional flow reserve (FFR)* for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

3. What is the diagnostic accuracy of *stress CCTA* for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

4. What is the diagnostic accuracy of *stress nuclear imaging*? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

5. What is the diagnostic accuracy of *stress echocardiography*? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

1.3 Research Key Questions

The following Key Questions focus on ***the impact on clinical outcomes*** for the use of CCTA, stress nuclear imaging, and stress echocardiography to diagnose CAD **in patients with known or suspected CAD who are *symptomatic.***

1. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) in leading to improved *clinical outcomes* (e.g., MI, mortality)?

2. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with respect to *clinical decision-making* including additional testing and treatments?

3. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with regard to *harms or adverse events* which may result directly from testing or additional, downstream testing?

4. Does effectiveness (in terms of clinical outcomes) or safety of noninvasive cardiac anatomic or functional imaging (CCTA, stress nuclear imaging, stress echocardiography) differ in *special populations* (e.g., women, those with comorbidities, the elderly)?

5. What is the *cost-effectiveness* of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) for clinical outcomes?

1.4 Key Considerations Highlighted by Clinical Experts: Cardiac Imaging for CAD (symptomatic patients with suspected or known CAD)

1.4.1 Interventions

The use and complexity of noninvasive cardiac imaging has expanded substantially in the past three decades. Despite numerous advances in the technical performance of various cardiac imaging modalities, the precise role(s) of some of these tests and when to use them remains unclear. There is lack of consensus and some controversy across the clinical community with regard to the optimal noninvasive imaging approach(es) for evaluating patients with symptoms of ischemic heart disease, particularly in patients with low to intermediate pre-test risk for CAD.[221] Some clinicians suggest that

there is overuse of such imaging and note that inappropriate cardiac stress tests in particular costs the U.S. health care system as much as one half a billion dollars each year and expose patients to unnecessary radiation.[206] In contrast, some clinicians suggest that imaging tests may assist with risk stratification and initiation of appropriate medical therapy. Many clinicians question whether noninvasive imaging is necessary at all, in patients who are at very low, low or even intermediate risk of CAD. In these populations, a large number of false positive tests are generally seen which may lead to additional testing and clinical evaluation and/or initiation of unnecessary or inappropriate treatment. In addition, many clinicians cite lack of evidence that testing in these populations leads to better clinical outcomes such as myocardial infarction. In general, appropriate use criteria indicate that imaging tests in populations with low pretest CAD probability presenting with non-acute chest pain, interpretable ECG and ability to exercise are rarely appropriate or use may be uncertain.[259]

In addition to the question of whether *any* testing is needed in patients with low to intermediate CAD risk, there continues to be controversy regarding whether anatomic tests such as CCTA or functional tests such as stress ECG, stress echocardiography or stress nuclear imaging should be the initial test for evaluating patients for suspected or known CAD or those with suspected ACS. While anatomic tests allow for visualization of coronary artery obstruction, the presence of obstruction does not always correspond to patient symptoms and does not provide information on the impact of the obstruction on myocardial function. Acute MI frequently occurs in patients without prior obstructive plaque.[206] Stress testing provides information on the functional impact of obstruction on the myocardium when hemodynamically significant stenosis is present but does not provide direct visualization of plaque (obstructive or not).[206] CCTA is the primary noninvasive imaging test that is used to specifically evaluate coronary anatomy. The primary functional *imaging* tests used to diagnose CAD are stress echocardiography and stress nuclear imaging via SPECT and less commonly, PET.

The choice of which test(s) to use for the evaluation of CAD is a function of historical practice, institutional availability, local expertise to perform and interpret exams and reimbursement. Each test has its proponents, pros and cons. All require substantial expertise for performance and interpretation; thus, the accuracy of the test will vary according to technical and reader expertise.

Stress ECG (exercise treadmill testing, ETT) has been used for decades to evaluate possible ischemic heart disease due to coronary artery obstruction and remains a common initial functional test in many settings. It has the advantages of being widely available, portable, relatively easy and quick to perform and interpret and is inexpensive. Changes on the electrical signals identified with ECG however, may not be apparent unless there is substantial ischemia (or infarction) due to obstruction of the coronary arteries and does it not provide visualization of the heart. None-the-less it is often the first test considered and may be standard of care in many settings. It is one of the functional comparators described in studies of CCTA, nuclear stress testing and stress echocardiography included in this report.

Stress echocardiography has also been used for decades to image and evaluate changes in wall motion due to myocardial ischemia (or infarction) induced when stress via exercise or pharmacologic agents is applied, thus providing functional assessment of impact of obstruction on cardiac function and anatomy. Changes in wall motion are seen earlier in a patient's clinical course if ischemia is present compared with electrical changes. Echocardiography may also provide valuable information regarding the integrity of

various cardiac structures (e.g., papillary muscle and related valve function) that may have been impacted by CAD. Stress echocardiography is widely available, portable, and relative to other imaging modalities for CAD, relatively inexpensive and does not involve ionizing radiation. Stress echo may be difficult to perform and interpret in obese patients or those with pulmonary disease. It is operator dependent and requires substantial expertise for comprehensive, accurate interpretation.

Nuclear stress testing via SPECT or PET, (often collectively referred to as myocardial perfusion imaging) also provide functional information via evaluation of cardiac wall motion and function. Both require the use of radioactive tracers in addition to pharmacologic stress agents and involve specialized equipment which may not be readily available in smaller clinical settings. SPECT is most commonly used.

PET is less commonly used largely due to its availability outside of larger institutions coupled with equipment reliability and maintenance issues. Both require expertise for comprehensive, accurate interpretation.

CCTA is used to evaluate coronary artery anatomy and visually estimate the amount of coronary artery obstruction. Its use has become more common in the past 15 to 20 years as the technology has advanced, including use of methods for reducing radiation exposure. Advantages include CCTA's ability to rapidly visualize coronary obstruction and presence of plaque in the vessels. As with SPECT and PET, CCTA involves radiation exposure and requires specialized equipment. In addition to potential concerns regarding radiation exposure, particularly if contrast is used, image artifacts in patients with substantial coronary artery calcium may render images uninterpretable. A certain level of expertise is required for interpretation.

Although a number of RCTs comparing CCTA with functional testing have been conducted in the past decade in particular, as previously mentioned, there is lack of consensus and some controversy across the clinical community with regard to the optimal noninvasive imaging approach(es) for evaluating patients with symptoms of ischemic heart disease, particularly in patients with low to intermediate pre-test risk for CAD.[221] This may be part due to somewhat conflicting results across trials on the impact of CCTA compared with functional testing on clinical outcomes, referral for ICA, diagnosis of new CAD and impact on treatment decisions. Proponents of the CCTA approach cite reduced myocardial infarctions and the ability to introduce preventative medical therapy as the advantages of it.[154] In particular, many feel that the predictive values of CCTA can reduce unnecessary downstream testing.[154] However, the 2017 meta-analysis referenced above found that CCTA leads to an increase in downstream invasive procedures. This systematic review and meta-analysis of trials published through 2017, found that CCTA, when compared to functional stress testing, may reduce the incidence of myocardial infarction but had no significant impact on death or cardiac hospitalization.[73] One included trial, the SCOT-HEART was the main driver for the reduction in myocardial infarctions.[215] In this trial, 85% of patients in the CCTA arm received functional stress testing. When it was removed from the analysis, the difference in myocardial infarctions was no longer significant. The same review found that CCTA increases rates of invasive coronary angiography and coronary revascularization, as well as new coronary artery disease diagnoses and new prescriptions for aspirin and statin medications compared with functional testing.

One primary disadvantage of CCTA is that it does not provide functional information on the impact of the hemodynamic significance of obstruction. Clinicians may therefore also order one of the functional tests previously described for further clinical decision making, including the need for referral to ICA. Recently, studies have evaluated the use of FFR derived from CCCT data (FFRct) and CT perfusion (CTP), which uses pharmacologic stress during CT to evaluate the hemodynamic impact of obstruction to complement anatomic visualization. These adjuncts to CCTA are not widely used currently and their role in routine evaluation of CAD is not established. Limited clinical studies of these have evaluated the incremental value of adding them to CCTA and have been conducted in highly specialized settings. Overall, both FFRct and CTP have showed better accuracy than CCTA alone but have low overall positive predictive value[46]; accuracy is impacted by CAD prevalence and pre-test probability. With regard to FFRct, only one device/analysis method, the HeartFlow is currently commercially available and FDA approved (510K) for use. It uses CTTA imaging data that are transferred to HeartFlow, Inc. a sole vendor, for analysis. This may limit the utility of this technology. Concerns regarding the diagnostic accuracy of FFRct (including the number of false positives), potential higher use of ICA when used as a substitute for planned noninvasive cardiovascular testing and limited evidence of clinical utility or impact on clinical outcomes have been noted in a recent review.[100] In addition, concerns regarding timely reporting of results in an acute care setting have been raised. A recent study evaluating a strategy of CCTA with selective FFRct in stable outpatients reported no difference in cost or clinical outcomes compared with standard care.[44] (This study did not meet the inclusion criteria for this HTA.) Anecdotally, it may be used in low-risk patients, particularly women, who many clinicians feel should not be tested. This may be of concern as middle-aged women may be at higher risk of radiation induced cancers.

CT myocardial perfusion imaging evaluates the impact of epicardial and microvascular disease on myocardial blood flow. There are limitations to its use including the need for extra time to prepare for and perform stress imaging in addition to the CT anatomic imaging, timing the use of pharmacologic stressors as well as additional contrast and radiation exposure that are involved.

1.4.2 Costs

Stress ECG is the least costly of the primary tests that are used to evaluate symptomatic patients for CAD. With regard to noninvasive imaging, the least expensive is stress echocardiography. CCTA is slightly less expensive than SPECT. In addition to costs related to primary testing, the costs of any additional downstream testing needed to follow-up inconclusive tests, false positives, incidental findings and treatments need to be considered. The choice of test is also influenced by reimbursement.

1.4.3 Patient considerations

The value of doing a test is related to the pre-test likelihood of disease and the extent to which a test helps confirm or rule out a given diagnosis. The pre-test likelihood of CAD is largely based on sex, age, type of chest pain as well as other symptoms and factors. This is important when considering use of a diagnostic test and in comparing the results of studies validating diagnostic tests. Predictive values are influenced by the pre-test probability of disease. Cardiac imaging in patients who are asymptomatic is

not routinely done or considered appropriate by many clinicians, evidence-based clinical guidelines and recent USPSTF evaluations and guidelines.

Evaluation of patient pre-test CAD probability has traditionally been based on the work of Diamond and Forrester[55], however a wide variety of other methods have been used and proposed. The HEART ((History, Electrocardiogram, Age, Risk factors, Troponin) methods is frequently used in emergency departments to triage patients presenting with acute chest pain or suspicion of acute coronary syndrome and determine next steps for testing and care.[16,219]

CCTA and nuclear stress testing are noninvasive imaging tests, they do, however, expose the patient to ionizing radiation. Given the cumulative nature of radiation exposure, consideration of patient age, habitus, and other factors need to be weighed in considering the types and sequences of tests. For CCTA since scanning includes not only the coronary arteries but surrounding structures as well, potential abnormalities in structures other than the coronary arteries with CCTA and heart might be observed, and further evaluation may be required. The costs and implications of incidental findings should be considered.

A recent CADTH rapid report on patient and caregiver perspectives on advanced cardiac imaging suggest that patient-provider communication needs to extend beyond the general benefits and risks of scanning to include information about the processes and pathways of attending the scan, why they are undergoing such imaging, why it is important and what they can expect from the process.[231]

1.4.4 Professional considerations

The primary goal of doing testing is to provide information on the need (or lack thereof) for initiating appropriate treatment. In many instances, guideline directed medical therapy and lifestyle change recommendations serve as the primary recommendations in patients with low to intermediate risk of CAD. Recent studies suggest that for patients at low to intermediate risk, results may be similar for guideline directed medical therapy and PCI. The local availability of testing and expertise in preforming and interpreting various types of non-invasive imaging need to be considered.

1.4.5 Ethical considerations

Although CCTA and nuclear stress testing are noninvasive tests, they do expose the patient to ionizing radiation, a factor which clinicians need to consider and put in the context of other tests that may be part of the clinical pathway which also may use ionizing radiation. Radiation accountability frameworks have been recommended to promote shared decision making with patients and drive appropriate imaging utilization.[62] There is also lack of consensus regarding how to best handle interpretations and follow-up of non-emergent incidental findings that are frequently seen particularly with CCTA.[24,124,125]

These factors should be considered when weighing the benefits, risks and costs need to be discussed with the patient.

1.5 Outcomes Assessed

The primary clinical outcomes of interest for this report are listed below.

- Myocardial infarction*
- All-cause mortality*
- Cardiac death*
- Safety/adverse events*

The clinical management outcomes of interest for this report include:

- Referral for additional testing (ICA or noninvasive imaging)*
- Referral for treatment (revascularization)*
- Changes in medication therapy
- Hospitalizations or ED visits

Other outcomes reported included, major adverse cardiac events (MACE), other cardiac events as reported (e.g., cardiac arrest, unstable angina, stroke, cerebrovascular accident), the Seattle Angina Questionnaire (SAQ), validated health-related quality of life measures, and length of hospital stay.

Outcomes are detailed in the evidence tables in the appendices and/or the body of the report.

Strength of evidence was assessed only for the outcomes with an asterisk above.

1.6 Washington State Utilization Data

1.6.1 Population

Administrative claims and encounter data for coronary computed tomography angiography (CCTA), stress nuclear imaging, and stress echocardiography from the following Washington State health programs were assessed: the Public Employees Benefit Board Uniform Medical Plan (PEBB/UMP), Medicaid managed care (MC) and fee-for-service (FFS), and the Department of Labor and Industries (L&I) Workers' Compensation Plan.

The assessment includes final paid and adjudicated claims and encounters. Denied claims or rejected encounters are excluded. Individuals that were dually eligible for both Medicare and Medicaid are excluded from the Medicaid program analysis. The PEBB/UMP experience includes claims for non-Medicare services.

1.6.2 Noninvasive cardiac imaging procedures

The assessment includes only procedures and services specific to noninvasive cardiac imaging with a date of service between January 1, 2017, and December 31, 2020. Analysis does not include additional services associated with imaging procedures.

Claims and encounters with qualifying procedures or services according to current procedural terminology (CPT) code or level II healthcare common procedure coding system (HCPCS) during the period were extracted for analysis.

Table 1. Utilization of noninvasive cardiac imaging, by state health program (2017-2020)

Medicaid	2017	2018	2019	2020	Total (unique)
Fee for service (FFS)					
Individuals with at least one noninvasive cardiac imaging-related procedure	981	940	900	670	**3,248**
Female, count	412	416	394	267	**1,393**
Male, count	569	524	506	404	**1,856**
Amount paid (estimated), noninvasive cardiac imaging	$509,656	$470,920	$455,855	$335,634	**$1,772,065**
Individuals	981	940	900	670	**3,248**
Average payments per individual	$533	$512	$515	$528	**$561**
Managed care (MC)					
Individuals with at least one noninvasive cardiac imaging	10,587	10,440	9,974	8,557	**36,263**
Female, count	5,474	5,365	5,016	4,297	**18,575**
Male, count	5,115	5,076	4,959	4,260	**17,694**
Amount paid (estimated), noninvasive cardiac imaging	$4,979,782	$4,414,031	$4,158,069	$3,627,905	**$17,179,787**
Individuals	10,314	10,211	9,772	8,297	**35,383**
Average payments per individual	$411	$333	$387	$371	**$410**
Public Employees Benefit Board Uniform Medical Plan (PEBB/UMP)					
Individuals with at least one noninvasive cardiac imaging-related procedure/service	6,175	6,227	6,174	5,758	**21,426**
Female, count	2,973	3,029	2,875	2,805	**10,506**
Male, count	3,202	3,198	3,299	2,953	**10,920**
Amount paid, noninvasive cardiac imaging	$3,607,911	$3,638,766	$3,698,590	$3,739,730	**$14,684,997**
Individuals	6,175	6,227	6,174	5,758	**21,426**
Average payments per individual	$598	$596	$613	$669	**$701**

Washington State Department of Labor and Industries (L&I)					
Individuals with at least one noninvasive cardiac imaging-related procedure/service	74	67	60	51	**249**
Female, count	13	NR	11	NR	**41**
Male, count	61	57	49	44	**208**
Amount paid, noninvasive cardiac imaging	$49,611	$43,603	$36,891	$38,631	**$168,735**
Individuals	74	67	60	51	**249**
Average payments per individual	$699	$692	$683	$788	**$718**
Washington State – Combined Medicaid, UMP, L&I					
Individuals with at least one noninvasive cardiac imaging-related procedure/service	17,817	17,674	17,108	15,036	**61,186**
Female, count	8,872	8,820	8,296	7,376	**30,515**
Male, count	8,947	8,855	8,813	7,661	**30,678**
Amount paid, noninvasive cardiac imaging	$9,146,960	$8,567,320	$8,349,405	$7,741,900	**$33,805,584**
Amount paid, by modality and procedure code					
SPECT	$5,500,304	$5,162,988	$4,886,019	$4,606,205	**$20,155,516**
Stress Test	$2,230,498	$2,058,511	$1,965,027	$1,821,426	**$8,075,462**
Stress Echocardiography	$945,737	$900,264	$954,111	$965,075	**$3,765,187**
PET	$180,756	$153,821	$223,613	$70,408	**$628,598**
CCTA	$133,228	$146,242	$188,466	$151,934	**$619,870**
Other Noninvasive Cardiac Imaging	$149,952	$134,222	$117,250	$125,351	**$526,775**
General Nuclear Imaging	$6,485	$11,272	$14,919	$1,500	**$34,176**

Data notes: Annual members for Medicaid excludes members that are dually eligible for Medicaid and Medicare. NR = not reported; small numbers suppressed to protect patient privacy. Managed care amount paid reflects an estimate of the amount paid for the procedure. UMP data does not reflect patient cost share. Individuals who had a procedure in more than one year are only counted once in the "Total" summary. Amounts paid of $0 were excluded from amount paid table value calculations. PET codes revised in 2020 were not included in utilization data; radiopharmaceutical codes for PET scans were not included.

Table 2. Demographics of Medicaid beneficiaries with at least one noninvasive cardiac imaging procedure, SFY 2017-2020

Age	Total (count)
20 years and below	452
21-44 years	10,204
45 years and above	28,865
Total	**39,384**

Table 3. Codes and cost by HCPCS/CPT code (maximum allowable), by state health program and setting

Code	Description	Medicaid FFS		L&I	
		Non-facility	Facility	Non-facility	Facility
75571	Computed tomography, heart, without contrast material, with quantitative evaluation of coronary calcium	$61.60	EAPG pricing	$199.40	$199.40
75572	Computed tomography, heart, with contrast material, for evaluation of cardiac structure and morphology (including 3D image post-processing, assessment of cardiac function, and evaluation of venous structures, if performed)	$146.21	EAPG pricing	$473.25	$473.25
75573	Computed tomography, heart, with contrast material, for evaluation of cardiac structure and morphology in the setting of congenital heart disease (including 3D image post-processing, assessment of LV cardiac function, RV structure, and function and evaluation of venous structures, if performed)	$196.41	EAPG pricing	Not covered	Not covered
75574	Computed tomographic angiography, heart, coronary arteries and bypass grafts (when present), with contrast material, including 3D image post-processing (including evaluation of cardiac structure and morphology, assessment of cardiac function, and evaluation of venous structures, if performed)	$211.41	EAPG pricing	$684.30	$684.30
78451	Myocardial perfusion imaging, tomographic (SPECT) (including attenuation correction, qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); single study, at rest or stress (exercise or pharmacologic)	$202.01	EAPG pricing	$653.87	$653.87
78452	Myocardial perfusion imaging, tomographic (SPECT) (including attenuation correction, qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); multiple studies, at rest and/or stress	$282.01	EAPG pricing	$912.83	$912.83

	(exercise or pharmacologic) and/or redistribution and/or rest reinjection				
78453	Myocardial perfusion imaging, planar (including qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); single study, at rest or stress (exercise or pharmacologic)	$181.81	EAPG pricing	$588.49	$588.49
78454	Myocardial perfusion imaging, planar (including qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); multiple studies, at rest and/or stress (exercise or pharmacologic) and/or redistribution and/or rest reinjection	$261.01	EAPG pricing	$844.86	$844.86
78459	Myocardial imaging, positron emission tomography (PET), metabolic evaluation	$816.02	EAPG pricing	$2,937.24	$2,937.24
78466	Myocardial imaging, infarct avid, planar	$120.01	EAPG pricing	$388.44	$388.44
78468	Myocardial imaging, infarct avid, planar	$115.41	EAPG pricing	$373.55	$373.55
78469	Myocardial imaging, infarct avid, planar	$134.01	EAPG pricing	$433.76	$433.76
78472	Cardiac blood pool imaging, gated equilibrium; planar, single study at rest or stress (exercise and/or pharmacologic), wall motion study plus ejection fraction, with or without additional quantitative processing	$136.41	EAPG pricing	$89.99	$89.99
78473	Cardiac blood pool imaging, gated equilibrium; multiple studies, wall motion study plus ejection fraction, at rest and stress (exercise and/or pharmacologic), with or without additional quantification	$172.81	EAPG pricing	$559.35	$559.35
78481	Cardiac blood pool imaging (planar), first pass technique; single study, at rest or with stress (exercise and/or pharmacologic), wall motion study plus ejection fraction, with or without quantification (single/multiple)	$105.21	EAPG pricing	$340.53	$340.53
78483	Cardiac blood pool imaging (planar), multiple first pass study at rest and stress, and requires two injections of appropriate radiopharmaceutical agent(s).	$144.01	EAPG pricing	$466.13	$466.13
78491	Myocardial imaging, positron emission tomography (PET), perfusion; single study at rest or stress	$1,502.51	EAPG pricing	$3,066.34	$3,066.34
78492	Myocardial imaging, positron emission tomography (PET), perfusion; multiple studies at rest and/or stress	$1,510.11	EAPG pricing	$3,097.99	$3,097.99
78494	Diagnostic nuclear medicine procedures on the cardiovascular system	$135.21	EAPG pricing	$437.64	$437.64

78496	Diagnostic nuclear medicine procedures on the cardiovascular system	$25.40	EAPG pricing	$82.22	$82.22
78499	Unlisted cardiovascular procedure, diagnostic nuclear medicine	By Report	EAPG pricing	By Report	By Report
93015	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; with supervision, interpretation and report	$41.40	Not covered	$134.01	$134.01
93016	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; supervision only, without interpretation and report	$12.80	Not covered	$41.43	$41.43
93017	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; tracing only, without interpretation and report	$20.00	EAPG pricing	$64.74	$64.74
93018	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; interpretation and report only	$8.60	Not covered	$27.84	$27.84
93350	Echocardiography, transthoracic, real-time with image documentation (2D, with or without M-mode recording), during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report	$111.61	EAPG pricing	$361.25	$361.25
93351	Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed	$138.21	EAPG pricing	$447.35	$447.35
93352	Echocardiography procedures	$19.80	Not covered	$64.09	$64.09

Data notes: Medicaid FFS from 10-1-2020 Physician-Related Services Fee Schedule and OPPS Fee Schedule (accessed October 1, 2021; webpage). L&I from 2020 provider fee schedule (accessed October 1, 2021). PEBB/UMP fees are confidential and not publicly available (proprietary).

Copyright Statement

2 Background

2.1 Nature and Burden of Disease

Coronary artery disease (CAD), also referred to as coronary heart disease (CHD) or ischemic heart disease (IHD), is a leading cause of death for both men and women in the United States and is the most common form of cardiovascular disease. The public health and economic burdens of CAD are substantial. It is estimated that around 20.1 million individuals in the United States 20 years or older have CAD, with a higher prevalence among males compared with females aged 60 and older.[251] Centers for Disease Control and Prevention (CDC) reported 690,882 deaths related to heart disease alone in the United States in the year 2020.[9] Estimates also suggest that roughly 720,000 individuals will have a new coronary event annually, and 335,000 individuals will have a recurrent event. Recent trends project an estimated incidence of 805,000 myocardial infarction events (605,000 new attacks, 200,000 recurrent attacks); roughly 21% (170,000 MIs) are estimated to be silent events.[251] Accordingly, CAD is associated with significant health system utilization and associated expenses. According to The National Ambulatory Medical Care Survey (NAMCS), around 11.1 million physician office visits occurred for CAD in 2016, and in 2018, 469,000 visits to the emergency department (ED) were identified as having a primary diagnosis of CAD. As of 2016, health care spending related to CAD was over $89 billion (54% public payer, 42% private payer, 4% out of pocket); around half (50%, or 44.5 billion) was attributed to inpatient care services and 24% (or $21.4 billion) was attributed to ambulatory care services. Selecting the appropriate assessment, testing, and treatment approach for an individual with suspected or known CAD has the potential to improve patient outcomes, patient satisfaction and optimal use of health system resources.

CAD is a disease of the blood vessels that supply the heart muscle. Atherosclerosis is the most common underlying cause of CAD and is the result of plaque buildup on artery walls. Plaque is a sticky, fatty deposit comprised of cholesterol and other cellular waste products. The buildup of plaque may partially or completely block blood flow in the coronary arteries via two primary mechanisms: 1) progressive narrowing of the vessel lumen and (2) thrombotic occlusion of the artery wherein the hard surface of the plaque tears away exposing inner fatty prothrombotic and platelet activating components at the site creating enlargement of the obstruction. The resulting decrease in blood flow can be chronic or acute and leads to a deficiency in the amount of oxygen and nutrients getting to the myocardium[50], which subsequently impairs the heart's ability to supply oxygenated blood to the body either at rest or during exertion. Atherosclerosis may lead to disruptions in normal vascular function, i.e., the ability to relax and constrict the artery walls or the microvasculature. Vascular dysfunction resulting from atherosclerosis can occur in instances of significant plaque buildup but may also occur in the absence of significant plaque in individuals with atherosclerotic risk factors or comorbidities such as diabetes, history of smoking, and sedentary lifestyle. Atherosclerotic plaque occurs commonly and is asymptomatic for years; symptoms usually don't occur until the artery is blocked by at least half. Most people with plaque will never develop clinical CAD. Ischemia and impaired function may also be present in the absence of observed obstruction on angiography.[103]

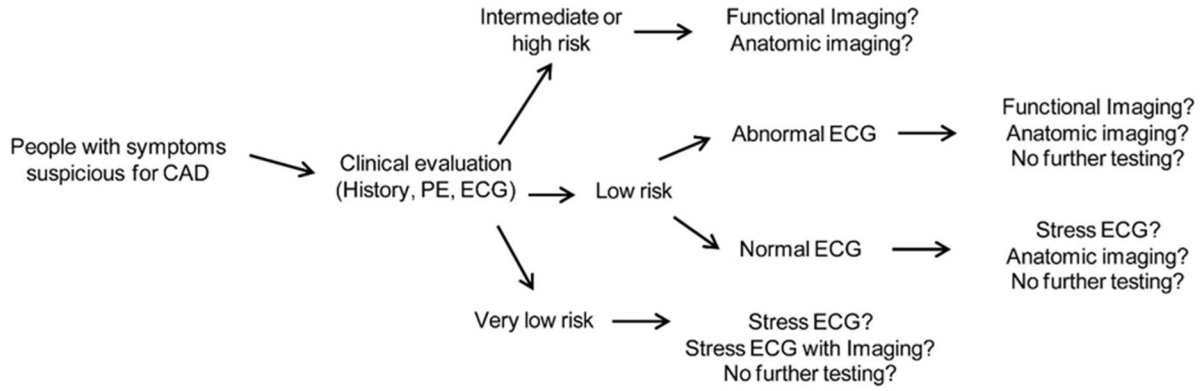
Chest pain (angina) is the most common symptom of obstructive CAD and is the first presenting symptom in most patients. Other symptoms of an acute coronary event related to CAD can include cold sweats, dizziness, light-headedness, nausea or feelings of indigestion, neck pain, shortness of breath, disturbances in sleep, and general weakness; common symptoms of chronic CAD may include shortness of breath with physical exertion, fatigue, and neck pain.[173] Plaque distribution, presence of collateral circulation and degree of vessel narrowing are factors which may influence symptom development and clinical impact of CAD; however, symptoms do not always correlate with lesion severity. For example, patients with obstructive CAD may be asymptomatic for many years (as has been observed in patients with diabetes) or may not present with symptoms until disease has progressed to the stage of heart failure.[118] It is estimated that roughly half of individuals who have a MI and no previous diagnosis of CAD did not report prior symptoms of obstructive CAD.[247] Studies have also shown that common symptoms of obstructive CAD are present in several noncardiac conditions such as gastroesophageal reflux, esophageal spasm, chronic obstructive pulmonary disease, and cervical disc disease, thus they are less reliable predictors of CAD. Non-specific symptoms may promote delayed testing or identification of obstructive CAD. Women and people with diabetes are less likely to experience classic angina, adding to the challenges of early CAD diagnosis in these populations.

2.2 Assessing risk of CAD

When assessing patients presenting with symptoms of CAD, their pretest risk or probability of CAD helps inform the choice and flow of testing. There are many available tools to assess pre-test risk of CAD, but the methods and models used can vary widely. Across included studies for this HTA, a wide variety of methods was used.

The American College of Cardiology (ACC) risk stratification model offers a framework for determining the likelihood that a patient's symptoms are related to obstructive CAD, according to age, sex and presenting symptoms.[71] Other factors, such as comorbid conditions (diabetes, hypertension, dyslipidemia) and the person's health history (smoking, family history of heart disease) may also be considered. A patient's chest pain symptoms are further characterized as typical, atypical, or non-anginal.[230] Risk groups are defined as low (<10%), intermediate (10% to 90%), and high (>90%). Patients assessed to be in the low to intermediate risk group comprises a broad spectrum of patients for whom a noninvasive test is usually recommended. Diagnostic challenges for intermediate risk patients will be discussed more the following section.

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



Evaluation of patient pre-test probability of CAD has traditionally been assessed according to the Diamond and Forester method[55], a validated risk prediction tool. Recent studies suggest the model may overestimate pre-test risk of CAD among low-risk patients.[38] New prediction tools and methods have since emerged to address concerns of applicability and relevance to certain populations and settings; however, they may not be commonly used in clinical practice and may not prevent unnecessary invasive treatment and testing.[42,150] An assessment of patient history and physical evaluation remains the most routinely used to determine a patient's risk of CAD and is most cost effective. In accordance with the core factors identified in Diamond and Forester and current guidelines, clinicians typically consider patient age, sex, and current symptoms (such as type of chest pain) when assessing pre-test risk of CAD. Recent studies suggest that clinical discretion to defer testing among patients with low pre-test risk of CAD may decrease unnecessary studies and downstream treatments.[221]

In the emergency department setting, the HEART risk score (History, Electrocardiogram, Age, Risk factors, Troponin) is frequently utilized to objectively assess pre-test probability of CAD to support clinical decision making. The AHA recommends this assessment approach in the ED; however there remains uncertainty about the ideal thresholds to define low, moderate, and high pre-test risk to prevent unnecessary testing and invasive procedures.[219] In this setting, clinician assessment of type of chest pain is often a primary factor when determining the course of care, if electrocardiography (ECG) or troponin test results are unclear; however, this subjective assessment may not be accurate in correctly distinguishing patients for next line testing.[12,28,32] Other risk assessment and clinical decision-making tools have been developed for patients presenting with acute coronary syndromes (ACS) (e.g., Global Registry of Acute Coronary Events [GRACE], thrombolysis in myocardial infarction [TIMI] risk scores), but evidence suggests they may not prevent unnecessary care and may increase early invasive testing and treatment.[12,39]

The effectiveness of non-invasive imaging tests is influenced by patient pretest probability/underlying disease prevalence which impacts test performance for measures that are influenced by disease prevalence. The choice of test is influenced by pre-test probability. For example, in patients at high risk of CAD invasive testing is typically the approach taken. In contrast, Anecdotally, in patients with a low

pre-test probability of CAD, CCTA may be more likely to be used, while in patients with intermediate to high pre-test probability, stress echo or SPECT may be more frequently used and be more predictive of CAD presence, based on general precepts from the ACCF/AHA 2012 guideline. For any test, in patients with low pre-test probability of CAD, the number of potential false positive results necessitating further follow-up needs to be weighed against the potential for accurate detection of CAD. In some included RCTs, the frequency of MI and death was low, reflecting the low pre-test probability in these trials. In these instances, the benefit of testing may be unclear as the event rate in a low-risk population would likely be similar whether or not testing was employed.

2.3 Diagnosis of CAD

Accurate and early assessment of patients with symptomatic CAD is important for risk stratification and initiation of appropriate treatments to reduce morbidity and mortality. Noninvasive techniques used to diagnose CAD fall into two general categories, those that evaluate the anatomical aspects of vessel occlusion and those that evaluate the impact of occlusion on cardiac function. Each has strengths and limitations. Noninvasive anatomic tests provide information on location and extent of blockage and include coronary CT angiography (CCTA) and cardiac magnetic resonance imaging (CMRI). Functional tests allow assessment of whether symptoms are correlated with narrowing leading to ischemic areas and include exercise ECG, exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single-photon emission computed tomography (SPECT) or positron emission tomography (PET). There has been recent interest in using pharmacologic stress with magnetic resonance imaging (MRI) or computed tomography (CT perfusion imaging) and in determining fractional flow reserve (FFR) with CT. The choice of testing is dependent on a variety of patient and other factors, particularly in patients with stable CAD. The patient's pre-test probability of CAD in addition to accuracy of the test and the likelihood that test results would change management and lead to better outcomes are important considerations, as outlined above. Clinical decision-making regarding choice of test(s) needs to include consideration of the potential for additional/downstream testing, availability of other tests, cumulative radiation exposure and how results will inform appropriate management strategies and lead to improved outcomes while avoiding risks of testing such as additional radiation, false positives and incidental findings. There remains a lack of consensus regarding a single testing strategy or sequence of testing for the diagnosis of CAD, particularly for those at low to intermediate pre-test risk.[19] Low to intermediate pre-test risk as defined in the ACC/AHA guidelines (10% to 90%) may overestimate pre-test risk and observed prevalence has been shown to be much lower in real world clinical setting.[38] It also constitutes a very wide range of CAD risk. There is also recent evidence that suggests guidelines that focus on symptomology at presentation, as opposed to guidelines that take a more formal risk-based assessment, may safely characterize as low risk and prevent unnecessary testing.[5]

Historically, in the outpatient setting, the exercise stress test is used as a gatekeeper to more invasive cardiac testing, though the evidence is unclear on the prognostic benefit for patients with suspected CAD.[206,222] With the advent of low risk, non-invasive cardiac tests, there is a debate about the optimal diagnostic testing strategies for patients with suspicion of CAD[34,201,221] or known CAD. Some experts question the need for testing particularly among low-risk patients. Guidelines and expert opinion are

mixed when it comes to defining the current reference standard among non-invasive cardiac tests.[199,222] ACCF guidelines and ACR AUC recommend that for patients with suspected CAD and stable chest pain who are capable of physical exertion and an interpretable ECG, an exercise stress test with ECG or echocardiogram is the preferred first test among patients with intermediate pre-test probability.[71,222,259] However, NICE updated their guidance in 2016 to remove formal pre-test probability scoring and advised CCTA as the first line diagnostic test for all patients with suspected CAD presenting with chest pain or non-anginal pain with an abnormal electrocardiogram, prior to moving to functional testing as needed.[129] The 2019 ESC guidelines recommend non-invasive functional imaging, or CCTA, as the first line test for suspected CAD; like ACCF guidelines, if the first line CCTA test is equivocal, then functional imaging is recommended.[132] For patients that present to the ED with suspected ACS, CCTA has emerged as the predominant test to differentiate patients at high risk of a serious cardiovascular event.[12,18] High sensitivity troponin assays are increasingly used as a first line noninvasive test to rule out an acute coronary event. The utilization of biomarkers such as troponin may have implications for if and when noninvasive imaging, such as CCTA, is utilized in this setting.[260]

Exercise electrocardiogram treadmill testing (ETT) and the imaging tests CCTA, stress nuclear imaging and stress echocardiography have become established as diagnostic tests for CAD. The focus of this HTA is on the imaging tests and will not include ETT, except as a comparator test. As established testing modalities, the focus will be on evaluating their impact on clinical decision making for directing management that leads to improved patient outcomes. This HTA does not evaluate specific sequences of tests or incremental benefits of adding a specific test to another given the lack of consensus across the cardiology community and vagueness of evidence-based clinical guidelines.

2.4 Technologies and interventions

Given the invasive nature and risks associated with coronary angiography, non-invasive methods of assessing presence of CAD are important. All noninvasive methods have strengths and limitations. There is a continued debate with respect to the roles of various non-invasive tests in both ED and outpatient settings, such as which test should be the first-line test, and which test to use subsequently based on findings of the primary test. In the ED, the goal is to quickly identify patients without CAD who can be discharged, which reduces the need for ICA referral and observation. In an outpatient setting, the focus is on appropriate testing of patients presenting with stable, non-emergent symptoms of suspected CAD. Among patients presenting with stable CAD, there is no definitive algorithm for determining which imaging test to use based on patient outcomes and costs; variations in guidelines present additional complexity for clinical decision making.[250]

2.4.1 Invasive coronary angiography

ICA (also called coronary catheterization) is a 20-to-30-minute procedure where X-rays are taken of the heart's arteries while radiopaque contrast is injected simultaneously via catheter inserted in the wrist or groin artery. ICA provides information about the anatomy of the coronary arteries and size and location of obstructions in the lumen, as well as areas that may be stenotic. This information, taken together, helps to quantify the degree of disease that may be present. When determining a diagnosis of CAD,

thresholds of anywhere from ≥50% to ≥70% occlusion have been used. The rate of nondiagnostic or indeterminate studies from ICA is estimated to be 10%.[27] Potential harms include exposure to radiation, allergic reaction to contrast dye, bruising at site of catheter insertion; major harms are rare but may include arrythmias, blood clots, heart attack or stroke, and very rarely, death.

As stated previously, the advantage of ICA is that it provides accurate information about blockages in the heart's arteries and help identify reasons why the heart may not be functioning correctly. Historically, ICA has been considered the standard reference diagnostic test for anatomic CAD. However, an increasing body of evidence suggests it is an imperfect diagnostic standard. While size and location of plaques are visible, plaques with characteristics that may indicate high risk for future coronary events are not evident when reviewing images obtained from ICA, limiting the prognostic value of the test.[230] Only about 41% of patients undergoing elective procedure of catheter-based coronary angiographies are diagnosed with obstructive CAD.[202] A long-known limitation of the test is in the interpretation of results, due to variation in interobserver and intraobserver findings.[49,214,265] One study however suggests substantial interobserver agreement based on per-segment analysis.[31] There may be issues with accuracy, as evidence has shown that for lesions with less than 60% percent stenosis there may be significant under or over estimation of the severity of lesions.[242,254] Toth et al. similarly found the 50% threshold for the left main region significantly underestimated legion severity when compared to fractional flow reserve.[242] While there have been technological advances for decreasing radiation contrast toxicity and improving effective diagnosis with ICA in the past few decades, potential sources of error due to the equipment operation, technical interpretation, and natural biological fluctuations that may occur in response to the dye or during the procedure, remain. As noted elsewhere, expertise for performance and interpretation is important with all tests for CAD.

2.4.2 Coronary Computed Tomography Angiography

CCTA is a noninvasive, relatively quick anatomic imaging test that obtains x-ray images of the heart. Using contrast dye (iodine-based), images taken by CCTA will visualize the structure of the heart and any obstructive disease present in the heart's anatomy. Many hospitals have access to the machine and complimentary software packages used to process images and state of the art machines have a 64-slice or greater scanner. CCTA is typically used to rule out CAD diagnosis in patients with chest pain and low pretest probability of disease due to its perceived high negative predictive value and high sensitivity. It is also recommended for patients with atypical symptoms, with nondiagnostic results of a stress test or at high risk of catheterization. Abnormal findings on CCTA are defined as any irregularities of the lumen, which will determine next steps in prevention of disease progression and other possible disease sequalae. High risk findings on CCTA are typically defined as ≥50% stenosis in the left main region, proximal LAD stenosis ≥70%, or 3 vessel disease. CCTA is also useful for identifying causes of chest pain unrelated to heart function. The rate of nondiagnostic or indeterminate studies from CCTA imaging is estimated to be 2%.[27]

Key disadvantages to CCTA include exposure to radiation, moderate specificity (60-80%), and issues around diagnostic image quality.[52] There are quantification challenges due to cardiac motion artifact, "bloom artifact" due to calcification, and uncontrolled or irregular heart rate. Optimizing temporal

resolution can be challenging. In addition, distal vessels may be difficult to visualize. Furthermore, CCTA as a standalone test will not confirm ischemia. Regarding harms, aside from exposure to low levels of radiation during the procedure, some patients may experience allergic reaction to the contrast dye, and additional consideration is taken for patients with impaired renal function. Incidental findings on CCTA are not uncommon and can sometimes lead to unnecessary worry for the patient.

2.4.2.1 Fractional flow reserve (FFR) with coronary computed tomography angiography (CTTA)

FFR CT combines the anatomic coronary CT test with a functional test of coronary artery blood flow, providing both a quantification of anatomical obstruction and a calculation of pressure and flow for all coronary artery branches. FFR is defined as the ratio of maximum flow in a stenotic artery to maximum blood flow if the same artery were normal. Thus, the pressure measurements at the distal vessels illustrate the cumulative loss of pressure or blood flow and the effect of any diseased tissue near where the measurement is taken.[178] This relatively new combination approach requires previously acquired CT images of good image quality and there remains uncertainty about the extent to which biological factors affect test accuracy.[67] Currently, the only Food and Drug Administration (FDA) approved device/software for measuring FFR during either ICA or CCTA is Heart Flow. Information on the diagnostic accuracy of FFR CT can be found in the Contextual Question section of this report.

2.4.2.2 CT perfusion imaging

Like FFR CT, stress myocardial computed tomography perfusion (CTP) is a novel examination that provides both anatomic and physiological information (i.e., myocardial perfusion). CTP assesses blood flow distribution to the different regions of the myocardium at rest and after stress by using coronary vasodilator agents (adenosine, dipyridamole, or regadenoson), similarly to other non-invasive imaging techniques such as nuclear imaging myocardial perfusion imaging (MPI).[170] CTP utilizes iodinated contrast which attenuates X-rays proportionally to iodine content in tissue. Thus, myocardial perfusion defects can be directly visualized as hypoattenuating or non-enhancing areas containing reduced amounts of contrast material.[78] Information on the diagnostic accuracy of CTP can be found in the Contextual Question section of this report.

2.4.3 Nuclear stress imaging (myocardial perfusion imaging)

Nuclear stress imaging is a functional, non-invasive imaging test that shows how well blood flows through (perfuses) the heart muscle. It can show areas of the heart muscle that aren't getting enough blood flow by evaluating how well the heart muscle is pumping. It does not directly visualize the coronary arteries. This test is often called a nuclear stress test. There are 2 techniques for MPI: SPECT and PET. Both require injection of radioactive tracers (called radionuclides) which transmit radiation, allowing a specialized camera to take images of the heart that can be converted by a computer program for interpretation.

2.4.3.1 Single Photon Emission Computed Tomography (SPECT)

SPECT is a noninvasive nuclear imaging test. After injection of radionuclides (99mTc- sestamibi or 99mTc- tetrofosmin) into the blood, thin slice images of the heart are taken as a camera detects signals from the tracers and a computer program translates this information into 3-D images. Imaging takes about 20 minutes, with the stress imaging (exercise or pharmacologic) occurring 1 hour after the rest study is complete; overall, the rest-stress protocol is typically completed over 3-4 hours and may be completed in one- or two-day protocols. SPECT can show how well blood is flowing to the heart, how well the heart is working, and whether the patient previously experienced a heart attack. Providers can assess the ventricular size and function, wall motion abnormalities, and overall viability of the heart. SPECT can be used to diagnose CAD. It is a preferred approach for patients with left bundle branch block and is useful for patients with poor echocardiography windows. The rate of indeterminate studies from SPECT imaging is estimated to be 6.9%.[27,220] Compared to other noninvasive methods such as ECG, SPECT provides improved sensitivity and specificity. SPECT can also be used to inform decisions about treatment or therapy, based on findings.

Abnormal findings on SPECT are defined as detection of any perfusion defect and any wall motion abnormalities. High risk findings include a perfusion defect impacting ≥10% of heart tissue, more than one perfusion of moderate concern, a large, fixed defect with transient left ventricular dilation or increase in lung to heart ratio, or a stress induced defect of moderate severity with transient ischemic left ventricular dilation or increase in lung to heart ratio. SPECT results can be limited by soft tissue attenuation and motion artifact. SPECT is also limited in the quantification of blood flow since it measures relative flow, as opposed to absolute flow (and may miss three vessel disease). Harms may include exposure to some radiation from radionucleotides.

2.4.3.2 Positron Emission Tomography (PET)

PET is a noninvasive nuclear imaging test. Radionuclides (15O, 82Rb, 13NH3 or 18F- flurpiridaz) are injected into the blood, and a PET scanner will detect the radiation released by the tracer to produce images of the heart.[54] PET scans can identify diseased or damaged tissue, as well as healthy tissue, and assess whether enough blood is flowing through the heart. Scans take about 30-60 minutes, and the full rest-stress protocol may be completed in either 1 or 2 days. PET scans can be used to diagnose CAD and can identify damage to the heart due to heart attack. PET assesses ventricular size and function, as well as ischemia and viability. PET is also used to determine which patients may benefit from PCI, CABG, or another treatment. PET is the preferred approach for assessment of suspected CAD in women and patients who are obese. Abnormal findings on PET are defined as any perfusion defect. High risk findings are defined as a perfusion defect ≥10% of heart tissue, with particular attention to the anterior myocardium. The rate of indeterminate studies from PET imaging is estimated to be 4%.[220]

PET provides a more accurate assessment of blood flow than SPECT, due to measurement of absolute blood flow with trace kinetic modeling and attenuation correction. PET scans also have high image quality, which support clearer interpretation of findings. Regarding disadvantages, PET scans are expensive, and PET scanners are less available than other noninvasive imaging technologies in clinical

settings due to space and storage requirements. PET scans are limited to pharmacologic stress. Harms may include allergic reaction to the radioactive tracers and minimal exposure to radiation. Patients who are claustrophobic may be uncomfortable during a PET scan.

2.4.4 Stress echocardiography

Echocardiography is a noninvasive test that uses high frequency sound waves (i.e., ultrasound), to produce live images of the heart. Stress echocardiography is an established technique for assessing CAD. It evaluates how the well the heart is functioning under stress and is commonly used to identify areas of the heart affected by ischemia; the coronary vessels are not directly visualized, however. Stress can be induced by either exercise (stationary bicycle or treadmill) or pharmacologic agents (dobutamine typically). The major advantages of stress echocardiography are that the test protocol is simple, inexpensive, takes a relatively short amount of time to complete and it does not expose the patient to radiation, unlike other noninvasive imaging techniques. However, it tends to be less sensitive in detecting single vessel disease or mild stenosis since a significant amount of myocardium needs to be affected by ischemia for the test result to be positive; specificity has been, on average, somewhat higher than nuclear cardiology techniques and exercise ECG. Stress echocardiography also requires a high level of expertise to achieve accurate and reproducible results. Interpretation of findings may be limited by image quality, and it does not allow for quantitative analysis.

Abnormal findings on stress echocardiography are defined as new wall motion abnormalities and abnormal left ventricular ejection function during stress. High risk findings include left ventricular ejection function <35% (rest or exercise), wall motion abnormalities that include a minimum of 2 segments that develops with either exercise or pharmacologic stress, more than two segments displaying wall motion abnormalities at heart rate of <120 bpm, or evidence of severe ischemia during the stress test. The rate of nondiagnostic or indeterminate studies from stress echocardiography imaging is estimated to be 15%.[27,98]

2.4.5 Hybrid tests

Diagnostic tests that combined more than one imaging type also were considered if at least one component focused on myocardial perfusion, including PET/CT, and SPECT/CT. All of these tests are performed in conjunction with exercise- or pharmacologically-induced stress.

2.4.6 Harms

Primary harms identified for noninvasive imaging for suspected CAD include radiation exposure, reactions to stressor or contrasts agents used during the imaging test, possibility of incidental findings unrelated to heart disease, and multifaceted effects of downstream testing.

2.4.6.1 Radiation exposure

Radiation exposure is a measure of the quantity of ionization produced in air by photon irradiation. Radiation dose ("absorbed radiation dose") refers to the amount of radiation energy deposited in the human body as a result of exposure to ionization and is typically calculated from the exposure and from estimates of energy absorption per kilograms of body weight.[167]

Medical imaging is the largest controllable source of radiation exposure in the United States.[79] Cardiovascular-related tests and procedures comprise about 40% of all medical radiation exposure.[107] There is conflicting evidence regarding the risk of developing cancer at the levels and types of radiation associated with medical imaging and with the exception of mammography, there is currently no federal regulation of patient radiation dose.[167] 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. Patient-centered shared decision making can prompt a discussion and improve transparency and education related the justification for the test, expected level of exposure to radiation, and steps the laboratory has taken to optimize the radiation dose used.[62]

As cardiac imaging has increased over time, there are concerns about the effects of increased radiation not only on a test-by-test basis, but also in consideration of the cumulative exposure across other tests that may be utilized as part of a patient's course of care. Excluding radiation therapy, the average per capita radiation exposure from medical sources increased 6 times from the period 19080-1982 to 2006.[61,212] In response, the National Council on Radiation Protection issued a report in 2017 indicating that the steep increase in imaging procedures may have plateaued, and that greater awareness of radiation risk may be a factor. However, large scale registries and international studies have shown wide variation in average radiation dose per procedure, indicating at least one area for improvement in and implementation of best practices (e.g., standard reporting, regional diagnostic reference levels) to minimize or reduce radiation exposure.[106]

A variety of factors can affect the radiation dose administered for a given test, including the model of the machine, the length of the scan, the number of scans, if gating is used, x-ray tube potential, tube current-time product, and patient size.[30] The values in the following table (Table 4) 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

Radiation Exposure Type			Total Effective Dose (mSv)
	ICA	Range reported by Einstein 2014	2–20
		Range reported by ACR	1–10 (with or without ventriculography)
		Carpeggiani, 2017†	Mean (SD): 9.64 (9.7)
	CCTA	Range from studies included in Skelly 2016 (AHRQ 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
		Hirshfeld, 2018 (consensus document)‡	Helical, no tube current modulation: 8.0 to 30
			Helical, tube current modulation: 6.0 to 20
			Prospectively triggered axial: 0.5 to 7.0
			High-pitch helical: <0.5 to 3.0
		NICE, 2016 (guideline)	2.0 to 5.0
		Carpeggiani, 2017†	Mean (SD): 11.2 (8.1)
		Husmann, 2010	2.1 (0.7)
		Pursnani, 2015	All protocols and scanners: 9.9 (4.9)§
			Prospectively gated CCTA: 6.5 (3.8)
			Retrospectively gated CCTA: 10.4 (4.9)
			128-slice DSCT (n=78): 5.7 (3.7)
			CT scanners, excluding 128-slice DSCT: 10.7 (4.7)
		Mettler 2020 (non-cardiac CCTA)	Based on ICRP Publication 60 tissue weighting factors: 5.4
			Based on ICRP Publication 103 tissue weighting factors: 5.4
		Studies included in this report	Studies reporting mean effective dose: 5.3 to 12.7
			Studies reported median effective dose: 3.5 to 11.8
	Fluoroscopy for PCI	Range reported by Einstein 2014	5–57
	PET	Range from studies included in Skelly 2016 (AHRQ report)	6.0
		Range reported in Einstein	2 (^{13}N ammonia); 4 (^{82}Rb); 7

Radiation Exposure Type			Total Effective Dose (mSv)
		2014	(^{18}F FDG – not currently FDA approved)
		Carpeggiani, 2017†	Mean (SD): 1.4 (0.7)
	SPECT	Range from studies included in Skelly 2016 (AHRQ 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)
		Carpeggiani, 2017†	Mean (SD): 10.0 (2.7)

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

*Adapted using data from[33,35,62,63,79,95,107,110,112,156,157,177,198,230]

† Based on 476 exams with primary aim to detect and characterize ischemic heart disease performed as part of the RADIationdOse subproject of the EVINCI study. Doses varied substantially across 12 study centers)

‡ The data included in this consensus document were reproduced with permission from Einstein, 2014.

Einstein AJ, Berman DS, Min JK, et al. Patient-centered imaging: shared decision making for cardiac imaging procedures with exposure to ionizing radiation. J Am Coll Cardiol. 2014 Apr 22;63(15):1480-9. PMID: 24530677.

2.4.6.2 Contrast materials

Contrast materials are used to better visualize the endocardium and improve interpretability and diagnostic accuracy of noninvasive imaging tests. Contrast materials may lead to decreased renal function or have serious adverse effects in persons with impaired renal function at baseline. Contrast induced nephropathy (CIN) is associated with reduced renal function within 48-72 hours of IV contrast administration. Definitions of CIN have varied over time, and other risk factors for CIA have been proposed in addition to renal insufficiency (e.g., diabetes, dehydration).[255] Patients may experience allergic reactions to iodine-based contrast agents, such as hives, rash, or anaphylaxis. There is evidence that allergic reactions may be infrequent; one study suggested roughly 1.7% of patients experienced an allegoric reaction (mild to severe) during the CCTA test.[23] Similarly, some studies of contrast use in stress echo suggest similar adverse event rates and infrequent allergic reactions when comparing patients who received contrast and those that did not.[4,15] Patient risk for adverse reaction to contrast should be considered when selecting the test technique.

2.4.6.3 Pharmacologic stress agents

Pharmacologic stress agents are used in noninvasive cardiac imaging when a patient does not have the capacity to undergo exercise induced stress, or for MPI tests such as PET (since the radionuclides used

for PET tests have a short half-life, pharmacologic stress is required). Agents include dobutamine (which increases coronary flow reserve in a manner similar to exercise), and coronary vasodilators, such as adenosine, dipyridamole, and regadenoson. Use of pharmacologic stress agents requires patients to limit caffeine intake prior to the test and may necessitate temporary halting of any cardiac medications to minimize risk of interfering with test procedures or results.[183] Side effects of pharmacologic induced stress include dizziness and chest pain; however, the safety profile of specific agents may be lacking in specific subpopulations or patients with certain conditions (e.g., obesity, history of seizures).[65]

2.4.6.4 Incidental findings

Some noninvasive imaging modalities, including CCTA, image other non-cardiac structures, such as the lungs, bones, and upper abdomen. Findings of pathologies unrelated to the heart may be incidentally identified when reviewing the test output. The most common extracardiac findings are pulmonary nodules; other common emphysema, pulmonary infiltration, hiatal hernia, and aortic abnormalities.[125] This can lead to additional specialty referrals and possible invasive procedures. Studies of patients undergoing CCTA suggest that any incidental extracardiac findings are common (range 28-35% of patients); one study suggested that 21% of incidental extracardiac findings led to additional clinical follow up or testing, and that the number of extracardiac findings was associated with increasing patient age and greater experience of the clinician reading the scan.[24,124,200] The potential for identification of other non-cardiac related pathologies is a factor to consider when deciding on a noninvasive diagnostic testing strategy for suspected CAD. The follow-up of incidental findings requires additional resources.

2.4.6.5 Subsequent testing

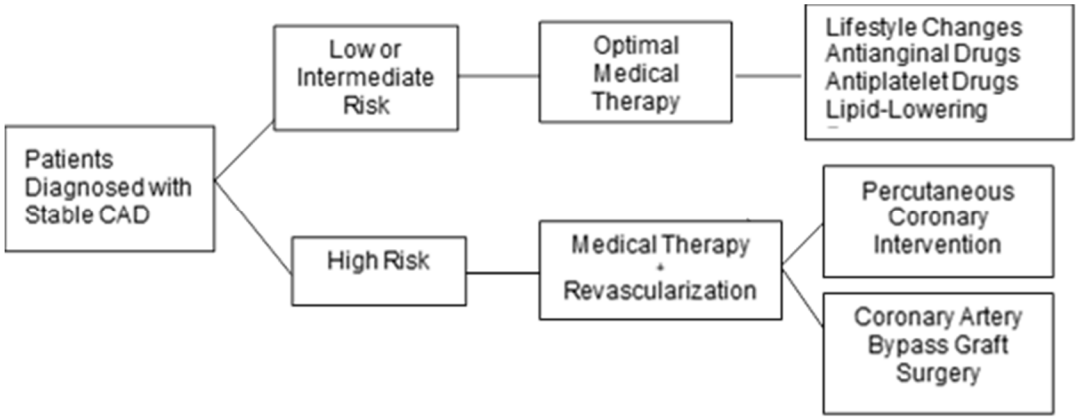
Downstream testing may be ordered if findings are equivocal or indeterminant. Additional testing may increase risk of false positive findings, increase patient anxiety, increase cost of care, and increase potentially avoidable tests.

2.5 Management

This HTA focuses on noninvasive imaging modalities as diagnostic tests for patients with symptomatic CAD. For a diagnostic test to be of value, it must lead to use of effective and appropriate treatments that impact patient outcomes. Where treatment outcomes are comparable, a treatment with higher specificity is a judicious choice to prevent a false positive result. Patients tested for symptomatic CAD have a variety of treatment pathways available and may be referred to different options depending on findings of the diagnostic test. A comparison of referral for treatment by noninvasive imaging modality critical to understanding how utilization of strategies affect the clinical course for the patient.
Once results of the diagnostic test are available, the patient risk of can be calibrated, in combination with pertinent patient history, symptoms and pre-existing comorbidities. Guidelines recommend categorizing patients into three primary risk groups according to their predicted risk of cardiac mortality per year, with low risk defined as <1% , intermediate risk as 1%-3% per year, and high risk defined as >3% rate of cardiac death annually among comparable patients. Patients determined to be at low or

intermediate risk are recommended medical therapy; more intensive revascularization procedures are reserved for patients categorized as high risk, based on their diagnostic test findings. Ultimately, the goal of treatment for stable CAD is to reduce the probability of death or other complications related to CAD, while optimizing the health, well-being, and function of the patient by minimizing symptoms. These considerations are balanced with the preferences and treatment goals of the patient.[71]

Figure 2. Initial treatment pathways for patients diagnosed with CAD



2.5.1 Optimal medical therapy

Optimal (or guideline-directed) medical therapy is optimized on a per-patient basis depending on patient characteristics and guideline recommendations. This may include lifestyle changes to physical activity, smoking cessation, weight management and diet modifications. Therapy will also encompass treatment of comorbidities that can affect (or be affected by) disease progression (e.g., diabetes, hypertension). Evidence suggests that 90% of the risk of having an MI is associated with modifiable risk factors, such as diabetes, smoking, hypertension, obesity; lifestyle modifications are a prudent foundation of any treatment approach for symptomatic CAD.[261] Other risk management strategies may be included, such as antiplatelet drugs and lipid-lowering drugs. Management of comorbidities with appropriate pharmacologic treatment can prevent further plaque buildup, rupture, and thrombosis.[71,232] To support relief of chest pain symptoms, beta-blockers, calcium channel blockers, nitrates, or ranolazine may be prescribed. These drugs reduce oxygen demand by the heart and aim to prevent the occurrence of anginal episodes; there is evidence suggesting up to 50% reduction in anginal episodes for use of beta-blockers and calcium channel blockers, but effect on serious cardiovascular outcomes is uncertain.[253] Medical therapy may be recommended alone, or in addition to revascularization procedures. Evidence suggests that for patients referred for revascularization procedures (along with medical therapy) a reduction in death was not observed, when compared to patients referred to medical therapy alone.[233] The recent ISCHEMIA trial found that patients with moderate to severe ischemia randomized to invasive treatment (revascularization) experienced increased rates of early MI and similar rates of death, when compared to patients randomized to medical therapy only.[152] Most patients with

symptomatic CAD will benefit from comprehensive and personalized guideline directed medical therapy, allowing for the prevention or deferral of unnecessary invasive procedures.

2.5.2 Revascularization

Revascularization methods include coronary artery bypass graft surgery and percutaneous coronary interventions (PCI). The selection of the type of procedure depends on patient presentation and diagnostic findings, as well as patient history. The severity of CAD and related anatomic features, such as the number of vessels involved and the spread and scale of stenosis, is a primary consideration when determining if the patient is a suitable candidate for a particular revascularization approach. The SYNTAX score is recommended as a tool to characterize the complexity, scale, and scope of CAD. In addition to other patient characteristics including age, findings of peripheral vascular disease and whether the patient has a history of smoking are important factors. Revascularization procedures aim to reduce risk of future serious cardiac events and death and have demonstrated success in reducing the risk of death in patients with severe left main artery stenosis, and patients determined to be at highest risk for poor cardiovascular outcomes.

Percutaneous coronary interventions (PCI) are non-surgical, invasive procedures to reduce the narrowing or obstruction of affected coronary arteries to improve blood flow to the heart tissue. PCI involves insertion of a catheter through a main artery to the site of the affected vessel, guided by x-ray images of the heart and the use of contrast dye. There, a device, such as a balloon, is used to open the vessel; a stent may be placed to keep the vessel open. The procedure is performed in a catheterization lab and can take 1-3 hours. A variety of PCI have emerged beyond the standard balloon angioplasty, such as angioplasty with implantation of bare metal stents or drug eluting stents. The introduction of drug eluting stents aims to prevent formation of scar tissue at the site of the stent placement to preserve blood flow and prevent development of further stenosis.

There is mixed evidence on which patient groups may benefit most from PCI, compared to medical therapy alone. There is some evidence suggesting improvement in angina symptoms and events, compared to medical therapy alone.[71] The evidence is less clear for prevention of serious cardiovascular events. One meta-analysis suggested that for patients with symptomatic CAD with ischemia identified by functional diagnostic testing, a significant reduction in death or nonfatal MI was not observed among those treated with PCI (with medical therapy) compared to patients who received medical therapy alone.[236] More recently, a meta-analysis of 10 797 patients with obstructive CAD and ischemia yielded similar results – patients treated with PCI (with medical therapy) did not experience a significant reduction in nonfatal MI, compared to patients who received medical therapy alone at median follow-up of 5 years.[233] This is concordant with earlier trials where the reduction in death and serious nonfatal events from PCI, vs medical therapy lone, yet to be clearly proven.[127,128,244]

Coronary artery bypass graft surgery (CABG) is a surgical procedure to divert blood flow from stenotic or obstructed vessels to improve blood flow to the heart. The procedure involves grafting arteries or veins from another part of the body, such as mammary arteries, radial arteries, or greater saphenous veins, to above and below the ischemic area of the heart. The typical duration of the procedure is 3 to 6

hours. Recent studies in patients with symptomatic CAD suggest that CABG (with medical therapy) appeared to reduce nonfatal MI compared to medical therapy alone; this was not observed when comparing PCI to medical therapy alone.[233] Patients undergoing CABG have a higher rate of complete revascularization, compared with patients undergoing PCI, which has been suggested as an explanation for the observed improved outcomes among patients who undergo CABG vs. PCI long term.[121] CABG may be preferred in patients where the primary goal of treatment is reduction in risk of mortality.

ACC guidelines recommend CABG for patients with significant left main coronary stenosis but suggest PCI as an alternative when patient has low risk of complications with PCI, and clinical factors that would suggest an increased risk of poor surgical outcomes.[71] When comparing PCI to CABG, trials suggest that while survival is similar at 1 and 5 years, relief of chest pain may be more effective with CABG than with PCI at 1 and 5 years, and repeat revascularization was less frequent for patients with CABG than those with PCI.[29]

2.5.3 Management of acute coronary syndromes

The primary goal of treatment for patients presenting with acute coronary syndromes is to relieve pain, improve blood flow and restore heart function as quickly as possible. This typically requires a combination of medical therapy and revascularization, depending on the type of acute coronary syndrome. In patients presenting with STEMI, non-STEMI or unstable angina, revascularization with PCI is considered appropriate if presenting within the first 12 hours of symptom onset.[190] All patients will receive guideline-directed medical therapy as well. Due to the acute presentation of the patient, if PCI is not available or patient is a suitable candidate for PCI then fibrinolytic therapy is recommended (for STEMI only). For non-STEMI patients, pharmacologic therapy, such as antiplatelet therapy and anticoagulants is recommended no matter the initial treatment strategy. Other pharmacologic treatments for either STEMI or non-STEMI may include beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers.

2.6 Previous Systematic Reviews of Noninvasive Cardiac Testing for Suspected CAD

Systematic reviews (SRs) were found by searching PubMed, the Cochrane Database of Systematic Reviews, and the ECRI Guideline Trust from database inception to March 23rd, 2021. Reference lists of relevant studies and the bibliographies of SRs were hand searched. See Appendix B for search terms and full search strategy.

Twelve SRs evaluating the effectiveness and/or safety of noninvasive cardiac stress testing in adult patients with suspected coronary artery disease (CAD) (stable or acute) were identified. Of these, eight included high-quality evidence (i.e., RCTs only) of which four were considered to provide the most comprehensive summary of the evidence to date, including trials summarized in the prior HTA and those published subsequently and are summarized below (Table 5).[73,113,227,228] Studies contained in these reviews that met inclusion criteria for this HTA were included. All four SRs provided quantitative syntheses; three did meta-analyses of head-to-head trials[73,113,227] and one conducted a network meta-analysis[228]. All four SRs compared CCTA with functional testing; in addition, the network meta-analysis compared one functional stress test versus another.

Across all three SRs evaluating head-to-head trials, compared with functional stress imaging, CCTA as an initial diagnostic strategy was associated with a reduced incidence of myocardial infarction (MI) but an increased incidence of downstream invasive procedures (i.e., ICA and revascularizations), with no difference in mortality. One SR also reported a reduction in downstream noninvasive testing with CCTA. Similar results were seen across the subgroups of stable chest pain and acute chest pain. One SR[73] evaluated the extent to which stable and unstable patients had different risk estimates by performing a formal test for interaction and found no difference between the two populations. The network meta-analysis found similar results regarding increased ICA and revascularization rates with CCTA versus any functional testing, but no difference in the risk of future MI in either low-risk ACS or stable CAD; however, authors notes that estimates were imprecise, especially for patients with stable CAD, and any differences could not be ruled out. No conclusions could be drawn regarding one functional test versus another, mainly because of the limited number of trials contributing to each comparison.

These SRs differ from our current review in a few important ways. Some include RCTs that were excluded from our review (i.e., did not meet our inclusion criteria) and there were differences in how time periods were considered or evaluated. Regarding statistical methods, we conducted our meta-analyses using profile-likelihood random effects models, which is a more conservative than the Dersimonian and Laird model; this approached is considered standard methodology for meta-analyses.

Table 5. Previous systematic reviews evaluating noninvasive testing for CAD.

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
Siddiqui (2020) **Search:** January 1, 2007 to July 1, 2018 MEDLINE, PubMed, Cochrane Library, Embase **Funding**: None	**Suspected CAD** (N=21,210) • Stable chest pain: 70.5% (n=14,947) • Acute chest pain: 29.5% (n=6,263) **CCTA**: n=10,937 **Functional stress testing**: n=10,273 • With imaging: n=9,758 • Without imaging: n=515 **Pretest risk**: Variable/NR **Setting**: Outpatient (4 RCTs, stable chest pain) and ED (9 RCTs, acute chest pain) **Follow-up**: range, 1 to 25 months • 1 month: 3 RCTs • 2-4 months: 3 RCTs • 6 months: 3 RCTs	**Objective**: To compare CCTA to functional stress testing for suspected underlying CAD in patients who presented with chest pain, with subgroup analyses of stress testing (with and without imaging) and chest pain (acute chest pain or stable chest pain).	**Appraisal:** Cochrane ROB tool for RCTs; overall trial quality not described **Overall Quality** (strength) of evidence: NR **Evidence base:** 16 RCTs (N=21,210) • Stable chest pain: 6 RCTs (n=14,947) • Acute chest pain: 10 RCTs (n=6,263) **Analysis:** Meta-analysis, Head-to-head studies **Publication bias:** Not assessed.	***CCTA vs. any functional test*** No. RCTS (n patients), RR (95% CI): **Clinical outcomes** • New myocardial infarction (during follow-up): ○ Stable: 4 RCTs (n=14,984), **0.66 (0.5-0.88)**, I^2=0% ○ Acute: 8 RCTs (n=5,315), **0.88 (0.54-1.44)**, I^2=0% ○ ST with imaging: 10 RCTs (n=19,249), **0.7 (0.54-0.89)**, I^2=0% ○ ST without imaging: 2 RCTs (n=1,050), **1.14 (0.35-3.75)**, I^2=0% ○ Total: 12 RCTs (n=20,299), **0.71 (0.56-0.91)**, I^2=0% • All-cause mortality: ○ Stable: 4 RCTs (n=14,984), **0.95 (0.71-1.25)**, I^2=0% ○ Acute: 8 RCTs (n=4,715), **0.75 (0.30-1.89)**, I^2=0% ○ ST with imaging: 10 RCTs (n=18,649), **0.92 (0.70-1.21)**, I^2=0% ○ ST without imaging: 2 RCTs (n=1,050), **1.26 (0.21-7.71)**, I^2=0% ○ Total: 12 RCTs (n=19,699), **0.93 (0.71-1.21)**, I^2=0% **Clinical decision making:** • ICA (cumulative): ○ Stable: 5 RCTs (n=11,278), **1.44 (1.30-1.61)**, I^2=0% ○ Acute: 10 RCTs (n=5,775), **1.35 (1.13-1.62)**, I^2=8% ○ ST with imaging: 12 RCTs (n=15,943), **1.37 (1.21-1.55)**, I^2=11% ○ ST without imaging: 3 RCTs (n=1,110), **1.39 (1.04-1.85)**, I^2=0% ○ Total: 15 RCTs (n=17,053), **1.41 (1.28-1.55)**, I^2=1% • Revascularization (cumulative)*: ○ Stable: **1.7 (1.16-2.51)**, I^2=77% ○ Acute: **1.95 (1.42-2.69)**, I^2=17% ○ ST with imaging: **1.77 (1.34-2.33)**, I^2=60% ○ ST without imaging: **2.36 (1.40-3.98)**, I^2=0% ○ Total: **1.84 (1.44-2.35)**, I^2=53% • Follow-up testing (cumulative):

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
	• 12 months: 5 RCTs • 20-25 months: 2 RCTs			○ Stable: 3 RCTs (n=936), **0.17 (0.04-0.77)**, I^2=80% ○ Acute: 4 RCTs (n=1,068), **0.83 (0.44-1.55)**, I^2=70% ○ ST with imaging: 5 RCTs (n=1,456), **0.43 (0.16-1.14)**, I^2=86% ○ ST without imaging: 2 RCTs (n=548), **0.39 (0.28-0.56)**, I^2=0% ○ Total: 7 RCTs, **0.45 (0.22-0.90)**, I^2=86% **Other:** • ER visits or hospitalizations: ○ Stable: 4 RCTs (n=5,153), **0.5 (0.21-1.23)**, I^2=86% ○ Acute: 9 RCTs (n=5,213), **0.86 (0.72-1.04)**, I^2=22% ○ ST with imaging: 11 RCTs (n=9,818), **0.92 (0.83-1.02)**, I^2=0% ○ ST without imaging: 2 RCTs (n=548), **0.27 (0.15-0.48)**, I^2=27% ○ Total: 13 RCTs (n=10,366), **0.75 (0.60-0.94)**, I^2=63% • New unstable anginas*: ○ Stable: **1.21 (0.93-1.58)**, I^2=4% ○ Acute: **1.15 (0.90-1.48)**, I^2=0% ○ ST with imaging: **1.18 (0.98-1.40)**, I^2=0% ○ ST without imaging: **1.09 (0.20-5.92)**, I^2=49% ○ Total: **1.18 (0.99-1.41)**, I^2=0% • True positive ICA: ○ Stable: 4 RCTs (1,210), **2.79 (2.19-3.55)**, I^2=0% ○ Acute: 7 RCTs (n=260), **3.2 (1.83-5.60)**, I^2=0% ○ ST with imaging: 8 RCTs (n=1,310), **2.84 (2.25-3.59)**, I^2=0% ○ ST without imaging: 3 RCTs (n=160), **4.67 (1.15-18.91)**, I^2=48% ○ Total: 11 RCTs (n=1,470), **2.85 (2.28-3.56)**, I^2=0% **Safety/Harms**: • Procedural complications (stroke, bleeding, anaphylaxis, or renal failure)*: ○ Total: **0.98 (0.35-2.74)**, I^2=0% • Cumulative radiation dose* ○ Total: 7.3±6.6 vs. 2.6±6.5, **0.47 (0.08-0.86)**, I^2=97%

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				Overall Author's Conclusions: Compared with functional stress imaging, CCTA was associated with a significant reduction in downstream MIs, hospital visits, and follow-up testing, but increased ICA and revascularizations; there was no difference in mortality. In the future, more RCTs are needed utilizing scoring methods to identify more robust downstream investigations, cost analysis, and radiation exposure.
Foy (2017) **Search:** January 1, 2000 to July 10, 2016 MEDLINE, PubMed **Funding**: NR	**Suspected CAD** (N=20,092) • Stable chest pain: 73.7% (n=14,817) • Acute chest pain: 26.3% (n=5,275) **CCTA**: n=10,315 **Functional stress testing**: n= 9,777 • Multiple modalities (plus no testing): 31% (4 RCTs) • MPI: 31% (4 RCTs) • Exercise ECG: 23% (3 RCTs) • Stress Echocardiography: 8% (1 RCT) • Modality not specified: 8% (1	**Objective**: To compare the clinical effectiveness of CCTA with that of functional stress testing for patients with suspected CAD. **Key Question**: For patients with suspected coronary artery disease, what is the effect on clinical outcomes of coronary computed tomography angiography	**Appraisal:** Cochrane ROB tool for RCTs; trial quality was variable, overall was considered moderate (45 of 98 domains [46%] judged to be at high or questionable risk for bias). **Overall Quality** (strength) of evidence of high, moderate, low or very low; Authors provide overall rating per outcome but do not provide detail of how this was derived. **Evidence base:** 13 RCTs (N=20,092) • Stable chest pain: 4 RCTs (n=14,817) • Acute chest pain: 9	***CCTA vs. any functional test†*** No. RCTS (n patients), RR (95% CI), quality (strength) of evidence: **Clinical outcomes** • Myocardial infarction: ○ Stable: 4 RCTs, **0.68 (0.49-0.95)**, I^2=0%, Moderate ○ Acute: 9 RCTs, **0.84 (0.44-1.61)**, I^2=0%, Moderate ○ Total: 13 RCTs, **0.71 (0.53-0.96)**, I^2=0%, Moderate • All-cause mortality ○ Stable: 4 RCTS, **0.96 (0.72-1.27)**, I^2=0%, Moderate ○ Acute: 9 RCTs, **0.66 (0.27-1.59)**, I^2=0%, Moderate ○ Total: 13 RCTs, **0.93 (0.71-1.21)**, I^2=0%, Moderate **Clinical decision making:** • ICA referral: ○ Stable: 4 RCTs, **1.27 (0.96-1.70)**, I^2=83%, Moderate ○ Acute: 9 RCTs, **1.39 (1.10-1.76)**, I^2=29%, Moderate ○ Total: 13 RCTs, **1.33 (1.12-1.59)**, I^2=59%, Moderate • Revascularization (any): ○ Stable: 4 RCTs, **1.70 (1.12-2.60)**, I^2=84%, Moderate ○ Acute: 9 RCTs, **1.96 (1.45-2.65)**, I^2=4%, High ○ Total: 13 RCTs, **1.86 (1.43-2.43)**, I^2=60%, High • Therapeutic medication change – aspirin: ○ Stable: 3 RCTs (n=4,814), **3.50 (2.69-4.54)**, I^2=31%, Low

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
	RCT) **Pretest risk**: Variable/NR **Setting**: Outpatient (4 RCTs, stable chest pain) and ED (9 RCTs, acute chest pain) **Mean follow-up**: 18 months • Stable: 23 months • Acute: 5 months	compared with functional stress testing?	RCTs (n=5,275) **Analysis:** Meta-analysis, Head-to-head studies **Assessed publication bias:** Visually using funnel plots; visual asymmetry noted for the following outcomes in favor of CCTA: • All-cause mortality (PROSPECT trial) • ICA (PERFECT trial) • Revascularization (SCOT-HEART, PERFECT trials) • New CAD diagnosis (2 small trials) Removal of trials did not significantly change overall effect estimate	○ Acute: 2 RCTs (n=811), **1.27 (0.99-1.61)**, I^2=16%, Low ○ Total: 5 RCTs (n=5,625), **2.21 (1.20-4.04)**, I^2=93%, Low • Therapeutic medication change – statin: ○ Stable: 3 RCTs (n=4,814), **3.48 (2.63-4.61)**, I^2=34%, Low ○ Acute: 2 RCTs (n=811), **1.21 (0.93-1.58)**, I^2=0%, Low ○ Total: 5 RCTs (n=5,625), **2.03 (1.09-3.76)**, I^2=92%, Low **Other:** • Cardiac hospitalization: ○ Stable: 4 RCTs (n=14,817), **1.21 (0.96-1.53)**, I^2=0%, Moderate ○ Acute: 8 RCTs (n=4,584), **0.83 (0.66-1.04)**, I^2=0%, Moderate ○ Total: 12 RCTs (n=19,401), **0.98 (0.79-1.21)**, I^2=23%, Moderate • New CAD diagnosis: ○ Stable: 3 RCTs (n=4,814), **2.35 (1.51-3.66)**, I^2=69%, High ○ Acute: 6 RCTs (n=3,979), **3.37 (1.92-5.89)**, I^2=75%, High ○ Total: 9 RCTs (n=8,793), **2.80 (2.03-3.87)**, I^2=71%, High **Safety/Harms**: • NR **Economic**: NR **Overall Author's Conclusions**: Compared with functional stress testing, CCTA is associated with a reduced incidence of myocardial infarction but an increased incidence of invasive coronary angiography, revascularization, CAD diagnoses, and new prescriptions for aspirin and statins. Despite these differences, CCTA is not associated with a reduction in mortality or cardiac hospitalizations. Tradeoffs involve an increase in downstream invasive procedures, many of which may be unnecessary.
Hwang (2017) **Search:**	**Suspected CAD** (N=20,014) • Stable chest pain:	**Objective:** To investigate the mid- to long-term	**Appraisal:** Cochrane ROB tool for RCTs. Overall trial quality was not reported	***CCTA vs. any functional test*** No. RCTS (n patients), RR (95% CI) **Clinical outcomes**

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
January 1, 2000 to July 10, 2016 MEDLINE, Embase, Cochrane **Funding**: Grant from the National Evidence-based Healthcare Collaborating Agency, Republic of Korea	76.5% (n=15,302) • Acute chest pain: 23.5% (n=4,712) **CCTA**: n=10,268 **Functional stress testing**: n= 9,627 **Pretest risk**: Variable/NR **Setting**: Outpatient (5 RCTs, stable chest pain) and ED (7 RCTs, acute chest pain) **Follow-up**: Mean 20.5 months (range, 6 to 42 months)	clinical outcomes following the initial strategies of noninvasive testing in patients with suspected CAD by comparing anatomical testing using CCTA with usual care with functional testing.	but all were considered Low ROB for detection bias, reporting bias and other bias; Low or Unclear ROB for selection bias and attrition bias; and High RoB (all but the CATCH trial) for performance bias. **Overall Quality** (strength) of evidence not assessed. **Evidence base:** 12 RCTs (N=20,014) • Stable chest pain: 5 RCTs • Acute chest pain: 7 RCTs **Analysis:** Meta-analysis, Head-to-head studies **Assessed publication bias:** Funnel plots suggested the presence of publication bias for ICA, however the influence was not significant (trim-and-fill analysis)	• Myocardial infarction: ○ Stable: 4 RCTs (n=14,984), **0.68 (0.48-0.97)**, I^2=0% ○ Acute: 5 RCTs (n=3,328), **0.74 (0.42-1.29)**, I^2=15% ○ Total: 9 RCTs (n=18,312), **0.70 (0.52-0.94)**, I^2=0% • All-cause mortality ○ Stable: 5 RCTS (n=15,281), **0.96 (0.72-1.26)**, I^2=0% ○ Acute: 5 RCTs (n=3,604), **0.50 (0.19-1.30)**, I^2=10% ○ Total: 10 RCTs (n=18,885), **0.91 (0.69-1.18)**, I^2=0% • MACE ○ Stable: 4 RCTS (n=14,793), **0.68 (0.39-1.20)**, I^2=71% ○ Acute: 7 RCTs (n=4,472), **0.82 (0.64-1.06)**, I^2=0% ○ Total: 11 RCTs (n=19,265), **0.82 (0.64-1.04)**, I^2=38% **Clinical decision making:** • ICA ○ Stable: 5 RCTS (n=15,279), **1.98 (1.10-3.55)**, I^2=88% ○ Acute: 6 RCTs (n=3,844), **1.32 (0.86-2.02)**, I^2=59% ○ Total: 11 RCTs (n=19,123), **1.61 (1.14-2.27)**, I^2=80% • Revascularization (any) ○ Stable: 5 RCTS (n=15,237), **1.52 (1.05-2.20)**, I^2=77% ○ Acute: 7 RCTs (n=3,881), **1.97 (1.15-3.35)**, I^2=29% ○ Total: 12 RCTs (n=19,118), **1.65 (1.23-2.21)**, I^2=60% Similar results were observed in subgroup analyses of the RCTs with long-term follow-up durations. **Safety/Harms**: • NR **Economic**: NR **Overall Author's Conclusions**: Anatomical testing with CCTA as an

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				initial diagnostic strategy reduced the risk of nonfatal MI in patients with suspected CAD, compared with the usual care, during mid- to long-term follow-up. The reduction in the risk of nonfatal MI was at the expense of increased use of ICA and coronary revascularization. Future trials of advanced CT technology may further demonstrate the clinical benefits of the anatomical testing strategy over usual care.
Siontis 2018 **Search:** 2005 to November 2015 Medline, Medline in process, Embase, Cochrane Library for clinical trials, PubMed, Web of Science, SCOPUS, WHO International Clinical Trials Registry Platform, and Clinicaltrials.gov. **Funding**: None	**Suspected CAD** (N=33,391) • Stable CAD: 66.1% (n=22,062) • Low-risk ACS: 33.9% (n=11,329) **Pretest risk**: Variable/NR **CCTA vs. various functional testing** **Functional testing vs. functional testing** **Setting**: Outpatient and ED **Follow-up**: Variable	**Objective:** To evaluate differences in downstream testing, coronary revascularization, and clinical outcomes following non-invasive diagnostic modalities used to detect coronary artery disease.	**Appraisal:** Cochrane ROB tool for RCTs. Overall, ROB ratings were: Low, 43% (13 RCTs); Moderate, 43% (13 RCTs); and High, 14% (4 RCTs) **Overall Quality** (strength) of evidence not assessed. **Evidence base:** 30 RCTs (N=33,391) • **Stable CAD: 12 RCTs (N=22,062)** ○ CCTA vs. any functional (2 RCTs) ○ CCTA vs. SPECT (2 RCTs) ○ CCTA vs. stress ECG (1 RCT) ○ CCTA vs. standard care (1 RCT) ○ SPECT vs. stress ECG	***CCTA vs. individual diagnostic strategies*** OR (95% CI) **Clinical outcomes** • Myocardial infarction: ○ Stable CAD ▪ Stress echo: **2.14 (0.03-162.0)** ▪ CMR: **2.62 (0.67-10.30)** ▪ Stress ECG: **2.11 (0.34-13.0)** ▪ SPECT: **1.31 (0.84-2.06)** ▪ RTMCE: **3.26 (0.04-286.0)** ▪ Standard care: **1.66 (0.99-2.79)** τ^2<0.001 ○ Low-risk ACS ▪ Stress echo: **0.78 (0.10-6.30)** ▪ CMR: **2.46 (0.29-20.7)** ▪ Stress ECG: **0.54 (0.08-3.60)** ▪ SPECT: **2.38 (0.77-7.34)** ▪ Standard care: **1.36 (0.80-2.31)** τ^2<0.001 • Death: ○ Stable CAD ▪ Stress echo: **3.90 (0.12-123)** ▪ CMR: **1.05 (0.28-3.93)**

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
			(2 RCTs) ○ Stress echo vs. exercise ECG (1 RCT) ○ RTMCE vs. Stress echo: (2 RCTs) ○ CMR vs. SPECT vs. standard care (1 RCT) • **Low-risk ACS: 18 RCTs (N=11,329)** ○ CCTA vs. standard care (7 RCTs) ○ CCTA vs. SPECT (2 RCTs) ○ CCTA vs. stress ECG (1 RCT) ○ SPECT vs. standard care (2 RCTs) ○ Stress echo vs. stress ECG (3 RCTs) ○ Stress echo vs. stress ECG vs. standard care (1 RCT) ○ CMR vs. standard care (2 RCTs) **Analysis:** Meta-analysis, Network	▪ Stress ECG: **1.27 (0.35-4.60)** ▪ SPECT: **0.98 (0.72-1.35)** ▪ RTMCE: **3.70 (0.11 to 121.0)** ▪ Standard care: **1.27 (0.69-2.32)** τ^2<0.001 ○ Low-risk ACS: NR **Clinical decision making:** • ICA: ○ Stable CAD ▪ Stress echo: **0.57 (0.12-2.79)** ▪ CMR: **0.50 (0.15-1.65)** ▪ Stress ECG: **0.90 (0.45-1.80)** ▪ SPECT: **0.54 (0.30-0.98)** ▪ RTMCE: **1.10 (0.15 to 7.95)** ▪ Standard care: **1.44 (0.60-3.45)** τ^2=0.336 ○ Low-risk ACS ▪ Stress echo: **0.28 (0.14-0.57)** ▪ CMR: **0.32 (0.15-0.71)** ▪ Stress ECG: **0.53 (0.28-1.00)** ▪ SPECT: **0.78 (0.58-1.03)** ▪ Standard care: **0.85 (0.69-1.05)** τ^2=0.023 • Revascularization (any): ○ Stable CAD ▪ Stress echo: **0.64 (0.19-2.14)** ▪ CMR: **0.84 (0.40-1.74)** ▪ Stress ECG: **0.63 (0.38-1.04)** ▪ SPECT: **0.57 (0.37-0.87)** ▪ RTMCE: **1.36 (0.36 to 5.10)**

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				▪ Standard care: **0.75 (0.45-1.24)** τ^2=0.084 ○ Low-risk ACS ▪ Stress echo**: 0.44 (0.16-1.24)** ▪ CMR: **0.17 (0.04-0.65)** ▪ Stress ECG: **0.56 (0.21-1.49)** ▪ SPECT: **0.57 (0.41-0.79)** ▪ Standard care: **0.68 (0.53-0.88)** τ^2<0.001 • Downstream testing ○ Stable CAD ▪ Stress echo: **0.24 (0.08-0.74)** ▪ CMR: **0.95 (0.41-2.22)** ▪ Stress ECG: **3.87 (2.33-6.41)** ▪ SPECT: **0.57 (0.37-0.87)** ▪ Standard care: **1.11 (0.61-2.01)** τ^2=0.137 ○ Low-risk ACS ▪ Stress echo: **0.27 (0.04-1.67)** ▪ CMR: **2.87 (0.32-25.9)** ▪ Stress ECG: **0.69 (0.14-3.44)** ▪ SPECT: **0.60 (0.12-2.98)** ▪ Standard care: **4.11 (1.74-9.74)** τ^2=1.21 ***CCTA vs. grouped diagnostic strategies*** OR (95% CI) **Clinical outcomes** • Myocardial infarction: ○ Stable CAD

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				▪ Functional testing: **1.35 (0.87-2.09)** ▪ CMR: **2.66 (0.68-10.41)** ▪ Standard care: **1.66 (0.99-2.79)** τ^2<0.001 o Low-risk ACS ▪ Functional testing: **1.59 (0.60-4.23)** ▪ CMR: **2.52 (0.30-21.28)** ▪ Standard care: **1.40 (0.82-2.37)** τ^2<0.001 • Death: o Stable CAD ▪ Functional testing: **0.99 (0.73-1.36)** ▪ CMR: **1.06 (0.28-3.95)** ▪ Standard care: **1.27 (0.69-2.32)** τ^2<0.001 o Low-risk ACS: NR **Clinical decision making:** • ICA: o Stable CAD ▪ Functional testing: **0.63 (0.44-0.90)** ▪ CMR: **0.56 (0.27-1.13)** ▪ Standard care: **1.51 (0.90-2.53)** τ^2=0.102 o Low-risk ACS ▪ Functional testing: **0.71 (0.53-0.96)** ▪ CMR: **0.32 (0.15-0.72)** ▪ Standard care: 0.85 **(0.68-1.07)** τ^2=0.032 • Revascularization (any): o Stable CAD

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				▪ Functional testing: **0.57 (0.41-0.78)** ▪ CMR: **0.84 (0.48-1.44)** ▪ Standard care: **0.77 (0.54-1.10)** τ^2=0.029 o Low-risk ACS ▪ Functional testing: **0.57 (0.42-0.78)** ▪ CMR: **0.17 (0.04-0.65)** ▪ Standard care: **0.68 (0.53-0.88)** τ^2<0.001 • Downstream testing o Stable CAD ▪ Functional testing: **1.18 (0.61-2.29)** ▪ CMR: **1.63 (0.35-7.48)** ▪ Standard care: **1.56 (0.51-4.81)** τ^2=0.578 o Low-risk ACS ▪ Functional testing: **0.58 (0.17-1.92)** ▪ CMR: **2.99 (0.33-27.50)** ▪ Standard care: **4.28 (1.79-10.23)** τ^2=1.23 ***Functional vs. Functional*** • Limited evidence for the various comparisons **Overall Author's Conclusions**: **Among patients with low-risk ACS**, initial functional testing in terms of stress echocardiography or CMR was most strongly associated with a reduction of referrals for downstream ICA and revascularization procedures, compared with anatomical testing using CCTA. No diagnostic strategy had an apparent effect on the

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				subsequent risk of MI, although estimates were imprecise. **Among patients with suspected stable CAD**, no clear discrimination was seen across *individual diagnostic strategies* for ICA referrals, mainly because of the limited number of trials contributing to each comparison. Stress echocardiography and SPECT resulted in less overall downstream testing than CCTA, whereas exercise ECGs required the most downstream testing. *After grouping of widely available functional tests*, a functional testing approach yielded fewer referrals for ICA and subsequent revascularizations than CCTA. Again, estimates were imprecise for the outcome of MI, and any differences could not be ruled out.

ACS = acute coronary syndrome; CAD = coronary artery disease; CCTA = coronary computed tomographic angiography; CI = confidence interval; CMR = cardiovascular magnetic resonance; ECG = electrocardiography; echo=echocardiography; ED = emergency department; ICA = invasive coronary angiography; MI = myocardial infarction; NR= not reported; RCT = randomized controlled trial; ROB = risk of bias; RR = risk ratio; RTMCE = real time myocardial contrast echocardiography; SPECT = single photon emission computed tomography; ST = stress testing; WHO = World Health Organization.

* No plot provided in article, number of RCTs (n patients) contributing to estimate not reported.

†Authors evaluated the extent to which stable and unstable patients had different risk estimates, and did a formal test for interaction – there was no modification of the treatment effect by the different populations.

2.7 Prior Government Report and Rapid Reviews

Two prior reports, one comparative effectiveness review published in 2016 by the Agency for Healthcare Research and Quality (AHRQ)[230] and one rapid review from 2019 prepared by the Veterans Affairs (VA) Evidence Synthesis Program[100], were identified searching PubMed, the Cochrane Database of and the ECRI Guideline Trust from database inception to March 23rd, 2021, and our summarized in Table 6 below. See Appendix B for search terms and full search strategy.

The most recent report was a VA Evidence Synthesis rapid review that evaluated evidence related to the capabilities, benefits and harms, and impact on resource use within the VA health system of CCTA with fractional flow reserve (FFRCT) technology (i.e., HeartFlow) for the diagnosis of CAD.[100] Since it is a rapid review, however, it does not provide a formal, systematic review of the available evidence. Evidence related to diagnostic accuracy from this review can be found in the Contextual Questions section. Regarding clinical and management outcomes (Table 6 below), the authors concluded that regular use of HeartFlow FFRCT in place of other noninvasive tests does not appear warranted, as HeartFlow FFRCT led to a higher rate of use of ICA when used as a substitute for planned noninvasive cardiovascular testing. They also found no evidence to support wider use of CCTA in place of other noninvasive tests in the VA healthcare system.

The AHRQ comparative effectiveness review evaluated noninvasive testing strategies for the diagnosis of CAD in symptomatic patients with suspected CAD, who had no known history of CAD, and whose condition was stable.[230] Results were stratified first based on pretest risk and then by anatomic versus functional tests and functional versus functional tests. Given the heterogeneity in how pretest risk was measured and defined across the studies, the results were organized by pretest risk as defined by the study authors (rather than by distinct pretest risk groups as originally intended), which included low-risk, intermediate-risk, low-to-intermediate-risk, intermediate-to-high-risk, high-risk, and mixed-risk populations (or pretest risk not reported). This review found no clear differences between testing strategies across settings with regard to clinical or management outcomes to recommend one strategy over another for any given pretest risk group that included intermediate pretest risk patients. Limited evidence from RCTs suggest 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. Assessment of harms was limited and there was inadequate comparative evidence to make judgments regarding radiation exposure for initial test or downstream testing. (See Table 6 below for details.) In contrast to the AHRQ report, this current report included symptomatic patients both with and without a history of CAD, as well as those who presented with acute coronary syndrome (ACS). We did not stratify results by pretest risk but did indicate pretest risk as defined by the authors. Since the AHRQ report, several new trials evaluating noninvasive treatment for CAD have been published and are included in this re-review.

A third review was identified by the Health Evidence Review Commission (HERC) which provided evidence on nuclear cardiac imaging for screening, diagnosis or risk stratification of CAD[99]; however, this report essentially relied on the evidence from the prior WA State HTA on nuclear cardiac imaging, so it is not summarized below.

Table 6. Prior government reports and rapid reviews evaluating noninvasive testing for CAD

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
Helfand (2019) Search: 2017 to August 2019 MEDLINE, Cochrane Database of Systematic reviews, Cochrane Central Register of Controlled trials. Funding: Department of Veteran Affairs, Veterans Health Administration (VHA), Health Services Research and Development. AMSTAR-2: NA	Symptomatic patients with Suspected CAD Pretest risk: Intermediate (primarily) Outpatient and ED settings Test comparisons: • CCTA-FFR vs. any functional test* • CCTA-FFR vs. ICA • CCTA-FFR vs. CCTA alone	Objective\Key Question: This is a rapid review intended to provide a conceptual overview of the capabilities, benefits and harms, and anticipated impact on resource use within the Veterans Health Administration of CCTA with FFR technologies for the diagnosis of CAD.	Appraisal: Cochrane ROBIS tool for SR's, QUADAS-2 for Diagnostic accuracy or therapeutic impact, and Cochrane ROBINS-I tool for cohort studies. Overall Quality: used Agency for *Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews*; Ratings ranged from high to insufficient. Evidence received a rating of low to moderate strength if it was comprised of several studies with low to moderate risk of bias and had consistent findings. Evidence base: N=6 studies (in 9 publications), 90-days (primarily) to 1 year <u>CCTA-FFR vs. any functional test*</u>: 2 studies (total N=3,727) (1 prospective [PLATFORM trial], 1 retrospective	<u>*CCTA-FFR vs. Any functional testing*</u>* MACE • 1 prospective cohort (vs. any functional testing): 0% vs. 1% Downstream ICA utilization • 1 prospective cohort (vs. any functional testing): 21% vs. 16%, p=NS • 1 retrospective cohort (vs. MPI): RD –4.2% (95% CI –6.9% to –1.6%)† Planned ICA with no obstructive disease • 1 prospective cohort (vs. any functional testing): 13% vs. 6%, p=NS • 1 retrospective cohort (vs. MPI): RD –12.8% (95% CI –22.2% to –3.4%)† Downstream noninvasive testing • 1 retrospective cohort (vs. MPI): 23% vs. 20%‡ Revascularization • 1 prospective cohort (vs. any functional testing): 10% vs. 7%, p=NS • 1 retrospective cohort (vs. MPI): RD 14.1% (95% CI 3.3 to 24.9%)† Safety/Harms: Cumulative radiation exposure: • 1 prospective cohort (vs. any functional testing): 9.6 vs. 6.4 mSv through 12 months; MD 3.1 (95% CI 0.6 to 5.7) Economic • 1 prospective cohort (vs. any functional testing): Mean 1 year of patient cost did not differ when using

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions

			comparative cohort)
			
			<u>CCTA-FFR vs. ICA:</u>
			1 prospective observational study (N=380)
			
			<u>CCTA-FFR vs. CCTA alone</u>:
			4 studies (total N=7,180) (3 retrospective comparative cohorts, 1 comparative registry study)
			
			Analysis: Qualitative analysis
			
			Publication bias:
			Assessed using Quadas-2 section bias was mostly Low with 2 studies being unclear.
				an CCTA-FFR cost weight of zero, but were higher when using an CCTA-FFR cost weight equal to CCTA.
				
				<u>*CCTA-FFR vs. ICA*</u>
				MACE: 1% vs. 1%, p=NS
				Planned ICA with no obstructive disease: 12% vs. 73%, RD –61% (95% CI –68.7% to –53.0%)
				Revascularization: 34% vs. 36%, p=NS
				Safety/Harms:
				• Cumulative radiation exposure: 10.7 vs. 10.4 mSv through 12 months, p=NS
				Economic
				• Mean 1 year patients' cost was 33% lower in CCTA-FFR vs. ICA group.
				
				<u>*CCTA-FFR vs. CCTA alone*</u>
				MACE
				• 1 registry:
				  ○ CCTA-FFR >0.80 = no death/MI within 90 days
				  ○ CCTA-FFR ≤0.80 = MACE, 0.6%; death/MI, 0.3%
				• 2 retrospective cohorts:
				  ○ No significant difference in 1-year cardiovascular events between patients with changed vs. unchanged management after CCTA-FFR
				  ○ 4 serious clinical events occurred, but not in any patients with cancelled ICA by CCTA-FFR
				Change in management plans (1 registry, 1 retrospective cohort)
				• 55% to 67% of patients
				Impact on subsequent ICA (2 retrospective cohorts)
				• Potentially reduced in the need for ICA in 48%

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				• In high-risk CCTA-FFR patients, ICA was cancelled in 75% Economic • According to the authors, key factors that could influence the impact and cost-effectiveness of HeartFlow FFRCT in VA include: reasons for direct referral to ICA with no noninvasive testing, frequency of CCTA use, probability of ICA referral after positive CCTA, and prevalence of intermediate stenosis identified by CCTA and functionally significant CAD in the population. The authors did not find data on these factors. Author's Conclusions: Regular use of HeartFlow FFRCT in place of other noninvasive tests does not appear warranted, as HeartFlow FFRCT led to a higher rate of use of ICA when used as a substitute for planned noninvasive cardiovascular testing. We found no evidence to support wider use of CCTA in place of other noninvasive tests in VA. The effect of FFRCT on MACE outcomes is uncertain. Future research should evaluate MACE outcomes on a longer-term basis. The effect of FFRCT on MACE outcomes is uncertain. Future research should evaluate MACE outcomes on a longer-term basis.
AHRQ (2016) *Noninvasive Testing for Coronary Artery Disease* Search: through July 2015	Stable, symptomatic patients with suspected CAD (no known history of CAD) Pretest risk: Variable	Objective: To assess the effectiveness of noninvasive technologies for the diagnosis of CAD or dysfunction that results in symptoms attributable to myocardial ischemia in	Low pretest risk (2 RCTs) • CCTA vs. UC (N=99, low risk subgroup) • SPECT vs. Exercise ECG (N=71, low risk subgroup) Intermediate pretest risk (7 comparative studies)	Low pretest risk (2 RCTs) • Insufficient evidence for all outcomes for both comparisons; evidence based on subgroup analyses from RCTs. Intermediate pretest risk • CCTA vs. UC: o No differences between groups for all-cause mortality (28-30 days in 2 trials), MI (index visit in 1

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
MEDLINE, Cochrane Database of Systematic reviews, Cochrane Central Register of Controlled trials, Evidence-Based Medicine Reviews–Health Technology Assessment	Outpatient and ED settings	patients who present with signs or symptoms suggestive of CAD, whose condition is stable, and who have no known history of CAD. Key Questions: 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)? 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)? 3. For patients considered to be at *intermediate to high*	• CCTA vs. UC: 2 RCTs (N=1,111), 1 prospective cohort (N=200) • CCTA vs. various functional testing: 1 RCT (N=10,003) • CCTA vs. SPECT: 1 RCT (N=400) • SPECT vs. exercise ECG: 2 RCTs (N=1,104) Low-to-Intermediate pretest risk (8 comparative studies) • CCTA vs. UC: 2 RCTs (N=1,430), 1 retrospective cohort (N=1,788) • CCTA vs. SPECT: 2 RCTs (N=952), 1 retrospective cohort (N=252) • CCTA vs. exercise ECG: 1 RCT (N=562), 1 retrospective cohort (N=498) Intermediate-to-High pretest risk (2 comparative studies) • CCTA vs. SPECT: 1 RCT	trial, 28-30 days in 2 trials and 3 months in 1 observational), 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), CABG (28 days in 1 trial and 3 months in 1 observational), 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). (Low SOE) • CCTA vs. functional testing: ○ No differences between groups 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). (Moderate SOE). ○ 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), PCI (4.8% vs. 2.4%, RD 2.4, 95% CI 1.7 to 3.1 per 100), and CABG (1.44% vs. 0.76%, RD 0.68, 95% CI 0.27 to 1.09 per 100) (High SOE). ○ 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) and minor side effects from testing (e.g., stress-induced symptoms, 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. • CCTA vs. SPECT:

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
		risk for CAD, what is the comparative effectiveness of anatomic tests (compared with each other, usual care, or no testing)? 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)? 5. What is the comparative effectiveness of anatomic tests versus functional tests in those who are at *very low or low risk* for CAD? 6. What is the comparative effectiveness of anatomic tests versus functional tests in those who are at	(N=180) • PET vs. SPECT: 1 registry study (N=1,113) High pretest risk (2 comparative studies) • CCTA vs. UC: 1 RCT (N=56, high-risk subgroup) • SPECT vs. exercise ECG: 1 RCT (N=106, high-risk subgroup) Mixed pretest risk (9 comparative studies) • CCTA vs. UC: 1 RCT (N=266) • CCTA vs. exercise ECG: 1 RCT (N=500), 1 administrative database (N=69,883) • CCTA vs. SPECT: 1 prospective registry (N=2,442), 1 administrative database (N=9,690) • CCTA vs. nuclear MPI: 1 prospective registry (N=1,856), 1 administrative database	○ No differences between tests for all-cause mortality (median 24.5 months), cardiac hospitalization (median 40.4 months), for ICA referral, any revascularization, PCI, and additional noninvasive testing, including myocardial perfusion imaging, stress echocardiography, and CCTA (through 12 months); and for minor adverse reactions (including headache, nausea, dizziness, or feeling of warmth), rash or pruritus, and posttest renal dysfunction. (Low SOE). ○ CCTA was associated with a higher risk of CABG procedures through 12 months (3.5% vs. 0.5%, RD 3.0, 95% CI 0.3 events to 5.7 per 100 persons) 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) (Low SOE). • SPECT vs. exercise ECG: ○ No difference between groups in mortality, revascularization and hospitalization for chest pain (Low SOE) through 24 months in one trial in woman only. ○ No difference between groups in ICA through 24 months in 1 trial (woman only), but SPECT was associated with fewer ICAs through 22 months in the second trial (Low SOE) ○ Across both trials, SPECT was associated with less additional noninvasive testing (Low SOE in 1 trial, Moderate SOE in 1 trial). Low-to-Intermediate pretest risk

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
		intermediate to high risk for CAD?	(N=141,163) • CCTA vs. stress echocardiography: 1 administrative database (N=89,424) • SPECT vs. exercise ECG: 1 RCT (N=457) • Stress echocardiography vs. exercise ECG: 1 RCT (N=158), 1 prospective cohort (N=5,894), 1 administrative database (N=144,667) • Stress echocardiography vs. SPECT: 1 administrative database (N=212,947) • Exercise ECG vs. Nuclear MPI: 1 administrative database (N=193,406)	• CCTA vs. UC: ○ No differences between tests for all-cause mortality (at 1 month in 1 trial and in the observational study), MI (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 two 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), bradyarrhythmia (1 trial) (Low SOE), and cardiac hospitalization (after index visit through 1 month in 1 trial) (Moderate SOE). ○ CCTA was associated with a decreased risk of additional noninvasive testing at the index visit (13.7% vs. 57.8%, RD -44.1, 95% CI -49.2 to -39.1 per 100) as well as through 1 month (23.1% vs. 66.4%, RD -43.3, 95% CI -48.4 to -38.1 per 100) in 1 trial and in one observational study (4% vs. 21%, p<0.001) and 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) (Moderate SOE). • CCTA vs. SPECT ○ No differences between groups in all-cause mortality at 6 months (2 trials) and at 30 months (1 observational study), MI and ICA referral at index visit and through 6 months (2 trials) (Low SOE), any revascularization through 6 months (2 trials), and cardiac hospitalization through 6 months (1 trial) and 30 months (1 observational) (Moderate SOE). ○ CCTA was associated with higher rates of additional noninvasive testing at the index visit: 10.2% vs. 0.9%

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions

				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) (SOE High).
				• CCTA vs. Exercise ECG
				  ○ No difference between groups in all-cause mortality (at 30 days in 1 trial and at 12 months in both studies) and MI (at index visit and 30 days in 1 trial, and at 12 months in the observational study). (Low SOE).
				  ○ CCTA was associated with higher referral rate for ICA (9.0% vs. 2.3%, RD 4.8, 95% CI 0.8 to 8.9 per 100 patients) and revascularizations (4.3% vs. 1.3%, RD 3.1, 95% CI 0.5 to 5.7 per 100 patients) through 12 months in 1 trial (Low SOE).
				
				Intermediate-to-High pretest risk
				• CCTA vs. SPECT:
				  ○ Insufficient evidence for death and MI (no incidences through a mean 1.8 months).
				  ○ No differences between tests through a mean 1.8 months for ICA referral, additional noninvasive testing, and CAD-related hospitalization (Low SOE).
				  ○ 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 SOE).
				• PET vs. SPECT:
				  ○ Insufficient evidence for all outcomes from one large, fair-quality, registry study.
				
				High pretest risk
				• Insufficient evidence for all outcomes for both

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				comparisons; evidence based on subgroup analyses from RCTs. Mixed pretest risk • CCTA vs. UC: ○ No differences between tests through 30 days for MI and contrast-inducted nephropathy in 1 RCT (Low SOE). • CCTA vs. Exercise ECG: ○ No differences between tests for all-cause mortality, MI, referral for ICA, and CABG through 12 months in 1 RCT. ○ CCTA was associated with a significantly decreased risk of additional noninvasive testing (2.4% vs. 31.3%, RD -29, 95% CI -37 to -23 per 100) and cardiac rehospitalizations (0.8% vs. 6.9%, RD -6.1, 95% CI -9.5 to -2.7 per 100) (Moderate SOE), but an increased risk of any revascularization (15.2% vs. 7.7%, RD 7.5, 95% CI 1.9 to 13.0 per 100) and PCI (11.9% vs. 4.9%, RD 7, 95% CI 2 to 12 per 100) through 12 months in 1 RCT (Low SOE). • CCTA vs. Nuclear MPI ○ No differences between tests for all-cause mortality at 6 months in 1 observational study (Medicare population) (Low SOE). ○ 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

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions

				1.52, 95% CI 1.37 to 1.69) through 6 months in the observational cohort of Medicare patients; and 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 a median 1.42 years in the second observational study in the general population (% NR, adjusted OR 1.62, 95% CI 1.20 to 2.18) (Low SOE).
				• SPECT vs. Exercise ECG:
				  ○ No differences between tests for all-cause mortality and MI but SPECT was associated with significantly fewer revascularizations (10.8% vs. 17.9%, RD -7.1, 95% CI -13.6 to -0.6 per 100) in 1 RCT with 22 months of follow-up (SOE Low).
				• Exercise ECG vs. Nuclear MPI:
				  ○ No differences between tests for all-cause mortality at 6 months in 1 observational study (Low SOE).
				  ○ 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 in 1 observational study, although it is unclear if the differences for any revascularization, PCI and CABG are clinically meaningful (Low SOE).
				• Stress echocardiography vs. Nuclear MPI:

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				○ No between tests for all-cause mortality at 6 months in 1 observational cohort (Low SOE). ○ 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 in 1 observational cohort, although it is unclear if the differences for any revascularization, PCI and CABG are clinically meaningful (Low SOE). • Stress echocardiography vs. Exercise ECG: ○ Insufficient evidence from 2 observational studies. Author's Conclusions: A review of current studies found no clear differences between testing strategies across settings regarding clinical or management outcomes to recommend one strategy over another for any given pretest risk group that included intermediate pretest risk patients. No conclusions regarding low-risk patients or those without ACS at high risk are possible. Limited evidence from RCTs trials 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

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				information on posttest risk stratification and subsequent decision-making 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 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 posttest risk stratification, its impact on clinical management (treatment and referral for additional testing), and longer term follow up to assess clinical outcomes is needed to determine optimal testing strategies and roles of tests in different pretest risk groups.

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CCTA FFR = coronary computed tomography angiography with fractional flow reserve; CI = confidence interval; ECG = electrocardiography; ED=emergency department; CABG = coronary artery bypass graft; ICA= invasive coronary angiography; MACE = major adverse cardiovascular events; MD = mean difference; MI = myocardial infarction; MPI = myocardial perfusion imaging; NR= not reported; OR = odds ratio; PCI = percutaneous coronary intervention; PET = positron emission tomography; RCT = randomized controlled trial; RD = risk difference; ROB= risk of bias; RR = risk ratio; SOE = strength of evidence; SPECT = single positron emission computed tomography; UC = usual care; VA = Veterans Affairs.
*Includes: CCTA, Stress Echo, Nuclear MPI, Ex ECG, CMR, other.
†Propensity score-matched analysis; however, sufficient information about the propensity scoring to assess its validity was not provided.
‡Unadjusted scores.

2.8 Clinical Guidelines

Table 7. Summary of Clinical Practice Guidelines for the Diagnosis of CAD in patients with chest pain

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons[71] 2012* *Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease*	CCTA in patients able **or** unable to exercise	5 meta-analyses, 3 controlled clinical trials	Because the presence of significant calcification often can preclude the accurate assessment of lesion severity or cause a false positive study, CCTA should not be performed in patients who have known extensive calcification or a high risk of CAD. CCTA is reasonable for patients with a low to intermediate pretest probability of IHD who are incapable of at least moderate physical functioning or have disabling comorbidity. CCTA might be reasonable for patients with an intermediate pretest probability of IHD who have at least moderate physical functioning or no disabling comorbidity.	• Class of recommendation: IIa • Level of evidence: B (Recommendation in favor of treatment or procedure being useful. Some conflicting evidence from single randomized trial or nonrandomized studies)
	CCTA in patients with inconclusive functional tests	1 prognostic study	CCTA is reasonable for patients with an intermediate probability of CAD who has any of the following: a) Continued symptoms with prior normal test, or b) Inconclusive exercise or pharmacological stress, or	• Class of recommendation: IIa • Level of evidence: C (Recommendation in favor of treatment or procedure being useful.

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
			c) Unable to undergo stress with MPI or Echo	Only divergent expert opinion, case studies, or standard of care available).
	Exercise with nuclear MPI or Echo in patients able to exercise	5 meta-analyses, 2 cost effectiveness studies, and 2 additional publications of unknown study design	Exercise stress with nuclear MPI or echocardiography is recommended for patients with an intermediate to high pretest probability of IHD who have an uninterpretable ECG and at least moderate physical functioning or no disabling comorbidity.	• Class of recommendation: I • Level of evidence: B
			Exercise stress with nuclear MPI or echocardiography is reasonable for patients with an intermediate to high pretest probability of obstructive IHD who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity.	• Class of recommendation: IIa • Level of evidence: B (Recommendation in favor of treatment or procedure being useful. Some conflicting evidence from single randomized trial or nonrandomized studies)
			Exercise stress with nuclear MPI is not recommended as an initial test in low-risk patients who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity.	• Class of recommendation: III (no benefit) • Level of evidence: C
	Pharmacological stress with nuclear MPI, Echo, or CMR in	1 observational study, 2 economic evaluations	Pharmacological stress with nuclear MPI, echocardiography, or CMR is not recommended for patients who have	• Class of recommendation: III (no benefit)

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
	patients able to exercise		an interpretable ECG and at least moderate physical functioning or no disabling comorbidity.	• Level of evidence: C
	Pharmacological stress with nuclear MPI or Echo in patients unable to exercise	5 meta-analyses, 1 observational study, 1 position statement, 1 economic evaluation	Pharmacological stress with nuclear MPI or echocardiography is recommended for patients with an intermediate to high pretest probability of IHD who are incapable of at least moderate physical.	• Class of recommendation: I • Level of evidence: B
	Pharmacological stress CMR in patients able to exercise	3 meta-analyses	Pharmacological stress with CMR can be useful for patients with an intermediate to high pretest probability of obstructive IHD who have an *un*interpretable ECG and at least moderate physical functioning or no disabling comorbidity.	• Class of recommendation: I • Level of evidence: B
	Pharmacological stress CMR in patients unable to exercise	3 meta-analyses, 1 RCT	Pharmacological stress CMR is reasonable for patients with an intermediate to high pretest probability of IHD who are incapable of at least moderate physical functioning or have disabling comorbidity.	• Class of recommendation: IIa • Level of evidence: B (Recommendation in favor of treatment or procedure being useful. Some conflicting evidence from single randomized trial or nonrandomized studies)

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
	Hybrid Imaging	N/A	This diagnostic imagining modality is discussed, but no specific recommendations for the use of hybrid imaging are included in this guideline.	N/A
The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)[133] 2019 *2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes*	Stress echocardiography, stress CMR, SPECT, PET, or CCTA	5 RCTs, 1 meta-analysis, and 1 recommendation document	Stress echocardiography, stress CMR, SPECT, PET, or CCTA is recommended as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone.	• Class of recommendation: I • Level of evidence: B
	Selection of initial non-invasive diagnostic test.	None cited.	It is recommended that selection of the initial non-invasive diagnostic test is done based on the clinical likelihood of CAD and other patient characteristics that influence test performance (e.g. characteristics determining ability to exercise, likelihood of good image quality, expected radiation exposure, and risks or contraindications), local expertise, and the availability of tests	• Class of recommendation: I • Level of evidence: C
	CCTA	None cited.	CCTA should be considered as an alternative to invasive angiography if another non-invasive test is equivocal or non-diagnostic.	• Class of recommendation: IIa • Level of evidence: C
			CCTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands, or any other conditions make obtaining good image quality unlikely.	• Class of recommendation: III • Level of evidence: C

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
National Institute for Health and Care Excellence (NICE)[2] 2016 *Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis*	CCTA	Specific references used to make this recommendation were not explicitly stated.	Offer 64-slice (or above) CCTA if: • clinical assessment indicates typical or atypical angina†, or • clinical assessment indicates non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves. The committee's view is that CCTA should be considered the first choice diagnostic test for all people assessed as having typical or atypical angina. However individual circumstances, including potential contraindications, should be considered when deciding the most appropriate strategy for diagnostic investigation.	NR
American College of Cardiology (ACC) and the American Heart Association (AHA)[14] 2014 *Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes*	ECG	1 position statement	In patients with chest pain or other symptoms suggestive of ACS, a 12-lead ECG should be performed and evaluated for ischemic changes within 10 minutes of the patient's arrival at an emergency facility.	• Level of evidence: C • Class of recommendation: I
	ECG	None cited.	If the initial ECG is not diagnostic but the patient remains symptomatic and there is a high clinical suspicion for ACS, serial ECGs (eg, 15- to 30-minute intervals during the first hour) should be performed to detect ischemic changes.	• Level of evidence: C • Class of recommendation: I
	Treadmill ECG, Stress MPI, Stress Echo	Treadmill ECG: 3 RCTs	It is reasonable for patients with possible ACS who have normal serial	• Treadmill ECG - Level of evidence: A

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
		Stress MPI/Stress Echo: 1 comparative cohort, 1 prognostic study	ECGs and cardiac troponins to have a treadmill ECG, stress myocardial perfusion imaging, or stress echocardiography before discharge or within 72 hours after discharge.	- Class of recommendation: IIa • Stress MPI, stress echo - Level of evidence: B - Class of recommendation: IIa
	CCTA	3 RCTs	In patients with possible ACS and a normal ECG, normal cardiac troponins, and no history of CAD, it is reasonable to initially perform (without serial ECGs and troponins) coronary CT angiography to assess coronary artery anatomy	• Level of evidence: A • Class of recommendation: IIa
	MPI	1 RCT, 1 case series	In patients with possible ACS and a normal ECG, normal cardiac troponins, and no history of CAD, it is reasonable to initially perform (without serial ECGs and troponins) rest myocardial perfusion imaging with a technetium-99m radiopharmaceutical to exclude myocardial ischemia	• Level of evidence: B • Class of recommendation: IIa
	Stress testing	4 observational studies	Noninvasive stress testing is recommended in low and intermediate-risk patients who have been free of ischemia at rest or with low-level activity for a minimum of 12 to 24 hours	• Level of evidence: B • Class of recommendation: I
	Exercise stress test	3 observational studies	Stress testing with an imaging modality should be used in patients who are	• Level of evidence: B

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
			able to exercise but have ST changes on resting ECG that may interfere with interpretation. In patients undergoing a low-level exercise test, an imaging modality can add prognostic information.	• Class of recommendation: I
	Pharmacological stress test	None cited.	Pharmacological stress testing with imaging is recommended when physical limitations preclude adequate exercise stress.	• Level of evidence: C • Class of recommendation: I

CCTA = coronary computed tomography, CMR = cardiac magnetic resonance, ECG = electrocardiogram, ECHO = echocardiography, IHD = ischemic heart disease, MPI = myocardial perfusion imaging, N/A = not applicable, NR = not reported, PET = positron emission tomography, RCT = randomized control trial, SPECT = single photon emission computed tomography.

* In 2014, an update to this guideline was published. However, none of the updates involved imagining modalities of interest to this review.

† According to NICE Guideline recommendation 1.3.3.1, assessing the typicality of chest pain should be done as follows:

· Presence of three of the features below is defined as typical angina.

· Presence of two of the three features below is defined as atypical angina.

· Presence of one or none of the features below is defined as non-anginal chest pain.

Anginal pain is:

· constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms

· precipitated by physical exertion

· relieved by rest or GTN within about 5 minutes.

2.9 Appropriate Use Criteria

Table 8. Summary of Appropriate Use Criteria for the Diagnosis of CAD in patients with chest pain

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and the Society of Thoracic Surgeons[56]* 2019 *2019 Appropriate Use Criteria for Multimodality Imaging in the Assessment of Cardiac Structure and Function in Nonvalvular Heart Disease*	F-18 FDG PET	Use of F-18 FDG PET for the initial evaluation when symptoms or signs suggest heart disease is rarely appropriate (test is not generally acceptable and is not a reasonable approach for the indication).	Median Appropriate Use Score: 2
		Use of F-18 FDG PET for the Initial evaluation of known or suspected HF (systolic or diastolic) based on symptoms, signs, or abnormal test results to assess systolic or diastolic function and to assess for possible etiology (CAD, valvular disease) is rarely appropriate (test is not generally acceptable and is not a reasonable approach for the indication).	Median Appropriate Use Score: 3
	MPI (SPECT/PET)	Use of MPI (SPECT/PET) for the initial evaluation when symptoms or signs suggest heart disease is rarely appropriate (test is not generally acceptable and is not a reasonable approach for the indication).	Median Appropriate Use Score: 2
		Use of MPI (SPECT/PET) for the Initial evaluation of known or suspected HF (systolic or diastolic) based on symptoms, signs, or abnormal test results to assess systolic or diastolic function and to assess for possible etiology (CAD, valvular disease) is appropriate (test is generally acceptable and is a reasonable approach for the indication).	Median Appropriate Use Score: 7
	CT (including CCTA)	Use of CT (including CCTA) for the initial evaluation when symptoms or signs suggest	Median Appropriate

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		heart disease may be appropriate (test may be generally acceptable and may be a reasonable approach for the indication). This also implies that more research and/or patient information is needed to classify the indication definitively.	Use Score: 4
		Use of CT (including CCTA) for the Initial evaluation of known or suspected HF (systolic or diastolic) based on symptoms, signs, or abnormal test results to assess systolic or diastolic function and to assess for possible etiology (CAD, valvular disease) may be appropriate (test may be generally acceptable and may be a reasonable approach for the indication). This also implies that more research and/or patient information is needed to classify the indication definitively.	Median Appropriate Use Score: 6
American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine[101]† 2009 *2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging*	Radionuclide Imaging	Use of Radionuclide Imaging for evaluation of ischemic equivalent (non-acute) in patients with: ● Low pretest probability of CAD ● ECG interpretable AND able to exercise is considered inappropriate.	Median Appropriate Use Score: 3
		Use of Radionuclide Imaging for evaluation of ischemic equivalent (non-acute) in patients with: ● Low pretest probability of CAD ● ECG uninterpretable OR unable to exercise is considered appropriate.	Median Appropriate Use Score: 7
		Use of Radionuclide Imaging for evaluation of ischemic equivalent (non-acute) in patients with: ● Intermediate pretest probability of CAD	Median Appropriate Use Score: 7

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		● ECG interpretable AND able to exercise is considered appropriate.	
		Use of Radionuclide Imaging for evaluation of ischemic equivalent (non-acute) in patients with: ● Intermediate pretest probability of CAD ● ECG uninterpretable OR unable to exercise is considered appropriate.	Median Appropriate Use Score: 9
		Use of Radionuclide Imaging for evaluation of ischemic equivalent (non-acute) in patients with: ● High pretest probability of CAD ● Regardless of ECG interpretability and ability to exercise is considered appropriate.	Median Appropriate Use Score: 9
		Use of Radionuclide Imaging in patients with chest pain and: ● Possible ACS ● ECG—no ischemic changes or with LBBB or electronically ventricular paced rhythm ● Low-risk TIMI score ● Peak troponin: borderline, equivocal, minimally elevated is considered appropriate.	Median Appropriate Use Score: 8
		Use of Radionuclide Imaging in patients with chest pain and: ● Possible ACS ● ECG—no ischemic changes or with LBBB or electronically ventricular paced rhythm ● High-risk TIMI score ● Peak troponin: borderline, equivocal, minimally elevated is considered appropriate.	Median Appropriate Use Score: 7

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		Use of Radionuclide Imaging in patients with chest pain and: ● Possible ACS ● ECG—no ischemic changes or with LBBB or electronically ventricular paced rhythm ● Low-risk TIMI score ● Negative peak troponin levels is considered appropriate.	Median Appropriate Use Score: 8
		Use of Radionuclide Imaging in patients with chest pain and: ● Possible ACS ● ECG—no ischemic changes or with LBBB or electronically ventricular paced rhythm ● High-risk TIMI score ● Negative peak troponin levels is considered appropriate.	Median Appropriate Use Score: 8
		Use of Radionuclide Imaging in patients with chest pain and definite ACS is considered inappropriate.	Median Appropriate Use Score: 1
		Use of Radionuclide Imaging in patients with chest pain (rest imaging only) and: ● Possible ACS ● ECG—no ischemic changes or with LBBB or electronically ventricular paced rhythm ● Initial troponin negative ● Recent or ongoing chest pain is considered appropriate.	Median Appropriate Use Score: 7
American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular	CCTA	Use of CCTA for the detection of CAD in symptomatic patients with the following conditions: ● ECG interpretable AND ● Able to exercise	Median Appropriate Use Score: 5

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance[240] 2010 *Appropriate Use Criteria for Cardiac Computed Tomography*		● Low pretest probability of CAD Is considered uncertain.	
		Use of CCTA for the detection of CAD in symptomatic patients with the following conditions: ● ECG interpretable AND ● Able to exercise ● Intermediate pretest probability of CAD Is considered appropriate.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with the following conditions: ● ECG interpretable AND ● Able to exercise ● High pretest probability of CAD Is considered inappropriate.	Median Appropriate Use Score: 3
		Use of CCTA for the detection of CAD in symptomatic patients with the following conditions: ● ECG interpretable AND ● Able to exercise ● Low pretest probability of CAD Is considered appropriate.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with the following conditions: ● ECG interpretable AND ● Able to exercise ● Intermediate pretest probability of CAD Is considered appropriate.	Median Appropriate Use Score: 8

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		Use of CCTA for the detection of CAD in symptomatic patients with the following conditions: ● ECG interpretable AND ● Able to exercise ● High pretest probability of CAD Is considered uncertain.	Median Appropriate Use Score: 4
		Use of CCTA for the detection of CAD in patients with acute symptoms with suspicion of ACS (urgent presentation) and definite MI is considered inappropriate.	Median Appropriate Use Score: 1
		Use of CCTA for the detection of CAD in patients with acute symptoms with suspicion of ACS (urgent presentation) and persistent ECG ST-segment elevation following exclusion of MI is considered uncertain.	Median Appropriate Use Score: 6
		Use of CCTA for the detection of CAD in patients with acute symptoms with suspicion of ACS (urgent presentation) and acute chest pain of uncertain cause (differential diagnosis includes pulmonary embolism, aortic dissection, and ACS [“triple rule out”]) is considered uncertain.	Median Appropriate Use Score: 6
		Use of CCTA for the detection of CAD in symptomatic patients with low pretest probability of CAD and normal ECG and cardiac biomarkers is considered appropriate.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with intermediate pretest probability of CAD and normal ECG and cardiac biomarkers is considered uncertain.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with high pretest	Median Appropriate

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		probability of CAD and normal ECG and cardiac biomarkers is considered uncertain.	Use Score: 4
		Use of CCTA for the detection of CAD in symptomatic patients with low pretest probability of CAD and an uninterpretable ECG is considered appropriate.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with intermediate pretest probability of CAD and an uninterpretable ECG is considered uncertain.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with high pretest probability of CAD and an uninterpretable ECG is considered uncertain.	Median Appropriate Use Score: 4
		Use of CCTA for the detection of CAD in symptomatic patients with low pretest probability of CAD and a nondiagnostic ECG or equivocal biomarkers is considered appropriate.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with intermediate pretest probability of CAD and a nondiagnostic ECG or equivocal biomarkers is considered uncertain.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with high pretest probability of CAD and a nondiagnostic ECG or equivocal biomarkers is considered uncertain.	Median Appropriate Use Score: 4
		Use of CCTA in patients with a prior normal ECG exercise test but continued symptoms is considered appropriate regardless of pretest probability of CAD.	Median Appropriate Use Score: 7
		Use of CCTA in patients with prior ECG exercise	Median

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		testing and a Duke Treadmill Score pointing to low risk findings is considered inappropriate.	Appropriate Use Score: 2
		Use of CCTA in patients with prior ECG exercise testing and a Duke Treadmill Score pointing to intermediate risk findings is considered appropriate.	Median Appropriate Use Score: 7
		Use of CCTA in patients with prior ECG exercise testing and a Duke Treadmill Score pointing to high risk findings is considered inappropriate.	Median Appropriate Use Score: 3
		Use of CCTA for sequential testing after stress imaging procedures resulting in discordant ECG exercise and imaging results is considered appropriate.	Median Appropriate Use Score: 8
		Use of CCTA on patients with prior stress imagining procedures and equivocal ischemia is considered appropriate.	Median Appropriate Use Score: 8
		Use of CCTA on patients with prior stress imagining procedures and mild ischemia is considered uncertain.	Median Appropriate Use Score: 6
		Use of CCTA on patients with prior stress imagining procedures and moderate or severe ischemia is considered inappropriate.	Median Appropriate Use Score: 2
		Use of CCTA on patients with a prior CAC score of zero >5 years ago is considered uncertain.	Median Appropriate Use Score: 2
		Use of CCTA on patients with a positive CAC score >2 years ago is considered inappropriate.	Median Appropriate Use Score: 2
		Use of CCTA on patients with a CAC score of <100 is considered appropriate.	Median Appropriate Use Score: 8

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		Use of CCTA on patients with a CAC score of 100 to 400 is considered appropriate.	Median Appropriate Use Score: 8
		Use of CCTA on patients with a CAC score of 401 to 1000 is considered uncertain.	Median Appropriate Use Score: 6
		Use of CCTA on patients with a CAC score of >1000 is considered uncertain.	Median Appropriate Use Score: 4
ACR/ACC/AHA/AATS/ACEP/ASNC/NASCI/ SAEM/SCCT/SCMR/SCPC/SNMMI/STR/STS[208] 2015 *Appropriate Utilization of Cardiovascular Imaging in Emergency Department Patients with Chest Pain*	CCTA	Use of CCTA in patients presenting to the ED with chest pain and who have had serial ECG and Troponin Negative for NSTEMI or ACS is considered appropriate.	NR
		Use of CCTA in patients presenting to the ED with chest pain and who have had serial ECG and Troponin borderline for NSTEMI or ACS is considered appropriate.	NR
	SPECT/PET Rest	Use of SPECT/PET Rest in patients presenting to the ED with chest pain and who have had serial ECG and Troponin Negative for NSTEMI or ACS is considered to be rarely appropriate.	NR
		Use of SPECT/PET in patients presenting to the ED with chest pain and who have had serial ECG and Troponin borderline for NSTEMI or ACS is considered to be rarely appropriate.	NR
	SPECT/PET Stress/Rest	Use of SPECT/PET Stress/Rest in patients presenting to the ED with chest pain and who have had serial ECG and Troponin Negative for NSTEMI or ACS is considered to be appropriate.	NR
		Use of SPECT/PET Stress/Rest in patients presenting to the ED with chest pain and who	NR

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		have had serial ECG and Troponin borderline for NSTEMI or ACS is considered to be appropriate.	
American College of Radiology[11] 2016 *Appropriateness Criteria®* *Chronic Chest Pain—High Probability of Coronary Artery Disease*	Tc-99m SPECT MPI rest and stress	Use of Tc-99m SPECT MPI rest and stress in patients with chronic chest pain and a high probability of CAD is considered to be usually appropriate.	Appropriate use rating: 9
	Arteriography coronary	Use of Arteriography coronary in patients with chronic chest pain and a high probability of CAD is considered to be usually appropriate.	Appropriate use rating: 9
	Rb-82 PET heart stress	Use of Rb-82 PET heart stress in patients with chronic chest pain and a high probability of CAD is considered to be usually appropriate.	Appropriate use rating: 8
	CTA coronary arteries with IV contrast	Use of CTA coronary arteries with IV contrast in patients with chronic chest pain and a high probability of CAD is considered to be usually appropriate.	Appropriate use rating: 8
	CT	Use of CT chest without and with IV contrast without and with IV contrast in patients with a high probability of CAD is considered to maybe be appropriate.	Appropriate use rating: 4
American College of Radiology[21] 2020 *Acute Nonspecific Chest Pain-Low Probability of Coronary Artery Disease*	CCTA	Use of CCTA coronary arteries with IV contrast in patients with acute nonspecific chest pain and low probability of CAD is considered to be usually appropriate.	NR
		Use of CCTA chest with IV contrast in patients with acute nonspecific chest pain and low probability of CAD is considered to be maybe appropriate.	NR
	CT	Use of CT chest without and with IV contrast in patients with acute nonspecific chest pain and low probability of CAD is considered to be	NR

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		maybe appropriate.	
		Use of CT heart function and morphology with IV contrast coronary in patients with acute nonspecific chest pain and low probability of CAD is considered to be usually not appropriate.	NR
	Arteriography coronary	Use of Arteriography coronary in patients with acute nonspecific chest pain and low probability of CAD is considered to be usually not appropriate.	NR
	SPECT or SPECT/CT MPI rest and stress	Use of SPECT or SPECT/CT MPI rest and stress in patients with acute nonspecific chest pain and low probability of CAD is considered to be usually not appropriate.	NR
American College of Radiology[216] 2018 *Chronic Chest Pain-Noncardiac Etiology Unlikely: Low to Intermediate Probability of Coronary Artery Disease*	CCTA	Use of CCTA coronary arteries with IV contrast in patients with chronic chest pain, noncardiac etiology unlikely, and low to intermediate probability of coronary artery disease is considered to be usually appropriate.	NR
	Rb-82 PET/CT heart	Rb-82 PET/CT heart in patients with chronic chest pain, noncardiac etiology unlikely, and low to intermediate probability of coronary artery disease is considered to be usually appropriate.	NR
	SPECT or SPECT/CT MPI	SPECT or SPECT/CT MPI rest and stress in patients with chronic chest pain, noncardiac etiology unlikely, and low to intermediate probability of coronary artery disease is considered to be usually appropriate.	NR
		SPECT or SPECT/CT MPI stress only in patients with chronic chest pain, noncardiac etiology unlikely, and low to intermediate probability of coronary artery disease is considered to be	NR

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		usually appropriate.	
		SPECT or SPECT/CT MPI rest only in patients with chronic chest pain, noncardiac etiology unlikely, and low to intermediate probability of coronary artery disease is considered to be usually not appropriate.	NR
	Arteriography coronary	Use of Arteriography coronary arteries without and with IV contrast in patients with chronic chest pain, noncardiac etiology unlikely, and low to intermediate probability of coronary artery disease is considered to be usually not appropriate.	NR
AIM Specialty Health[10] 2021 *Appropriate Use Criteria: Imaging of the Heart*	Nuclear Cardiology Myocardial Perfusion Imaging	**Among symptomatic patients with suspected CAD who have not had evaluation of CAD (MPI, stress echo, cardiac PET, coronary CTA or cardiac catheterization) within the preceding sixty (60) days, MPI is considered medically necessary in any of the following scenarios:** • Chest pain - With intermediate or high pretest probability of CAD **OR** - With low or very low pretest probability of CAD and high risk of CAD (using ASCVD Pooled Cohort Equations) • Atypical symptoms: shortness of breath (dyspnea), neck, jaw, arm, epigastric or back pain, sweating (diaphoresis), or exercise-induced syncope - With intermediate or high risk of CAD (using ASCVD Pooled Cohort Equations) • Other symptoms: palpitation, nausea, vomiting, anxiety, weakness, fatigue, or	NR

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		exercise-induced dizziness, lightheadedness, or near syncope, etc. - With high risk of CAD (using ASCVD Pooled Cohort Equations) • Patients with any cardiac symptom who have diseases/conditions with which coronary artery disease commonly coexists such as: - Abdominal aortic aneurysm; **OR** - Established and symptomatic peripheral vascular disease; **OR** - Prior history of cerebrovascular accident (CVA), transient ischemic attack (TIA) or carotid endarterectomy (CEA) or high grade carotid stenosis (>70%); **OR** - Chronic renal insufficiency or renal failure; **OR** • Patients who have undergone cardiac transplantation; **OR** • Patients in whom a decision has been made to treat with Interleukin 2; **OR** Patients awaiting solid organ transplantation **MPI is considered medically necessary for patients with established flow-limiting CAD (diagnosed by MPI, cardiac PET, stress echo, or coronary angiography (CCTA or invasive) demonstrating coronary stenosis greater than 70% or FFR less than or equal to 0.8) in patients who:** • Have new or worsening symptoms. • Have not undergone revascularization and have no symptoms or stable symptoms and	

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		either of the following scenarios applies: - No evaluation of coronary artery disease (MPI, stress echo, cardiac PET, coronary CTA, or cardiac catheterization) within the preceding 3 years - No evaluation of coronary artery disease (MPI, cardiac PET, stress echo, coronary CTA, or cardiac catheterization) within the preceding one (1) year in a patient who has undergone cardiac transplantation and has been found to have coronary artery disease since transplantation **MPI is considered medically necessary for patients who have established CAD and have had MI or unstable angina within the previous 90 days when BOTH the following criteria are met:** • Patient did not undergo coronary angiography at time of acute event • Patient is currently clinically stable **MPI is considered medically necessary for patients who have new onset arrhythmias (patient can be symptomatic or asymptomatic) in any of the following scenarios:** • Patients with sustained (lasting more than 30 seconds) or non-sustained (more than 3 beats but terminating within 30 seconds) ventricular tachycardia; OR • Patients with atrial fibrillation or flutter and high or intermediate risk of CAD (using ASCVD	

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		Pooled Cohort Equations); OR • Patients with atrial fibrillation or flutter and established CAD; OR • Patients who have frequent premature ventricular contractions (PVC) defined as more than thirty (30) PVCs per hour on ambulatory EKG (Holter) monitoring - It is not clinically indicated to perform MPI for evaluation of infrequent premature atrial or ventricular depolarizations **MPI is considered medically necessary for patients with abnormal exercise treadmill test (performed without imaging). This guideline applies to patients with suspected or established CAD.** • Abnormal findings on an exercise treadmill test include (chest pain, ST segment change, abnormal BP response or complex ventricular arrhythmias) **MPI is considered medically necessary for patients with abnormal findings on cardiac CT or CCTA** • Symptomatic patients with EITHER of the following: - Coronary artery calcium score > 400 Agatston units - Intermediate severity coronary stenosis on coronary CTA	
	CCTA and CT	**Indications where FFR-CT may be appropriate**	NR

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
	Derived Fractional Flow Reserve (FFR-CT)	**but is not a required capability of the performing imaging facility** • Suspected CAD in patients who have had abnormal exercise EKG test (performed without imaging) within the past 60 days. ○ When both the following apply: - Patient is symptomatic - During testing the patient had exercise-induced chest pain, ST segment change, abnormal blood pressure response, or complex ventricular arrhythmias. • Suspected CAD in patients who have had equivocal MPI or stress echocardiography within the past 60 days. ○ When both the following apply: - Patient is symptomatic - The imaging portion of the study is neither clearly normal nor clearly abnormal • Suspected CAD in patients who have had abnormal MPI or stress echocardiography within the past 60 days. ○ When both the following apply: - Patient is symptomatic - The imaging portion of the study is abnormal **Indications where FFR-CT may be appropriate and is a required capability of the imaging facility** • In symptomatic patients with suspected coronary artery disease who have abnormal	

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		resting EKG • In symptomatic patients with suspected coronary artery disease who have not had recent CAD evaluation - When no CAD imaging evaluation (MPI, cardiac PET, stress echo, CCTA or coronary angiography) has been performed within the preceding sixty (60) days.	
	PET Myocardial Imaging	Clinical Indications for PET Perfusion Imaging include: **Suspected coronary artery disease in symptomatic patients who have not had evaluation of coronary artery disease (MPI, stress echo, cardiac PET, coronary CTA or cardiac catheterization) within the preceding sixty (60) days** • Chest pain - With intermediate or high pretest probability of CAD (Table 1); **OR** - With low or very low pretest probability of CAD (Table 1) and high risk of CAD (SCORE) • Atypical symptoms: shortness of breath (dyspnea), neck, jaw, arm, epigastric or back pain, sweating (diaphoresis), or exercise-induced syncope - With intermediate or high risk of coronary artery disease (using ASCVD Pooled Cohort Equations) • Other symptoms: palpitation, nausea, vomiting, anxiety, weakness, fatigue, or exercise-induced dizziness, lightheadedness,	NR

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		or near syncope, etc. - With high risk of coronary artery disease (using ASCVD Pooled Cohort Equations) • Patients with any cardiac symptom who have diseases/conditions with which coronary artery disease commonly coexists such as: - Abdominal aortic aneurysm; **OR** - Established and symptomatic peripheral vascular disease; **OR** - Prior history of cerebrovascular accident (CVA), transient ischemic attack (TIA) or carotid endarterectomy (CEA) or high grade carotid stenosis (>70%); **OR** - Chronic renal insufficiency or renal failure; **OR** • Patients who have undergone cardiac transplantation; **OR** • Patients in whom a decision has been made to treat with Interleukin 2; **OR** • Patients awaiting solid organ transplantation **Patients with new onset arrhythmias (patient can be symptomatic or asymptomatic). (This guideline applies to patients with suspected or established CAD).** **Patients with new onset congestive heart failure or recently recognized left ventricular systolic dysfunction (patient can be symptomatic or asymptomatic). (This guideline applies to patients with suspected or established CAD).**	

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		Patients with abnormal exercise treadmill test (performed without imaging). (This guideline applies to patients with suspected or established CAD). **Patients with abnormal findings on cardiac CT or CCTA** • PET perfusion imaging is considered medically necessary in the following scenarios: • Symptomatic patients with EITHER of the following: - Coronary artery calcium score > 400 Agatston units - Intermediate severity coronary stenosis on coronary CTA	

ACS = acute coronary syndrome, ASCVD = AHA/ACC risk calculator, AUC = appropriate use criteria, CAC = coronary artery calcium, CAD = coronary artery disease, CCTA = coronary computed tomography, CT = computed tomography, ECG = electrocardiogram, ED = emergency department, FDG = Fludeoxyglucose, FFR = fractional flow reserve, IV = intravenous, MI = myocardial infarction, MPI = myocardial perfusion imaging, NR = not reported, NSTEMI = Non-ST-Segment Elevation Myocardial Infarction, PET = positron emission tomography, SPECT = single photon emission computed tomography, TIMI = Thrombolysis in Myocardial Infarction

* Imaging for each indication was then rated and classified as Appropriate (A), May Be Appropriate (M), or Rarely Appropriate (R) on the basis of these multiple rounds of review and revision.
Median Score 7 to 9: Appropriate test for specific indication (test is generally acceptable and is a reasonable approach for the indication).
Median Score 4 to 6: May Be Appropriate test for specific indication (test may be generally acceptable and may be a reasonable approach for the indication). May Be Appropriate also implies that more research and/or patient information is needed to classify the indication definitively.
Median Score 1 to 3: Rarely Appropriate test for specific indication (test is not generally acceptable and is not a reasonable approach for the indication).
† Score 7–9: Appropriate test for specific indication (test **is** generally acceptable and **is** a reasonable approach for the indication).
Score 4–6: Uncertain for specific indication (test **may** be generally acceptable and **may** be a reasonable approach for the indication). (Uncertainty also implies that more research and/or patient information is needed to classify the indication definitively.)
Score 1–3: Inappropriate test for that indication (test **is not** generally acceptable and **is not** a reasonable approach for the indication).

2.10 Expert Consensus Statements

Table 9. Summary Table of Expert Consensus Statements

Contributing Organization Year *Document Title*	Consensus
CCTA	
Society of Cardiovascular Computed Tomography[172] 2021 ***Expert consensus document on coronary computed tomographic angiography: A report of the society of Cardiovascular Computed Tomography***	**Evaluation of Stable Coronary Artery Disease: Coronary CTA in Native Vessels** • It is appropriate to perform CTA as the first line test for evaluating patients with no known CAD who present with stable typical or atypical chest pain, or other symptoms which are thought to represent a possible anginal equivalent (e.g. dyspnea on exertion, jaw pain). • It is appropriate to perform CTA as a first line test for evaluating patients with known CAD who present with stable typical or atypical chest pain, or other symptoms which are thought to represent a possible anginal equivalent (e.g. dyspnea on exertion, jaw pain • It is appropriate to perform coronary CTA following a non-conclusive functional test, in order to obtain more precision regarding diagnosis and prognosis, if such information will influence subsequent patient management. • It is recommended to perform CTA as the first line test when considering evaluation for revascularization strategies using the ISCHEMIA Trial. • It may be appropriate to perform CTA in selected asymptomatic high risk individuals, especially in those who have a higher likelihood of having a large amount of noncalcified plaque • It is rarely appropriate to perform coronary CTA in very low risk symptomatic patients, e.g., <40 years of age with non-cardiac symptoms (chest wall pain, pleuritic chest pain). • It is rarely appropriate to perform CTA in low- and intermediate risk asymptomatic patients **Evaluation of Stable Coronary Artery Disease: Coronary CTA Post Revascularization** • It is appropriate to perform coronary CTA in symptomatic patients with intracoronary stent diameter 3.0 mm. Measures to improve accuracy of stent imaging should be utilized, to include strict heart rate control (goal <60 bpm), iterative reconstruction,

Contributing Organization Year *Document Title*	Consensus
	sharp kernel reconstruction, and mono-energetic reconstructions (when available). Protocols to optimize stent imaging should be developed and followed. • It may be appropriate to perform coronary CTA in symptomatic patients with stents <3.0 mm, especially those known to have thin stent struts (<100 mm) in proximal, non-bifurcation locations. • It is appropriate to perform CTA for evaluation of patients with prior CABG, particularly if graft patency is the primary objective. • It is appropriate to perform CTA to visualize grafts and other structures prior to re-do cardiac surgery. **Evaluation of Stable Coronary Artery Disease: Coronary CTA with FFR or CTP** • It may be appropriate to perform CT derived FFR and CT myocardial perfusion Imaging to evaluate the functional significance of intermediate stenoses on CTA (30-90% diameter stenosis) particularly in the setting of multivessel disease to help guide ICA referral and revascularization treatment planning. LM stenosis ≥50% and severe triple vessel disease should undergo invasive coronary angiography. • Adding FFRCT and stress-CTP to CTA increases specificity, positive predictive value, and diagnostic accuracy over regular CTA. • FFRCT and stress-CTP may be largely comparable in diagnostic utility. CTP is a potentially valuable alternative particularly when CT-FFR is technically difficult (e.g., suboptimal CTA quality, prior revascularization). **Evaluation of Stable Coronary Artery Disease: Coronary CTA in Other Conditions** • It is appropriate to perform CTA for coronary artery evaluation prior to noncoronary cardiac surgery as an equivalent alternative to invasive angiography in selected patients, e.g., low-intermediate probability of CAD, younger patients with primarily non-degenerative valvular conditions. • CTA may be considered an appropriate alternative to other noninvasive tests for evaluation of selected patients prior to noncardiac surgery. • It is appropriate to perform CTA to exclude coronary artery disease in patients with suspected non-ischemic cardiomyopathy.

Contributing Organization Year *Document Title*	Consensus
	• It may be appropriate to perform late enhancement CT imaging to detect infiltrative heart disease or scar in selected patients who have non-ischemic or ischemic cardiomyopathy and who cannot undergo cardiac MRI. Such imaging may be performed if it has the potential to impact the diagnosis and/or treatment (e.g. planning for ablation therapy) • It may be appropriate to perform CTA as an alternative to invasive coronary angiography for the screening of patients for coronary allograft vasculopathy in selected clinical practice settings. • It is appropriate to perform CTA for the evaluation of coronary anomalies. • It is appropriate to EKG gate aortic dissection and aneurysm CTA, as well as pulmonary embolus studies in men >45 years and women >55 years, and analyze and report the coronary arteries. • CTA with a limited delayed image (60e90 sec) is an appropriate alternative to TEE when the primary aim is to exclude LA/LAA thrombus and in patients where the risks associated with TEE outweigh the benefits. In all situations CTA and TEE should be discussed with the patient in the setting of shared decision making. • It may be appropriate to perform late enhancement CT imaging for the evaluation of myocardial viability in selected patients who cannot undergo cardiac MRI. Such imaging may be performed if it has the potential to impact the diagnosis and/or treatment (e.g. planning for revascularization). **Reporting on CTA: Coronary and Non Coronary Information** • The CAD-RADs reporting is recommended. • It is appropriate to report prior myocardial infarction when its features are evident on CTA. • It is appropriate to report remote myocardial infarction when fatty metaplasia or calcification within an area of infarction are present.
Cardiovascular Medicine and Society[195] 2020	**To move forward toward a coronary CTA–first paradigm, this ACC Summit Team recommends the following:** 1. Use coronary CTA as the default test for evaluating patients with stable chest pain and low-

Contributing Organization Year *Document Title*	Consensus
Current Evidence and Recommendations for Coronary CTA First in Evaluation of Stable Coronary Artery Disease	to-intermediate pre-test probability of obstructive CAD and for those with high pre-test probability of significant obstructive CAD, to rule out the presence of left main CAD, particularly when a conservative treatment strategy is selected. 2. Increase payment for coronary CTA. Specifically, cardiac CT services should be moved to an Ambulatory Payment Classification group with tests that are more similar with respect to clinical scope and resource use. Importantly, increased advocacy, support, and collaboration with ACC will be needed to work with CMS and congress to implement such changes effectively. 3. Explore options for "bundled payments" for cardiac testing. Value-based models would increase incentives to use coronary CTA to avoid other, more costly noninvasive or invasive diagnostic procedures. To start, shared savings models that reduce current average cost from first chest pain onset to 90 days post-evaluation or postintervention could be developed. 4. Identify expert and financial support to increase the number of capable coronary CTA providers. 5. Develop strategies to improve provider and delivery team competency in performing coronary CTA: update training guidelines for cardiovascular fellows, CT technologists, and other ancillary staff, including continuing education and periodic quality assessment. Grandfather training rules to allow more practicing cardiologists to obtain credentials with the support of ACC and industry sponsors. Use remote technologies such as telemedicine to expand the reach of training and delivery. 6. Establish an ACC coronary CTA registry for evaluating chest pain. This registry should include medical and economic variables to evaluate "total cost of care" associated with coronary CTA. Ideally, commercial payers will collaborate with the ACC on this registry to validate costs. 7. Improve advocacy for coronary CTA by direct engagement with public and private payers. Work with CMS and Congress to establish more equitable payment for coronary CTA procedures. 8. Engage commercial payers in discussions on eliminating pre-approvals for coronary CTA and FFR CT for providers participating in the coronary CTA registry. 9. Improve education of cardiologists and primary care physicians on when to consider coronary CTA testing (vs. other techniques) and how to use the

Contributing Organization **Year** ***Document Title***	**Consensus**
	results in patient management.
Canadian Cardiovascular Society, Canadian Association of Radiologists Canadian Association of Nuclear Medicine, Canadian Nuclear Cardiology Society, Canadian Society of Cardiac Magnetic Resonance[22] 2007 ***Joint Position Statement on Advanced Non-invasive Cardiac Imaging using Positron Emission Tomography, Magnetic Resonance Imaging and Multi-Detector Computed Tomographic Angiography in the Diagnosis and Evaluation of Ischemic Heart Disease***	**CAD Detection with CT Angiography** <u>*Class I Indication*</u> 1. Assessment of anomalous coronary arteries (Level C evidence). *Class IIa Indications* 1. 16- or 64-slice MDCT for patient diagnosis of significant coronary artery disease (≥ 50% diameter stenosis)(Level B evidence); 2. 16- or 64-slice MDCT for identification of coronary artery segments with significant stenosis (≥ 50% diameter stenosis) in coronary segments ≥ 1.5 mm in diameter (Level B evidence); 3. 16- and 64-slice MDCT for the assessment of graft patency (Level B evidence). <u>*Class IIb Indication*</u> 1. 64-slice MDCT for the assessment of all coronary segments including those with vessel diameters < 1.5 mm (Level B evidence). <u>*Class III (no benefit or harmful)*</u> 1. Diagnosis of CAD in patients with a. irregular dysrhythmias (atrial fibrillation, frequent extrasystoles); b. severe coronary calcification; c. inability to perform sufficient breath-holds; d. renal failure or other contraindications to intravenous contrast agents; e. contraindications to radiation exposure.
Quantitative Cardiac Imaging Study Group[53] 2020 ***Clinical quantitative cardiac imaging for the assessment of myocardial ischemia***	**Cardiac CT** • CT perfusion imaging is not frequently used, whereas CT angiography offers highly accurate coronary angiography. • Challenges of cardiac CT include limited temporal resolution, beam and scatter artefacts, radiation dose and low contrast-to-noise ratios. • CT systems with increased rotation speed, photon counting energy-selective X-ray detectors and advanced machine learning technology, as well as two-compartment analysis could overcome the technological challenges. • The combined assessment of stenosis and characterization of atherosclerosis in

Contributing Organization **Year** ***Document Title***	**Consensus**
	relation to myocardial ischemia promises the greatest clinical value but requires testing in trials. • Evaluation of patients with insufficient angiographic image quality or borderline stenosis on coronary CT angiography might be improved with the use of CT for myocardial ischemia.
Nuclear Imaging (SPECT/PET)	
Canadian Cardiovascular Society, Canadian Association of Radiologists Canadian Association of Nuclear Medicine, Canadian Nuclear Cardiology Society, Canadian Society of Cardiac Magnetic Resonance[22] 2007 ***Joint Position Statement on Advanced Non-invasive Cardiac Imaging using Positron Emission Tomography, Magnetic Resonance Imaging and Multi-Detector Computed Tomographic Angiography in the Diagnosis and Evaluation of Ischemic Heart Disease***	**Myocardial Perfusion Imaging (MPI) using PET for Diagnosis and/or Risk Stratification of CAD** <u>*Class I Indications*</u> 1. Pharmacological MPI using PET for the diagnosis of CAD* and/or risk stratification of patients who a. have non-diagnostic non-invasive imaging tests or where such a test does not agree with clinical diagnosis (Level B evidence). b. may be prone to artifact that could lead to an equivocal other test, such as obese patients (Level B evidence); c. are unable to exercise or have left bundle branch block (LBBB) or ventricular pacing (Level B evidence). <u>*Class IIa Indications*</u> 1. Pharmacological MPI using PET for the diagnosis of CAD for patients with intermediate pretest likelihood of disease and/or risk stratification of patients who are able to exercise (Level B evidence); 2. For diagnosis and risk stratification of patients being considered for high-risk non-cardiac surgery who have intermediate clinical risk predictors; or have mild clinical risk predictors with poor functional capacity (<4 METS) (Level B/C evidence). <u>*Class IIb Indications*</u> 1. Exercise PET using MPI for the diagnosis of CAD and/or risk stratification (Level B evidence); 2. Quantification of myocardial flow to determine the hemodynamic significance of a given coronary stenosis or to diagnose balanced multivessel disease (Level B/C evidence); 3. Quantification of myocardial flow to define impaired microvascular function (e.g. Syndrome

Contributing Organization **Year** ***Document Title***	**Consensus**
	X) (Level B/C evidence). <u>*Class III (no benefit or harmful)*</u> 1. Contraindications to all pharmacological agents (dipyridamole, adenosine, dobutamine); 2. Unstable pattern of ischemic chest pain; 3. Contraindications to radiation exposure.
Quantitative Cardiac Imaging Study Group[53] 2020 ***Clinical quantitative cardiac imaging for the assessment of myocardial ischemia***	**SPECT** • SPECT is most commonly used in the clinic for myocardial perfusion imaging. • Challenges of SPECT include radiation dose and limited quantification of myocardial perfusion. • Dedicated cardiac SPECT cameras have emerged, with improved sensitivity and resolution at lower radiation doses and in patients with challenging features (including those with a high BMI). • Quantitative measures of the perfusion defect size have become more widely available as diagnostic and prognostic markers with the introduction of solid- state detector CZT technology. • Dynamic imaging enables compartmental modelling and provides absolute measures of myocardial ischemia, thereby bringing SPECT closer to PET as the reference standard. **PET** • PET is the clinical reference standard for the quantification • of myocardial perfusion. • Challenges of PET use include limited visual assessment of quantitative 15O- water PET and the lower spatial resolution of PET compared with CT or MRI perfusion imaging. • Small or 13N- ammonia cyclotrons, as well as the availability of 18F- labelled tracers, could improve the cost- effectiveness of cardiac PET imaging, as well as logistics and dissemination. • Quantitative measures of myocardial ischemia are provided with the addition of the measurement of viability and functional parameters during a single scan.

Contributing Organization Year *Document Title*	Consensus
	• Hybrid imaging combining PET perfusion imaging with coronary CT angiography data might provide comprehensive assessment, especially in patients with multivessel disease.
Society of Nuclear Medicine and Molecular Imaging & ASNC[169] 2018 ***Clinical Quantification of Myocardial Blood Flow Using PET: Joint Position Paper of the SNMMI Cardiovascular Council and the ASNC***	**Assessment of Myocardial Blood Flow (MBF) and Myocardial Flow Reserve (MFR) using PET** • A relationship between the severity of epicardial coronary artery stenoses and PET measures of both peak hyperemic stress MBF and MFR has been established for more than 2 decades. • Though initially established using 15O-water, this finding was quickly replicated using 13N-ammonia and more recently using 82Rb. • The application of stress MBF and MFR for improving the diagnostic accuracy of PET MPI with clinical protocols has been investigated by many groups with both 13N-ammonia and 82Rb. • Although these studies have consistently demonstrated improved diagnostic sensitivity, at least 2 large studies have raised concerns about potential for decreased specificity, possibly due to the contributions of diffuse atherosclerosis and microvascular disease to stress MBF and MFR measurements. • Consequently, the positive predictive value of even severely depressed (<1.5) MFR is only modest. • Conversely, preserved MFR (>2.0) has an excellent negative predictive value for high-risk CAD (i.e., left main and 3-vessel disease), and high-risk disease is extremely uncommon with an MFR of more than 2.5.
Myocardial CT Perfusion	
Society of Cardiovascular Computed Tomography[188] 2020 ***Society of cardiovascular computed tomography expert consensus document on myocardial computed tomography perfusion imaging***	**Absolute contraindications to pharmacologic stress myocardial CT perfusion** • High-risk unstable angina • Decompensated or inadequately controlled CHF • Uncontrolled hypertension (BP > 200/110) • Hypotension (SBP<90 mm Hg) • Known contrast allergy, unless pre-treated • Allergy to stress agent • Uncontrolled cardiac arrhythmias

Contributing Organization Year *Document Title*	Consensus
	• Severe symptomatic aortic stenosis. • Bronchospastic Lung Disease (avoid adenosine and dipyridamole; regadenoson may be considered unless active wheezing) • Acute pulmonary embolism. • Active CVA • Acute myocarditis or pericarditis. • Acute aortic dissection. • Severe pulmonary hypertension. • Acute myocardial infarction. • Acutely ill for any reason. • Severe renal Insufficiency (GFR<30mi/min/BSA) • High-degree (AV) block. • Unable to cooperate with breath hold instructions. • Any caffeine, theophylline, or chocolate consumption in the last 12 hours **Relative contraindications to pharmacologic stress myocardial CT perfusion** • Known left main coronary stenosis >50% • Hypertrophic obstructive cardiomyopathy or other forms of outflow tract obstruction • Electrolyte abnormalities • Significant tachyarrhythmias or bradyarrhythmia • Recent stroke • Recent seizure • Heart rate >100, and cannot be treated with beta blockers • Moderate renal insufficiency (GFR 30-60mi/min/BSA) • Morbid Obesity (BMI>40) **Key Consensus Statements for Myocardial CT Perfusion** 1. We recommend that myocardial CTP may be added to coronary CTA when there is a high likelihood of ischemic heart disease, known CAD, prior coronary intervention, or significant calcifications, Additionally, CTP may be added when there is a known stenosis of indeterminate functional significance. In such cases, myocardial CTP is

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	recommended if knowledge regarding the presence and severity of ischemia would impact patient management and CTP is feasible. 2. Myocardial CTP imaging with pharmacologic stress testing requires supervision by a trained medical provider who is experienced in the administration of pharmacologic stress agents and stress testing. 3. Continuous 12-lead ECG monitoring may be performed using radiolucent electrodes and leads. Alternatively, 12-lead ECG monitoring can be interrupted during scan acquisition while continuous rhythm is still being recorded and monitored by the scanner console. Upon the completion of imaging, a 12 lead ECG should be performed to ensure there are no significant changes from baseline suggestive of post-stress myocardial ischemia or injury. 4. If an automated bolus-tracking algorithm is utilized, a region of interest should be defined in either the proximal-ascending or mid-descending thoracic aorta. The automated trigger should be set to a Hounsfield Unit (HU) threshold that is ~80-100HU above the baseline HU of the selected reference area immediately prior to the contrast injection. After the scanner is triggered, a short pause (~5 seconds) is required to allow for breath-hold instructions to be given. Contrast dose and flow rate is typically ~60–70ml injected at 5–6ml/sec. 5. The optimal sequence of scans (rest first versus stress first) has not been determined and either sequence has advantages and disadvantages. Our committee suggests assessment of factors that could impair exclusion of obstructive CAD on coronary CTA (e.g. significant coronary calcium, prior coronary event or coronary revascularization, high pre-test probability of obstructive CAD) prior to decision to perform CTP. Those patients with a high likelihood or known significant coronary disease or severe amount of CAC may undergo stress myocardial perfusion imaging first; whereas, patients who lack the above features may undergo coronary CTA first. 6. A delay of 10–20 minutes between the rest and stress CT acquisitions is recommended to minimize myocardial contrast agent contamination and to eliminate the potential adverse interaction of pharmacologic stress agents and nitroglycerin administration. 7. There is no consensus about whether imaging should be performed at end-systole or during diastasis although most larger trials to date have selected diastole. A

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	multiphase acquisition which includes phases from both systole and diastole can be considered so that the phase with the least amount of artifact can be selected for analysis retrospectively. 8. For optimal image interpretation, images may be reconstructed from multiple phases of the cardiac cycle, typically at 5–10% intervals of the R-R image acquisition window and raw CTA and CTP data files should be retained until image interpretation is complete. 9. In static visual CTP interpretation, myocardial images are typically arranged using three standard orthogonal views - the short axis, vertical long axis, and horizontal long axis. CTP images usually use a narrow window width of ∼200–300 and level setting of ∼100–150 with an average slice thickness of 5–8 mm. Images may be viewed in minimal intensity projection (MinIP) or average intensity projections 10. Perfusion defects should be described in terms of size, transmurally, and reversibility in the context of the degree of stenosis in the supplying coronary artery.
Echocardiography	
Quantitative Cardiac Imaging Study Group[53] 2020 ***Clinical quantitative cardiac imaging for the assessment of myocardial ischemia***	**Echocardiography** • Echocardiography is most commonly applied for cardiac function imaging but is increasingly also being used for the assessment of myocardial perfusion and can be performed at the bedside. • The challenges of echocardiography include the common presence of noise and artefacts, lack of reproducibility, variable image quality and time- consuming manual analysis. • High frame rate echocardiography allows the estimation of myocardial blood velocity as a semiquantitative measure of myocardial ischemia with improved image quality. • Artificial intelligence solutions using machine learning for automated myocardial segmentation promise automated and fast segmentation and perfusion quantification. • Evaluation of patients with suspected acute coronary syndrome at the bedside is the primary strength of echocardiography when performed by experienced operators.

BMI = body mass index, CABG = coronary artery bypass graft, CAC = coronary artery calcium, CAD = coronary artery disease, CHF = congestive heart failure, CT = computed tomography, CTA = computed tomography angiogram, CTP = computed tomography perfusion, ECG = electrocardiogram, FFR = fractional flow reserve, MDCT = multi-detector

computed tomography, mm = millimeter, MPI = myocardial perfusion imaging, MRI = magnetic resonance imaging, PET = positron emission tomography, TEE = transesophageal echocardiogram.

2.11 Medicare and Representative Private Insurer Coverage Policies

Table 10. Summary table of payer policies for CCTA (including FFR)

Payer (year)	Evidence Base	Covered	Not Covered
CMS (2021) National Coverage Determination (NCD) for Noninvasive Fractional Flow CT *No other NCD was determined to be appropriate at this time*	2 SRs of diagnostic accuracy 5 diagnostic accuracy studies 1 prospective observational cohort 3 retrospective observational studies 1 registry study	FDA-approved FFRct technology may be considered reasonable and necessary in the management of patients with symptomatic, stable ischemic heart disease (SIHD) when the CCTA analysis is completed and demonstrates one of the following criteria: 1. Left main disease with intermediate coronary stenosis (lumen diameter reduction of 30-50%); **OR** 2. Proximal and mid-left anterior descending (LAD) coronary artery disease with intermediate stenosis (lumen reduction 40-70%); OR Proximal and mid-left circumflex disease with intermediate coronary stenosis (lumen reduction 40-70%; (considered equivalent to two-vessel disease); OR 3. Proximal two- or three-vessel disease with intermediate coronary stenosis in at least two vessels; OR 4. Right coronary disease with intermediate (lumen reduction 40-70%) coronary stenosis This service should be performed in patients with stable coronary symptoms. It should not be performed until after the base study (CCTA) has been completed and interpreted. If higher grade stenoses (i.e., >70%) are present, this study is not medically necessary, as the patient should proceed to catheterization. Similarly, low-grade stenoses (< 30%) do not require additional confirmatory data. If more than two intermediate risk coronary lesions are identified, the clinical situation is considered high risk, and the patient should proceed directly to catheterization.	FFRct is not considered reasonable in the following clinical circumstance: 1. Severe obesity (BMI > 39 kg/m2) 2. Prior placement of prosthetic valves 3. Known severe aortic stenosis 4. Prior placement of grafts in coronary bypass surgery 5. Suspicion of acute coronary syndrome (where MI or unstable angina have not been ruled out) 6. Intracoronary metallic stent 7. Status post-heart transplantation 8. Recent MI (30 days or less) 9. Prior pacemaker or defibrillator lead placement 10. Newly diagnosed systolic heart failure, with no prior left heart catheterization 11. Left main coronary artery disease with Intermediated Coronary Stenosis (lumen reduction less than or equal to 30%) 12. Non-obstructing stenosis (<50% of all major epicardial vessels) on CTA or catherization in the past twelve months, in the absence of a new symptom complex

Payer (year)	Evidence Base	Covered	Not Covered
Aetna (2019)	See Appendix N for references	Using 64-slice or greater, medically necessary for the following indications: A. Rule out obstructive coronary stenosis in persons with a low or intermediate pre-test probability of coronary artery disease or atherosclerotic cardiovascular disease by Framingham risk scoring, Pooled Cohort Equations, or by American College of Cardiology (ACC) criteria (see Appendix) who: i. Are symptomatic ii. Have a positive (i.e., greater than or equal to 1 mm ST segment depression) stress test C. Evaluation of asymptomatic persons at an intermediate pre-test probability of coronary heart disease or atherosclerotic cardiovascular disease by Framingham risk scoring or Pooled Cohort Equations who have an equivocal or uninterpretable exercise or pharmacological stress test or have resting electrocardiogram (ECG) changes (such as left bundle branch block (LBBB), pathologic q-waves, or right bundle branch block (RBBB) with left anterior fascicular block (LAFB) in which coronary artery disease (CAD) is a possible etiology. Note: Current guidelines from the American Heart Association recommend against routine stress testing for screening asymptomatic adults. D. Pre-operative assessment of/for: i. Persons scheduled to undergo 'high-risk" non-cardiac surgery, where an imaging stress test or invasive coronary angiography is being deferred unless absolutely necessary. The ACC defines high-risk surgery as emergent operations, especially in the elderly, aortic and other major vascular surgeries, peripheral vascular surgeries, and anticipated prolonged surgical procedures with large fluid shifts and/or blood loss involving the abdomen and thorax. ii. Planned non-coronary cardiac surgeries including valvular heart disease, congenital heart disease, and pericardial disease, in lieu of cardiac catheterization as the initial imaging study, in persons with low or intermediate pretest	Experimental and investigational for persons with any of the following contraindications to the procedure because its effectiveness above has not been established: • Body mass index (BMI) greater than 40 (except when 3rd generation Dual-Source CT (DSCT) 120-kv tube voltage is utilized). • Inability to image at desired heart rate (under 80 beats/min), despite beta blocker administration. • Person with allergy or intolerance to iodinated contrast material • Persons in atrial fibrillation (except when rate-controlled and 3rd generation Dual-Source CT (DSCT) 120-kv tube voltage is utilized) or with other significant arrhythmia. • Persons with extensive coronary calcification by plain film or with prior Agatston score greater than 1000. • for screening of asymptomatic persons, evaluation of atherosclerotic burden, evaluation of persons at high pre-test probability of coronary artery disease, evaluation of stent occlusion or in-stent restenosis, evaluation of persons with an equivocal PET rubidium study, identification of vulnerable plaques, monitoring of atheroma burden,

Payer (year)	Evidence Base	Covered	Not Covered
		risk of obstructive CAD. F. Detection and delineation of suspected coronary anomalies in young persons (less than 30 years of age) with suggestive symptoms (e.g., angina, syncope, arrhythmia, and exertional dyspnea without other known etiology of these symptoms in children and adults; dyspnea, tachypnea, wheezing, periods of pallor, irritability (episodic crying), diaphoresis, poor feeding and failure to thrive in infants). G. Calculation of fractional flow reserve (HeartFlow FFR) for persons who have a coronary CTA that has shown coronary artery disease of uncertain functional significance, or is non-diagnostic.	and for all other indications (e.g., atrial angiosarcoma). Note: The selection of CT angiography should be made within the context of other testing modalities such as stress myocardial perfusion images or cardiac ultrasound results so that the resulting information facilitates the management decision and does not merely add a new layer of testing. • Aetna considers coronary CT angiography experimental and investigational for assessment of coronary atherosclerosis in asymptomatic diabetics who do not otherwise meet the above criteria for CT coronary angiography because of insufficient evidence.
BCBS of NC Corporate Medical Policy (2018)	See Appendix N for references	The use of CT Coronary Angiography (CCTA), with or without Fractional Flow Reserve assessed by CT (FFR-CT) may be covered when accompanied by pre-test considerations as well as supporting clinical data and prerequisite information based on the following diagnostic indications: A. Indications where FFR-CT will not be required in conjunction with CCTA: i. Congenital coronary artery anomalies • For evaluation of suspected congenital anomalies of the coronary arteries. B. Indications where FFR-CT may be appropriate but is not a required capability of the performing imaging facility: i. Congestive heart failure/cardiomyopathy/LV dysfunction • For exclusion of coronary artery disease in patients with	The use of CT Coronary Angiography (CCTA), with or without Fractional Flow Reserve assessed by CT (FFR-CT) is considered investigational for all other indications.

Payer (year)	Evidence Base	Covered	Not Covered
		left ventricular ejection fraction <55% and low to moderate coronary heart disease risk (using standard methods of risk assessment, such as SCORE risk calculation) in whom CAD had not been excluded as the etiology of the cardiomyopathy. • Patients with high coronary heart disease risk should undergo cardiac catheterization. ii. Pre-operative evaluation for patients undergoing non-coronary cardiac surgery • Evaluation of symptomatic* or asymptomatic patients at moderate coronary heart disease risk (using standard methods of risk assessment, such as the SCORE risk calculation) to avoid an invasive angiogram, where all the necessary pre-operative information can be obtained using cardiac CT. • Procedures include open and percutaneous valvular procedures or ascending aortic surgery iii. Suspected coronary artery disease in symptomatic* patients who: • Have *not had evaluation* of coronary artery disease (MPI, cardiac PET, stress echo, CCTA or cardiac catheterization) within the preceding 60 days a. When both of the following apply: 1. Patient has low or moderate coronary heart disease risk (using standard methods of risk assessment such as the SCORE risk calculation) AND 2. During testing the patient had exercise-induced chest pain, ST segment change, abnormal BP response or complex ventricular arrhythmias • Have *had equivocal MPI or SE* within the past 60 days a. When both of the following apply: 1. Patient has low or moderate coronary heart disease risk (using standard methods of risk	

Payer (year)	Evidence Base	Covered	Not Covered
		assessment such as the SCORE risk calculation)AND 2. The imaging portion of the study is neither clearly normal nor clearly abnormal • Have had *abnormal MPI or stress echo* within the past 60 days a. When both of the following apply: 1. Abnormal MPI or stress echo is suspected to be false positive on the basis of low coronary heart disease risk (using standard methods of risk assessment such as the SCORE risk calculation) AND 2. The imaging portion of the study is abnormal • Have abnormal resting EKG • Have not had a recent CAD evaluation (MPI, cardiac PET, stress echo, CCTA or coronary angiography) within the preceding 60 days C. Indications where FFR-CT may be appropriate and is a required capability of the imaging facility i. Suspected CAD in symptomatic* patients who have abnormal resting EKG • When resting EKG abnormalities (left bundle branch block, electronically paced ventricular rhythm, left ventricular hypertrophy with repolarization abnormalities, resting ST segment depression 1 mm or more, digoxin effect or pre-excitation syndrome) would render an exercise treadmill test (without imaging) uninterpretable ii. Suspected CAD in symptomatic* patients who have not had recent CAD evaluation • When no CAD imaging evaluation (MPI, cardiac PET, stress echo, CCTA or coronary angiography) has been performed within the preceding sixty (60) days	

Payer (year)	Evidence Base	Covered	Not Covered
Cigna 2020	See Appendix N for references	A. Symptomatic individuals who have a 'low' or 'intermediate' pretest probability of CAD* B. 'Low' or 'intermediate' pre-test probability of coronary disease with persistent symptoms after a stress test. C. Replace performance of invasive coronary angiogram in individuals with low risk of CAD (i.e. Pre-op non-coronary surgery). D. For symptomatic individuals, evaluate post-CABG graft patency when only graft patency is a concern and imaging of the native coronary artery anatomy is not needed, such as in early graft failure. Additional Indications: E. Re-do CABG F. Evaluate coronary artery anomalies and other complex congenital heart disease of cardiac chambers or great vessels. G. Anomalous coronary artery(ies) suspected for diagnosis or to plan treatment and less than age 40 with a history that includes one or more of the following : i. Persistent exertional chest pain and normal stress test, ii. Full sibling(s) with history of sudden death syndrome before age 30 or with documented anomalous coronary artery, iii. Resuscitated sudden death and contraindications for conventional coronary angiography. iv. Prior nondiagnostic coronary angiography in determining the course of the anomalous coronary artery in relation to the great vessels, origin of a coronary artery or bypass graft location. H. Unexplained new onset of heart failure. I. Evaluation of newly diagnosed congestive heart failure or cardiomyopathy. i. No prior history of coronary artery disease, the ejection fraction is less than 50 ii. percent, and low or intermediate risk on the pre-test probability assessment, and iii. No exclusions to cardiac CT angiography.	NR

Payer (year)	Evidence Base	Covered	Not Covered
		iv. No cardiac catheterization, SPECT, cardiac PET, or stress echocardiogram has been performed since the diagnosis of congestive heart failure or cardiomyopathy. J. Ventricular tachycardia (6 beat runs or greater) if CCTA will replace conventional invasive coronary angiography. K. Equivocal coronary artery anatomy on conventional cardiac catheterization. L. Newly diagnosed dilated cardiomyopathy. M. Preoperative assessment of the coronary arteries in individuals who are going to undergo surgery for aortic dissection, aortic aneurysm, or valvular surgery if CCTA will replace conventional invasive coronary angiography. N. Vasculitis/Takayasu's/Kawasaki's disease O. Cardiac Trauma Indications for FFR-CT A. To further assess CAD seen on a recent CCTA that is of uncertain physiologic significance	
Wisconsin Physicians Service Insurance Corporation (2017) Local Coverage Determination States covered: Iowa, Kansas, Missouri, Nebraska, Indiana, Michigan.	None cited.	A. Alternative to invasive angiography and stress testing. For patients with anginal symptoms, patients with unclear stress tests results, patients in whom the stress test result contradicts the clinical assessment, to determine the patency of coronary artery bypass grafts, as an alternative when cardiac catheterization is impossible or carries a high risk, to rule out stenosis before non-coronary cardiac surgery such as valve replacement or resection of tumors, and clarifying unclear finding after invasive angiography. B. Assess patients suspected of having a congenital coronary anomaly of great vessels, cardiac chambers and valves. It is often used after an anomaly has been identified following a different test such as prior invasive coronary angiogram. CCTA is used to decide if surgery is indicated and for surgical planning. C. Evaluate acute chest pain in the emergency department (ED). The rationale is to quickly triage patients in order to rule out coronary artery disease as a possible cause of symptoms. Many will present	A. The test is never covered for screening, i.e., in the absence of signs, symptoms or disease. B. The test will be considered not medically necessary if the anticipated results are not expected to provide new, additional information to that already previously obtained from other tests (such as stress myocardial perfusion images or cardiac ultrasound). New or additional information should facilitate the management decision, not merely add a new layer of testing. C. The test will be considered not

Payer (year)	Evidence Base	Covered	Not Covered
		with a normal electrocardiogram and myocardial enzymes. D. Assess coronary or pulmonary venous anatomy. Coronary mapping is primarily for pre-surgical planning such as pacemaker lead placement in the lateral coronary vein to resynchronize cardiac contraction in patients with heart failure, or guiding biventricular pacemaker placement. Pulmonary vein anatomy can vary from patient to patient. Pulmonary vein mapping is primarily for catheter ablation which can isolate electrical activity from the pulmonary veins and allow for the elimination of recurrent atrial fibrillation, or help eliminate procedural complications. E. Assess etiology with new onset heart failure for evaluation of coronary arteries.	medically necessary if pretest evaluation indicates that the patient would require invasive cardiac angiography for further diagnosis or for therapeutic intervention. D. The test may be denied, on post-pay review, as not medically necessary when used for cardiac evaluation if there were pre-test knowledge of sufficiently extensive calcification of the suspect coronary segment that would diminish the interpretive value. (e.g., angina decubitus, unstable angina, Prinzmetal angina, etc.) E. Coverage is limited to devices that process thin, high resolution slices (1mm or less). The multi-detector scanners must have at least 64 slices per rotation capability. F. The administration of beta blockers and the monitoring of the patient during MDCT/CCTA by a physician experienced in the use of cardiovascular drugs is included as part of the test and is not a separately payable service. G. All studies must be ordered by the physician/qualified non-physician practitioner treating the H. patient and who will use the results of the test in the management of the patient. I. The test must be performed under

Payer (year)	Evidence Base	Covered	Not Covered
			the direct supervision of a physician, similar to the stress myocardial perfusion imaging. J. This LCD does not address electron beam tomography (EBT) technology or Ultrafast CT for coronary artery examination. There is no extension of coverage of EBT based on this policy. K. Quantitative calcium scoring is not a covered service and will be denied as not medically necessary. Calcium scoring reported in isolation is considered a screening service. When performed in association with CT angiography, there is neither separate nor additional included reimbursement for the calcium scoring. L. Atrial fibrillation or atrial flutter alone is not an indication; atrial fibrillation or atrial flutter with planned ablation therapy is allowed.
National Government Services, Inc. (2016) Local Coverage Determination Covered States: Connecticut, Illinois, Maine, Massachusetts, Minnesota, New Hampshire, New York	See Appendix N for references	A. **Patient presenting with chest pain syndrome.** These tests may be used in lieu of an imaging stress test. The clinician must have a high degree of suspicion that CAD is high on the differential diagnosis of the symptoms. B. **To facilitate the management decision of a patient with an equivocal stress test.** These tests might be chosen in select patients who have an equivocal stress (or stress imaging) test. The rationale is that a noninvasive coronary anatomic test (CCTA) allows an alternate method of assessing the coronary arteries, which would limit the number of negative invasive coronary angiograms.	A. These tests are never covered for screening, i.e., in the absence of signs, symptoms or disease. B. These tests will be considered not medically necessary if the anticipated results are not expected to provide new, additional information to that already previously obtained from other tests (such as stress myocardial perfusion images or cardiac ultrasound). New or additional

Payer (year)	Evidence Base	Covered	Not Covered
(Entire state, Downstate, Upstate, Queens), Rhode Island, Vermont, Wisconsin		C. **When the recurrence of symptoms in patients with known coronary artery disease may be related to progression/exacerbation of underlying disease.** The use of these tests in this setting would be to evaluate the extent of previously diagnosed coronary artery disease. Patients with known disease may have had remote invasive angiography and/or stress testing to evaluate prior events or symptoms. New or recurrent symptoms may relate to a change in the coronary anatomy that can be assessed with these tests. D. **When patients with prior bypass surgery or intracoronary artery stent placement present with chest pain or dyspnea.** Coronary bypass grafts are relatively well seen with these tests. The rationale for the tests would be to determine the patency and severity of possible graft stenoses that may be the source of chest pain. Patients with prior intracoronary stents often present with recurrent chest pain. The rationale for these tests as an alternative to invasive angiography is to rule out in-stent restenosis as the cause of symptoms. (Accurate assessment of in-stent restenosis may be limited by the artifact caused by the stent material itself and the quality of the scan and scanner). E. **Suspected congenital anomalies of the coronary circulation.** These tests are used to assess patients suspected of having a congenital coronary anomaly. The cross-sectional nature of this technique allows one to determine accurately both the presence and possible future harm that could result from the anomaly. It is often used after an anomaly has been identified following a different test such as prior invasive coronary angiogram. These tests are used to decide if surgery is indicated and for surgical planning. F. **The assessment of coronary or pulmonary venous anatomy.** This application of the tests for the coronary and pulmonary veins is primarily for pre-surgical planning. Coronary venous anatomy can be useful for the cardiologist who needs to place a pacemaker lead in the lateral coronary vein in order to resynchronize cardiac	information should facilitate the management decision, not merely add a new layer of testing. C. These tests will be considered not medically necessary if it is anticipated that the patient would require invasive cardiac angiography for further diagnosis or for therapeutic intervention. (e.g., angina decubitus, unstable angina, Prinzmetal angina, etc.) D. These tests may be denied, on post-pay review, as not medically necessary when used for cardiac evaluation if there were pre-test knowledge of sufficiently extensive calcification of the suspect coronary segment that would diminish the interpretive value. E. The administration of beta blockers and the monitoring of the patient during MDCT/CCTA by a physician experienced in the use of cardiovascular drugs is included as part of the test and is not a separately payable service. F. All studies must be ordered by the physician/qualified non-physician practitioner treating the patient and who will use the results of the test in the management of the patient. G. CCTA must be performed under the direct supervision of a physician. H. This LCD does not address electron

Payer (year)	Evidence Base	Covered	Not Covered
		contraction in patients with heart failure. This may be helpful to guide biventricular pacemaker placement. Pulmonary vein anatomy can vary from patient to patient. Pulmonary vein catheter ablation can isolate electrical activity from the pulmonary veins and allow for the elimination of recurrent atrial fibrillation. The presence of a pulmonary venous anatomic map may help eliminate procedural complications and allow for the successful completion of the procedure. G. **The patient undergoing non-coronary artery cardiac surgery.** - Certain patients who have non-coronary artery cardiac surgery (valve or ascending aortic surgery) may need a pre-operative invasive coronary angiogram. The surgical planning may also depend upon the exact location of the coronary arteries. The rationale for the use of CCTA in these patient subsets is to avoid potentially unnecessary invasive testing and still provide appropriate pre-surgical information. - The test may be medically necessary in patients presenting to the emergency room with complaints consistent with cardiac ischemia, but without diagnostic electrocardiography (ECG) or enzymes. - The test may be considered medically necessary in patients status post revascularization procedures who present with recurrent symptoms not clearly identifiable as ischemic. H. **FFRCT -** this test may be considered medically necessary when CCTA shows CAD of uncertain functional significance, or is non-diagnostic and where the addition of functional information provided by FFRCT can help the physician determine which patient may require invasive evaluation and / or treatment.	beam tomography (EBT) technology or Ultrafast CT for coronary artery examination. There is no extension of coverage of EBT based on this policy. I. Quantitative calcium scoring (CPT 75571) is not a covered service and will be denied as not medically necessary. Calcium scoring reported in isolation is considered a screening service. When performed in association with CT angiography, there is neither separate nor additional included reimbursement for the calcium scoring.
Noridian Healthcare Solutions, LLC (2020) Local Coverage	See Appendix N for references	FDA-approved FFRct technology may be considered reasonable and necessary in the management of patients with symptomatic, stable ischemic heart disease (SIHD), when the CCTA analysis is completed and demonstrates one of the following criteria:	FFRct is not considered reasonable in the following clinical circumstances: 1. Prior placement of prosthetic valves 2. Extensive coronary calcification

Payer (year)	Evidence Base	Covered	Not Covered
Determination Covered States: Alaska, Idaho, Oregon, Washington, Arizona, Montana, North Dakota, South Dakota, Utah, Wyoming		1. Left main disease with intermediate coronary stenosis (lumen diameter reduction of 30-50%); OR 2. Proximal left anterior descending (LAD) coronary artery disease with intermediate coronary stenosis (lumen reduction 50-70%); OR 3. Proximal left dominant circumflex disease with intermediate (lumen reduction 50-70%) coronary stenosis (considered equivalent to two-vessel disease); OR 4. Proximal two- or three vessel disease with intermediate coronary stenosis in at least 2 vessels.	3. Known severe aortic stenosis 4. Known severe 3-vessel disease 5. Prior placement of venous grafts in coronary bypass surgery 6. Suspicion of acute coronary syndrome 7. Severe obesity (BMI > 35 kg/m2)

CABG = coronary artery bypass graft, CAD = coronary artery disease, CCTA = coronary computed tomography, CT = computed tomography, ECHO = echocardiography, EKG = electrocardiogram, FFR = fractional flow reserve, MDCT = multi-detector computed tomography, MPI = myocardial perfusion imaging, PET = positron emission tomography, SPECT = single photon emission computed tomography.

* For the purposes of this guideline, a patient is considered to be "symptomatic" when one of the following (A-D) applies:

A. Chest pain

- With intermediate or high pretest probability of CAD; OR
- With low or very low pretest probability of CAD and high risk of CAD (SCORE)

B. Atypical symptoms: syncope, shortness of breath (dyspnea), neck, jaw, arm, epigastric or back pain, or sweating (diaphoresis)

- With moderate or high risk of CAD (SCORE)

C. Other symptoms; palpitation, dizziness, lightheadedness, near syncope, nausea, vomiting, anxiety, weakness, fatigue etc.

- With high risk of CAD (SCORE)

D. Patients with any cardiac symptom who have diseases/conditions with which coronary artery disease commonly coexists such as:

- Diabetes mellitus; OR
- Abdominal aortic aneurysm; OR
- Established and symptomatic peripheral vascular disease; OR
- Prior history of cerebrovascular accident (CVA), transient ischemic attack (TIA) or carotid endarterectomy (CEA) or high grade carotid stenosis (>70%); OR
- Chronic renal insufficiency or renal failure

Table 11. Summary table of payer policies for PET

Payer (year)	Evidence Base	Covered	Not Covered
CMS (2002)	• **Positron Emission Tomography (Australia , 2000):** This review of PET literature focused on the added value of PET in patients who have already had SPECT. The review found that PET seems more sensitive and specific than SPECT but that the two tests disagree on a relatively small number of patients. Only one study was correctly designed to determine the incremental value of PET over SPECT. Of the patients with discordant results, PET was overall the better predictor of myocardial recovery, with almost all PET results correct and SPECT results incorrect predictors. • **Functional Diagnostic Imaging in the Assessment of Myocardial Viability (Alberta, Canada, 1999):** This is a comprehensive review of many different functional diagnostic imaging tests including PET, SPECT anLLd dobutamine echo. This report found that there are few good data on the influence of any of the tests on patient management. Overall, the sensitivity of PET, SPECT and dobutamine echo was similar. The specificity of PET and dobutamine echo was similar, and both were better than SPECT. • **INAHTA summary (1999):** This summary of 11 different technology assessments found a general agreement on the "comparable or superior performance of PET to other myocardial perfusion imaging alternatives, particularly thallium-201 SPECT" but with no clear conclusions about the extent of the improvement due to PET. The summary notes that PET is more costly than other alternatives and that consideration should be given to the most overall cost-effective approach	On December 15, 2000, CMS published a Decision Memorandum on a request for broad coverage of PET for all oncological indications, heart disease, and neurological disorders. The December 15th decision memorandum stated that CMS had insufficient evidence to support coverage for the indication of myocardial viability except for the decision to cover the service following an inconclusive SPECT. CMS intends to revise the NCD at CIM 50-36 to state that: 1. Both SPECT or FDG PET are reasonable and necessary as a primary or initial diagnostic study for determining myocardial viability prior to revascularization 2. PET continues to be reasonable and necessary following an inconclusive SPECT 3. The greater specificity of PET makes using SPECT following an inconclusive PET of no added value and	NR

Payer (year)	Evidence Base	Covered	Not Covered
		thus not reasonable and necessary.	
Aetna (2020)	Not specified.	A. Evaluation of Coronary Artery Disease PET scans using rubidium-82 (Rb-82) or N-13 ammonia done at rest or with pharmacological stress are considered medically necessary for non-invasive imaging of the perfusion of the heart for the diagnosis and management of members with known or suspected coronary artery disease, provided such scans meet either one of the two following criteria: i. The PET scan is used in place of, but not in addition to, a single photon emission computed tomography (SPECT), in persons with conditions that may cause attenuation problems with SPECT (obesity (BMI	NR

Payer (year)	Evidence Base	Covered	Not Covered
		greater than 40), large breasts, breast implants, mastectomy, chest wall deformity, pleural or pericardial effusion); or ii. The PET scan is used following an inconclusive SPECT scan (i.e., the results of the SPECT are equivocal, technically uninterpretable, or discordant with a member's other clinical data). • In these cases, the PET scan must have been considered necessary in order to determine what medical or surgical intervention is required to treat the member.	
Cigna (2020)	1. Einstein AJ, Moser KW, Thompson RC, et al. Radiation Dose to Patients From Cardiac Diagnostic Imaging. Circulation. 2007;116(11):1290-1305.	PET – Perfusion B. Meets all of the criteria	PET – Absolute quantitation or

Payer (year)	Evidence Base	Covered	Not Covered
	doi:10.1161/circulationaha.107.688101. 2. Okumura W, Iwasaki T, Toyama T, et al. Usefulness of Fasting 18F-FDG PET in Identification of Cardiac Sarcoidosis. Journal of Nuclear Medicine. http://jnm.snmjournals.org/content/45/12/1989.full. Published December 1, 2004. 3. Sharkey RM, Goldenberg DM. Perspectives on Cancer Therapy with Radiolabeled Monoclonal Antibodies. Journal of Nuclear Medicine. http://jnm.snmjournals.org/content/46/1_suppl/115S.full. Published January 1, 2005. 4. Yoshinaga K, Chow BJ, Williams K, et al. What is the Prognostic Value of Myocardial Perfusion Imaging Using Rubidium-82 Positron Emission Tomography? Journal of the American College of Cardiology. 2006;48(5):1029-1039. doi:10.1016/j.jacc.2006.06.025. http://www.sciencedirect.com/science/article/pii/S073510970601641X?via%3Dihub. 5. Youssef G, Mylonas I, Leung E, et al. The Use of 18F-FDG PET in the Diagnosis of Cardiac Sarcoidosis: A Systematic Review and Metaanalysis Including the Ontario Experience. Journal of Nuclear Medicine. http://jnm.snmjournals.org/content/53/2/241.long. Published February 1, 2012. 6. Blankstein R, Osborne M, Naya M, et al. Cardiac Positron Emission Tomography Enhances Prognostic Assessments of Patients With Suspected Cardiac Sarcoidosis. Journal of the American College of Cardiology. 2014;63(4):329-336. doi:10.1016/j.jacc.2013.09.022.	for an imaging stress test and additionally any one of the following: i. Individual is obese (for example BMI >40 kg/m2) or ii. Individual has large breasts or implants C. Equivocal nuclear perfusion (MPI) stress test D. Routine use in post heart transplant assessment of transplant CAD PET – Metabolic A. Cardiac PET Metabolic (CPT® 78459 or CPT® 78429): To determine myocardial viability when a previous study has shown significant left ventricular dysfunction when under consideration for revascularization B. Cardiac PET Metabolic and Perfusion (MPI SPECT CPT® 78451 and CPT® 78459, or CPT® 78432, or CPT® 78433): to identify and monitor response to	myocardial blood flow • Performance of quantitation of myocardial blood flow by Cardiac PET is currently non-standardized between different vendor products. • Absolute quantitation of myocardial blood flow is considered experimental, investigational and/or unproven.

Payer (year)	Evidence Base	Covered	Not Covered
		therapy for established or strongly suspected cardiac sarcoid.	

BMI = body mass index, CMS = Centers for Medicare and Medicaid, FDG = Fludeoxyglucose, MPI = myocardial perfusion imaging, NR = not reported, PET = positron emission tomography, SPECT = single photon emission computed tomography.

Table 12. Summary table of payer policies for SPECT

Payer (year)	Evidence Base	Covered	Not Covered
CMS (2002)	• **Positron Emission Tomography (Australia , 2000):** This review of PET literature focused on the added value of PET in patients who have already had SPECT. The review found that PET seems more sensitive and specific than SPECT but that the two tests disagree on a relatively small number of patients. Only one study was correctly designed to determine the incremental value of PET over SPECT. Of the patients with discordant results, PET was overall the better predictor of myocardial recovery, with almost all PET results correct and SPECT results incorrect predictors. • **Functional Diagnostic Imaging in the Assessment of Myocardial Viability (Alberta, Canada, 1999):** This is a comprehensive review of many different functional diagnostic imaging tests including PET, SPECT and dobutamine echo. This report found that there are few good data on the influence of any of the tests on patient management. Overall, the sensitivity of PET, SPECT and dobutamine echo was similar. The specificity of PET and dobutamine echo was similar, and both were better than SPECT. • **INAHTA summary (1999):** This summary of 11 different technology assessments found a general agreement on the "comparable or superior performance of PET to other myocardial perfusion imaging alternatives, particularly thallium-201 SPECT" but with no	The single photon emission computed tomography (SPECT) acquires information on the concentration of radionuclides introduced into the patient's body. It is useful in the diagnosis of several clinical conditions including: • stress fracture. • spondylosis. • infection (e.g., discitis). • tumor (e.g., osteoid osteoma). • analyze blood flow to an organ, as in the case of myocardial viability. • differentiate ischemic heart disease from dilated cardiomyopathy.	• Frequency limitations: Medicare Administrative Contractor discretion. • In the case of myocardial viability, FDG positron emission tomography (PET) may be used following a SPECT that was found to be inconclusive. However, SPECT may not be used following an inconclusive FDG PET performed to evaluate myocardial viability.

Payer (year)	Evidence Base	Covered	Not Covered
	clear conclusions about the extent of the improvement due to PET. The summary notes that PET is more costly than other alternatives and that consideration should be given to the most overall cost effective approach		
Aetna (2019)	Not specified.	Aetna considers SPECT medically necessary for the diagnosis of coronary artery disease and for the assessment of prognosis in persons with coronary artery disease except as outlined in "exclusion criteria" below."	Aetna considers SPECT experimental and investigational for all other cardiac indications because its effectiveness for indications other than the ones listed above has not been established. Exclusion criteria: Aetna considers SPECT myocardial perfusion imaging experimental and investigational for the following indications for which the study is considered “inappropriate” according to appropriateness criteria from the American College of Cardiology (ACC): A. As a routine screening evaluation after a percutaneous transluminal coronary angioplasty (PTCA) with or without stenting or coronary artery bypass surgery (CABG) prior to discharge from the acute care setting; *or* B. As a routine screening evaluation after a re-vascularization procedure (PTCA with stenting or CABG) at an interval of less than 2 years from the procedure if there is no worsening in the members symptomatology and if the member had symptoms prior to the intervention, and there is no history of congestive heart failure. **Note**: If there is a history of congestive heart failure and the member is status post re-vascularization,

Payer (year)	Evidence Base	Covered	Not Covered
			repeat nuclear imaging as frequently as annually may be medically necessary; *or* C. Assessment of vulnerable plaque; *or* D. Evaluation of a member with an acute coronary event and hemodynamic instability, shock, or mechanical complications of the event; *or* E. In the setting of acute chest pain or equivalent symptoms with a high likelihood of being acute coronary syndrome, when there has been a diagnosis of acute myocardial infarction, in the immediate post-thrombolytic period, or when there is a high pre-test likelihood of significant coronary disease as demonstrated by marked ST segment elevation on the ECG; *or* F. Prior to high-risk surgery when the member is asymptomatic and there was a normal cardiac catheterization, coronary intervention (PTCA, stenting, CABG), or normal nuclear stress test less than 1 year before the surgical date; *or* G. Prior to intermediate-risk non-cardiac surgery if the member is capable of, and has no contraindication to standard stress testing**; *or* H. Prior to low-risk non-cardiac surgery for risk assessment; *or* I. Re-evaluation of members without chest pain or equivalent symptoms, without known coronary disease, at high-risk for coronary disease (based upon the Framingham score greater than 10)*, who have an initial negative radionuclear imaging study, when it has been less than 2 years since the last radionuclear

Payer (year)	Evidence Base	Covered	Not Covered
			study; *or* J. Re-evaluation of members without chest pain or equivalent symptoms or with stable symptoms, with known coronary disease as determined by prior abnormal catheterization or SPECT cardiac study (but without prior infarction), when it has been less than 1 year since the last radionuclear study. Note: if the member has worsening symptoms or if the member had silent ischemia, more frequent imaging or other diagnostic testing or interventions may be medically necessary; *or* K. Screening of members with chest pain or chest pain equivalent symptoms when there is a low probability of coronary disease (Framingham score less than 10)*, no history of diabetes, and there are no impediments or contraindications to non-nuclear stress testing; *or* L. Screening of members without chest pain or equivalent symptoms when there is a low probability of coronary disease (Framingham score less than 10)* and no history of diabetes

CABG = coronary artery bypass graft, FDG = Fludeoxyglucose, PET = positron emission tomography, PTCA = percutaneous transluminal coronary angioplasty, SPECT = single photon emission computed tomography.

3 The Evidence

3.1 Methods of the Systematic Literature Review

3.1.1 Objectives

The aim of this report is to evaluate the clinical impact, safety and cost-effectiveness of the three primary noninvasive imaging methods of diagnosing CAD, namely CCTA (including use of FFR), CT perfusion imaging, stress nuclear imaging and stress echocardiography. This review updates the 2008 CCTA HTA and 2013 nuclear imaging HTA and adds evaluation of stress echocardiography.

3.1.2 Contextual Questions

Prior to addressing research questions related to the impact of cardiac imaging on clinical outcomes ***the diagnostic accuracy (validity)*** of these modalities compared with invasive coronary angiography (the usual reference standard) will be briefly summarized for context, given the clinical maturity of these imaging modalities.

In patients with known or suspected CAD who are *symptomatic:*

1. What is the diagnostic accuracy of *CCTA* for anatomical confirmation of obstructive CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

2. What is the diagnostic accuracy of *CCTA with determination of fractional flow reserve (FFR)* for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

3. What is the diagnostic accuracy of *stress CCTA* for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

4. What is the diagnostic accuracy of *stress nuclear imaging*? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

5. What is the diagnostic accuracy of *stress echocardiography*? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

3.1.3 Research Key Questions

The scope of this report and final key questions were refined based on input from clinical experts. Clinical expert input was sought to confirm critical outcomes on which to focus. Draft Key Questions and PICOTS scope were published on the HCA website for public comment. None were received. Public comments as well as those from clinical experts and peer-reviewers were considered for finalization of this report.

The following Key Questions focus on ***the impact on clinical outcomes*** for the use of CCTA, stress nuclear imaging, and stress echocardiography to diagnose CAD **in patients with known or suspected CAD who are *symptomatic.***

1. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) in leading to improved *clinical outcomes* (e.g., MI, mortality)?

2. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with respect to *clinical decision-making* including additional testing and treatments?

3. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with regard to *harms or adverse events* which may result directly from testing or additional, downstream testing?

4. Does effectiveness (in terms of clinical outcomes) or safety of noninvasive cardiac anatomic or functional imaging (CCTA, stress nuclear imaging, stress echocardiography) differ in *special populations* (e.g., women, those with comorbidities, the elderly)?

5. What is the *cost-effectiveness* of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) for clinical outcomes?

3.1.4 Inclusion/Exclusion Criteria

Table 13 below provides a summary of the inclusion and exclusion criteria. Briefly, included studies met the following requirements with respect to participants, intervention, comparators, outcomes, and study design:

- **Population**: Adults with (1) symptoms of suspected (previously undiagnosed) CAD who present with stable (nonemergent) typical or atypical symptoms suspicious for CAD or suspected acute coronary syndrome (ACS) in emergency departments, or (2) known/established CAD.

- **Intervention:** CCTA (including use of FFR and pharmacologic stress with 64 slice or higher CT), stress nuclear imaging and stress echocardiography.

- **Comparators:** No testing, usual care, comparison of the above interventions with each other, and invasive coronary angiography.

- **Outcomes:** Primary clinical outcomes are 1) myocardial infarction (MI), 2) cardiac death, and 3) all-cause mortality. Clinical Decision-Making outcomes are 1) referral for treatment and 2) referral for additional testing. Safety outcomes include harms of testing (e.g., adverse events related to contrast agents, medication for pharmacologic stress testing), vascular complications (e.g., stroke) and risks and consequences of testing (radiation exposure, psychological

consequences of diagnosis, ramifications of additional testing, other). Economic outcomes are incremental cost effectiveness ratio (ICER) or similar outcome.

- **Studies:** The focus was on high quality (low risk of bias) comparative studies (e.g., randomized controlled trials, comparative cohort studies with concurrent controls) for Key Questions 1-3. Comparative cohort studies that were designed specifically to evaluate safety or comprehensive systematic reviews specifically on safety were considered for inclusion. For Key Question 4, RCTs that stratified on baseline patient characteristics and evaluated effect modification were included. Full, comparative, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) were sought for Key Question 5; studies using modeling may be used to determine cost-effectiveness.

Table 13. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Patients	Adult patients (≥18 years of age) with symptoms of suspected (previously undiagnosed) 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 non-chest pain symptoms, such as dyspnea or worsening effort tolerance) • Suspected acute coronary syndrome (ACS) in emergency departments. Symptomatic adults with known/established CAD including those who have had prior MI and/or revascularization. For all questions, data on special populations and circumstances including the following will be evaluated: • Women • Patients with atypical symptoms • Elderly patients • Patients with comorbidities (including renal insufficiency, DM), LBBB)	• Asymptomatic patients • Patients presenting for evaluation of cardiac pathologies other than CAD (e.g., congenital abnormalities, valvular disease, evaluation of cardiomyopathy etiology, CHF) • Patients with STEMI
Intervention	• Coronary CT Angiography (including use of FFR) and CT perfusion imaging (pharmacologic stress) with 64 slice or higher CT • Stress nuclear imaging (including PET, SPECT) • Stress echocardiography	• CACS • Screening • Novel uses of any of these tests • MRI/MRA • Comparisons of technical

Study Component	Inclusion	Exclusion
		performance parameters or variations of a testing modality (e.g., comparison different CT techniques) • Outdated equipment or methods
Comparator(s)	• No testing • Usual care* • Comparison of the above interventions with each other • Invasive coronary angiography	
Outcomes	Clinical health outcomes (PRIMARY) • MI, cardiac death, all-cause mortality Clinical decision making • Referral for treatment • Referral for additional testing Harms, risks and consequences of testing (initial testing and subsequent testing) • Harms of testing (e.g., adverse events related to contrast agents, medication for pharmacologic stress testing), vascular complications (e.g., stroke) • Risks and consequences of testing (radiation exposure, psychological consequences of diagnosis, ramifications of additional testing, other†) Economic: Incremental cost-effectiveness or similar outcome	• Intermediate outcomes
Timing	• Emergent or non-emergent • Any point in the diagnostic workup	• none
Setting(s)	• Emergency department • Non-emergent settings	• none
Studies	• Focus will be on studies with the least potential for bias. Focus will start with RCT evidence; in the absence of RCTs, high quality comparative observational studies that control for potential confounding will be considered. Observational studies will primarily be considered for test-related harms. • Studies published in English in peer-reviewed journals, technology assessments or publicly available FDA reports. • Full (comparative) economic studies • Studies published after 2000 (except for stress	• Non-comparative studies • Modeling studies for prediction • Prognostic studies • Costing studies • Studies evaluating the incremental benefit of adding a test to another. • Studies published prior to 2000 (except for stress echocardiography)

Study Component	Inclusion	Exclusion
	echocardiography)	

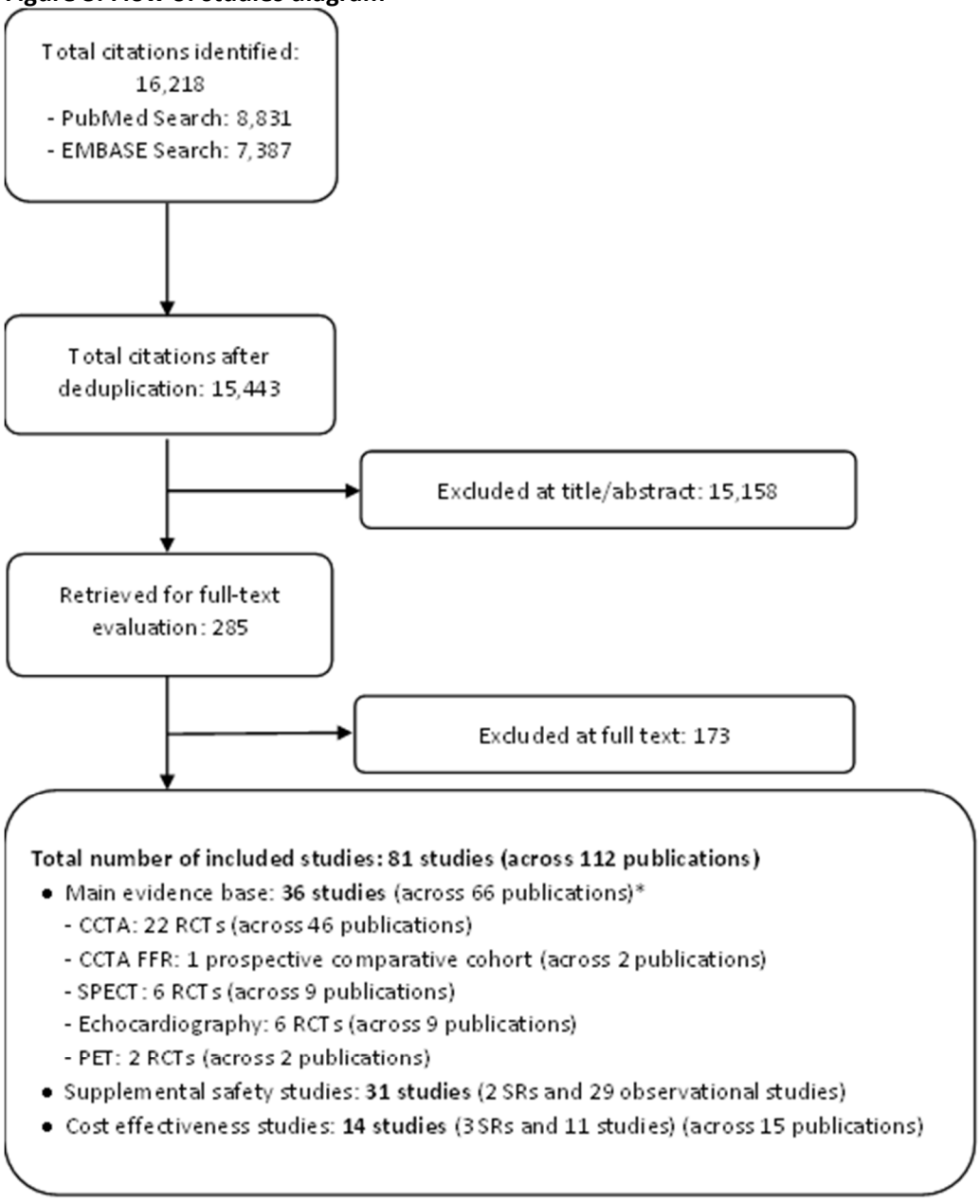
CACS = coronary artery calcium scoring; CAD = coronary artery disease; CHF = congestive heart failure; CT = computed tomography; DM = diabetes mellitus; FFR = fractional flow reserve; LBBB = left bundle branch block; RCT = randomized controlled trials; MI = myocardial infarction; PET = positron emission tomography; SPECT = single photon emission computed tomography; STEMI = ST-segment elevation myocardial infarction.
*Usual care typically includes no treatment/nothing if low pretest probability, "watchful waiting", or medical treatment if high pretest probability.
†Other may include impact on patients such as days lost from work, procedures cancelled (waiting for tests), vacations cancelled, etc.

3.1.5 Data Sources and Search Strategy

We searched electronic databases from January 1, 2000 to March 23, 2021 (for PubMed) and from database inception to March 23, 2021 (for all other databases) to identify publications assessing the capabilities of CCTA, stress nuclear imaging and stress echocardiography as diagnostic tests for CAD to direct patient management and improve patient outcomes that had been published since the prior reports. A formal, structured systematic search of the peer-reviewed literature was performed across a number of databases including PubMed, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews (see Appendix B for full search strategy) to identify relevant peer reviewed literature as well as other sources (ClinicalTrials.gov, ECRI Guidelines Trust, Center for Reviews and Dissemination Database) to identify pertinent clinical guidelines and previously performed assessments. We also hand searched the reference lists of relevant studies and the bibliographies of systematic reviews.

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The process involves four stages. The first stage of the study selection process consisted of the comprehensive electronic search and bibliography review. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria were included for full-text review. We excluded conference abstracts, non-English-language articles, duplicate publications that did not report different data or follow-up times, white papers, narrative reviews, preliminary reports, and incomplete economic evaluations. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the review and selection of those studies using a set of *a priori* inclusion criteria, again, by two independent investigators. Discrepancies were resolved through discussion and if necessary, adjudicated by a third investigator. A list of excluded articles along with the reason for exclusion is available in Appendix C. The remaining articles form the evidence base for this report.

Figure 3. Flow of studies diagram



CCTA = coronary computed tomography angiography; FFR = fractional flow reserve; PET = positron emission tomography; RCT = randomized control trial; SPECT = single photon emission tomography; SR = systematic review

* One trial (CECaT trial) provided data for both SPECT and Stress Echocardiogram.

3.1.6 Data Extraction

Reviewers extracted the following data from the clinical studies: study design, setting, country, source of funding, sample size, inclusion and exclusion criteria, study population characteristics, follow-up time, noninvasive testing protocol, definition of a positive test, study outcomes and adverse events. For economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted. An attempt was made to reconcile conflicting information among multiple reports presenting data from the same study. Detailed study and patient characteristics and results are available in Appendices F–L.

3.1.7 Quality Assessment: RoB, QHES Evaluation, and Overall SOE

The method used by Aggregate Analytics, Inc. (AAI) for assessing the quality of evidence of individual studies as well as the overall strength of evidence (SOE) are based on established methods for systematic reviews. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria. Assessment of RCTs followed appropriate criteria based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[40,104] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[1] In keeping with the AHRQ methods and the 2016 report on non-invasive imaging for CAD[230], each study was given a final rating of “good”, “fair”, or “poor” quality as described below. Discrepancies in ratings between reviewers were resolved through discussion and consensus. Criteria are detailed in Appendix D.

Table 14. Criteria for grading the quality of individual studies

Rating	Description and Criteria
Good	• Low risk of bias; study results generally considered valid • Employed valid methods for selection, inclusion, and allocation of patients to treatment; report similar baseline characteristics/key risk factors for testing groups being compared; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinded outcomes assessment); and use appropriate analytic methods (e.g., intention-to-test analysis); full reporting on pre-specified outcomes. • For studies of testing, pre-specification of thresholds for a positive test,
Fair	• Study is susceptible to some bias but not enough to necessarily invalidate results • May not meet all criteria for 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 • This category is broad; studies with this rating will vary in strengths and weaknesses; some fair-quality studies are likely to be valid, while others may be only possibly valid
Poor	• Significant flaws that imply biases of various kinds that may invalidate results; the study contains "fatal flaws" in design, analysis or reporting; large amounts of missing information; discrepancies in reporting or serious problems with intervention or test delivery • Study results are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions • Considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present

Risk of bias was not assessed for case series (single arm studies); all case series were considered to be at high risk of bias. Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al. in conjunction with consideration of epidemiologic principles that may impact findings.[182] Systematic reviews included as primary evidence were assessed using the AMSTAR-2tool.[224,225] Based on these quality criteria, each comparative study chosen for inclusion for a Key Question was given a risk of bias (RoB) (or QHES) rating; details of each rating are available in Appendix E. For contextual questions, general risk of bias was assessed for systematic reviews of diagnostic accuracy and reliability based on AMSTAR-2.[224,225] Individual reliability studies were assessed as described in Appendix D. Individual studies for diagnostic accuracy were not assessed.

SOE was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[89,92,93] as outlined by the Agency for Healthcare Research and Quality (AHRQ).[7] The strength of evidence was based on the highest quality evidence available for the primary outcomes.

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

- **Risk of bias**: the extent to which the included studies have protection against bias
- **Consistency:** the degree to which the included studies report results that are similar in terms of effect sizes, range and variability.
- **Directness**: describes whether the evidence is directly related to patient health outcomes or comparisons of interventions are direct (head to head).

- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication or reporting bias:** is considered when there is concern of selective publishing or selective reporting. This is difficult to assess particularly for nonrandomized studies.

Bodies of evidence consisting of RCTs are initially considered as High SOE. In general, the GRADE and AHRQ methodologies initially consider nonrandomized studies as Low SOE as such studies typically are at higher risk of bias due to lack of randomization and inability of investigators to control for critical confounding factors. The SOE could be downgraded based on the limitations described above. There are also situations where studies (particularly observational studies) could be upgraded if the study had large magnitude of effect (strength of association) or if a dose-response relationship is identified and there are no downgrades for the primary domains listed above and confounding is not a concern. Publication and reporting bias are difficult to assess, particularly with fewer than 10 RCTs and for observational studies.[25,213] Publication bias was unknown in all studies and thus this domain was eliminated from the strength of evidence tables. The final SOE was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable efficiencies precluding judgment.

Assessing the SOE for studies performing subgroup analysis for evaluation of differential effectiveness or safety requires additional considerations discussed below. Methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 5 was not assessed.

3.1.8 Analysis

Evidence was summarized qualitatively and quantitatively. Risk ratio (RR) and 95% confidence intervals were used for dichotomous outcomes to evaluate the presence of an association between testing and the outcome. Risk differences (RD) and 95% CIs were calculated if an association was seen for "hard" outcomes that might be reliably measured (e.g., death). Risk differences were not calculated for observational studies as causality cannot be inferred. In the absence of adjusted effect size estimates, for dichotomous outcomes, crude risk ratios (RR) and 95% confidence intervals (CI) were calculated using either STATA 14.0[235] or Rothman Episheet.[3] For instances with fewer than five observations per cell, exact methods were employed. Where effect estimates that were adjusted for confounding were

reported by study authors, they were preferred and reported. For continuous variables, mean differences (MD) and associated 95% CIs were calculated if the outcomes were reported using the same scale, and standardized mean difference (SMD) and 95% CI were used when the outcomes were reported in different scale

Meta-analyses were conducted as appropriate in order to summarize primary outcome data from multiple studies and to obtain more precise and accurate estimates using STATA 14.0. [235]To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. Statistical heterogeneity among the studies was assessed using Cochran's χ^2 test and the I^2 statistic.[105] To combine trials, we used a random effects model based on the profile likelihood method which provides a more conservative effect estimate. In the case of non-convergence with profile likelihood, the Der Simonian and Laird estimates were reported.[97] For continuous variables, differences in mean follow-up scores between treatments were analyzed to determine mean differences as an effect size. Methods for calculating the standard deviations and for imputing missing standard deviations followed the recommendations given in The Cochrane Handbook 7.7. Where no events occurred in one arm of a study, a value of 0.50 was used for that arm in accordance with Cochrane methods. Studies in which no events occurred in either study arm did not contribute to effect estimates (0% weight) but were retained in some plots for visual effect and completeness. Sensitivity analyses were conducted excluding poor-quality studies, outlying data and clinically heterogeneous trials where there were sufficient data. Given the limitations of ETT as a functional test, sensitivity analyses comparing CCTA with functional imaging tests only were also conducted. Tests for interaction related to study populations were done. Given that patients with acute symptoms presenting to the ED may have different need for and timing of hospitalization, we did not pool data for this outcome. Outcomes are detailed in the evidence tables in the appendices and/or the body of the report. Where results were reported at different time frames, we stratified by timing to evaluate results at the time of index test (primarily in studies in an ED setting) and then along common follow-up times as reported in included studies.

We did not conduct analyses to evaluate potential markers for publication bias given the substantial heterogeneity in study designs, programs, length of follow-up and patient populations and small number of trials available for some analyses in specific populations.[174,226]

To evaluate differential efficacy and safety (heterogeneity of effect, interaction), we focused on RCTs as they have the least potential for bias and confounding thus allowing for causal inference. Further, only RCTs that formally tested for interaction between subgroups were reported for Key Question 4. SOE for these studies is based on consideration of the overall study risk of bias (study quality) as well as whether subgroup variables and analyses were specified a priori, the hypothesized impact of a subgroup on the outcome/effect and sample size as evaluation of interaction requires greater sample size. Such analyses should be interpreted cautiously and consider the biologic plausibility of differential efficacy or safety. Such analyses are generally considered hypothesis generating, and additional confirmatory evidence should be sought.[185,239,252]

4 Contextual Questions

Diagnostic tests are recommended when evaluating the severity of a condition or predicting therapeutic response. However, for testing to be of value, results must lead to meaningful action that improve an individual's wellbeing. They must be accurate and reliable while minimizing harms, including those related to downstream testing. They must also impact the process of care and impact key patient outcomes. For years CCTA, stress nuclear imaging, and stress echocardiography as diagnostic tests for coronary artery disease (CAD) have been investigated for their abilities to direct patient management and improve patient outcomes, as well as for their cost-effectiveness. These tests are the most common modalities for CAD diagnosis in symptomatic patients other than ECG and ECG treadmill testing.

In the past decade, a growing number of randomized control trials have provided additional evidence to describe the impact of noninvasive imaging on clinical outcomes. Two prior reports published over a decade ago focused mostly on diagnostic accuracy. With more published data comes increased clinical evidence available for most modalities. In the last decade in particular, there is much more clinical evidence related to CCTA. However, it is still critical to consider the reliability and accuracy of available tests.

In recent years, the technologies and their application have evolved, and due to clinical maturity, we are now focusing on clinical characteristics of the tests, while simultaneously providing important context for accuracy, particularly compared with the historical referent of invasive angiography. Diagnostic accuracy and validity are addressed via the contextual questions below. Contextual questions represent issues in a review for which a valid, but not necessarily systematic, summary of current research is needed to provide important context. The contextual questions will provide important background information on diagnostic validity and reliability for the included tests.

In patients with known or suspected CAD who are *symptomatic:*

1. What is the diagnostic accuracy of CCTA for anatomical confirmation of obstructive CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?
2. What is the diagnostic accuracy of CCTA with determination of fractional flow reserve (FFR) for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?
3. What is the diagnostic accuracy of stress CCTA for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?
4. What is the diagnostic accuracy of stress nuclear medicine imaging? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?
5. What is the diagnostic accuracy of stress echocardiography? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

4.1 Terms and definitions

Diagnostic test performance measures were used in this report. Briefly for the contextual questions:

- **True positive (TP):** patients who test positive and who have the disease
- **False positive (FP):** patients who test positive but do not have the disease
- **False negative (FN):** patients who test negative but do have the disease
- **True negative (TN):** patients who test negative and do not have the disease
- **Sensitivity** (true positive rate) measures the ability of a diagnostic test to correctly identify patients with the disease, and can be calculated as follows: TP/(TP + FN) usually expressed as % of patients with the disease who test positive
- **Specificity** (true negative rate) measures the ability of a diagnostic test to minimize false positives, and can be calculated as follows: TN/ (FP + TN) usually expressed as % of patients who do not have disease who test negative
- Note that sensitivity and specificity are negatively correlated with one another: if the threshold of a positive test is set higher to maximize sensitivity, specificity will be lower, and vice versa.
- **Negative Predictive Value (NPV):** % of patients with negative test who do not have the disease; depends on prevalence can be calculated one of two ways: TN/(TN+FN) or

$$NPV = \frac{\text{specificity x (1-prevalence)}}{\text{(1-sensitivity) x prevalence + sp1ecificity x (1-prevalence)}}$$

- **Positive Predictive Value (PPV):** % of patients with positive test who have the disease; depends on prevalence; can be calculated one of two ways: TP/(TP+FP) or

$$PPV = \frac{\text{sensitivity x prevalence}}{\text{sensitivity x prevalence + (1-specificity) x (1-prevalence)}}$$

- **1 – negative predictive value (NPV).** The negative predictive value is the % of patients with a negative test who do not have the disease so 1- NPV is the percent of patients with a negative test who *do* have the disease.
- **Positive Likelihood Ratio (LR+):** how much odds of disease increase with a positive test; depends on sensitivity and specificity; can be calculated as follows: sensitivity/(1-specificity)
- **Negative Likelihood Ratio (LR-):** how much odds of disease decrease with a negative test; depends on sensitivity and specificity; can be calculated as follows: (1-sensitivity)/specificity)
- **Kappa statistic:** represents the extent to which the agreement observed exceeds that which would be expected by chance alone, and can be calculated as follows:

$$Kappa = \frac{\text{(\% agreement observed) – (\% agreement expected by chance alone)}}{\text{100\% – (\% agreement expected by chance alone)}}$$

4.2 Results for Diagnostic Accuracy

To provide a general overview of the diagnostic accuracy of the included noninvasive tests in the target population of symptomatic patients with suspected or known CAD in emergent or non-emergent settings, a targeted search of the literature was done to identify moderate- to high-quality systematic reviews (based on a modified AMSTAR-2 checklist[51,225]) that compared noninvasive tests included in this report with the historic gold standard of ICA in terms of traditional diagnostic test performance measures (i.e., sensitivity, specificity, positive/negative predictive value, positive/negative likelihood ratio). Where relevant, we included data on noninvasive tests compared with fractional flow reserve. Noninvasive tests included CT angiography, stress nuclear imaging, and stress echocardiography. Most studies reported 50% or greater stenosis in ICA, however some reported diagnostic accuracy of the test relative to a higher threshold or stenosis of 70%, see tables for details. ICA is an anatomic test, so accuracy for anatomic tests such as CCTA may differ from functional tests such as stress nuclear imaging or stress echocardiography when compared with ICA; a strict correspondence between ICA and functional tests is not expected.

The diagnostic test characteristics of all the included tests compared with the test results from ICA are summarized below in Table 15 through Table 25, with more specific details available in Appendix L**.** 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. Generally, authors did not describe the disposition or proportion of uninterpretable tests or account for them in the calculation of diagnostic accuracy parameters. The 2008 ICER report on CCTA used an "intent to diagnose" approach with non-diagnostic or indeterminate tests and considered them as having positive results.[184] This method assumes that clinicians refer non-diagnostic and indeterminate tests to ICA for further non-invasive testing, and conservatively estimates such cases to ultimately be false positive. This approach therefore may underestimate specificity and PPV because measures take into account false positives in their calculations.

Overall, evidence on diagnostic accuracy was available from five government-related reports[2,100,183,184,230] and nine systematic reviews[6,86,94,132,194,234,264] published in the peer review literature. The overall quality of systematic reviews published in the peer reviewed literature was moderate based on modified AMSTAR-2 ratings. Unfortunately, many studies were graded lower due to methodological issues, particularly a lack of rationale or listing of excluded studies and issues related to publication bias. The summary below provides information for each modality compared with the usual referent of ICA. Additional information for other comparators is found in Appendix L. Summary bullets are across the two ICA threshold of 50% or 70% stenosis, see tables for details. No studies focusing on specific subpopulations were identified. Additionally, key questions included considering differential accuracy based on specific populations, however included studies did not provide this.

For the diagnostic accuracy in patients with stable symptoms in outpatient settings:

- The diagnostic accuracy of **CCTA for anatomic imaging compared with ICA** across sources had the following ranges. Among these, Haase[94] investigated diagnostic accuracy using individual patient data.

  - Sensitivity (93.4% to 98%), specificity (72% to 84.4%)
  - PPV (58% to 93%), NPV (89% to 99%)
  - LR+ (3.43 to 5.98), LR- (0.02 to 2.64)
  - Prevalence of CAD (24.2% to 75.5%)
- The diagnostic accuracy of **CT myocardial perfusion compared with ICA** across sources had the following ranges
  - Sensitivity (54% to 66%), specificity (98% to 100%)
  - PPV (96% to 100%), NPV (66% to 100%)
  - LR+ (33.00 to 54.00), LR- (0.45 to 0.47)
  - Prevalence of CAD (NR)
- The diagnostic accuracy of **stress SPECT compared with ICA** across sources had the following ranges
  - Sensitivity (76% to 87%), specificity (70% to 78%)
  - PPV (32% to 95%), NPV (47% to 97%)
  - LR+ (2.88 to 3.68), LR- (0.24 to 2.33)
  - Prevalence of CAD (14.1% to 86%)
- The diagnostic accuracy of **stress PET compared with ICA** across sources had the following ranges
  - Sensitivity (90% to 91%), specificity (85% to 86%)
  - PPV (78% to 91%), NPV (84% to 94%)
  - LR+ (5.87 to 6.50), LR- (0.10 to 0.12)
  - Prevalence of CAD (36.5 to 62.5%)
- The diagnostic accuracy of **stress echocardiography compared with ICA** across sources had the following ranges
  - Sensitivity (64% to 90%), specificity (73% to 90%)
  - PPV (72% to 98%), NPV (36% to 97%)
  - LR+ (3.21 to 6.40), LR- (0.14 to 2.95)
  - Prevalence of CAD (35.1% to 90.8%)

For the diagnostic accuracy in patients with suspected or known CAD in outpatient settings:

- The diagnostic accuracy of **CCTA for anatomic imaging compared with ICA** across sources had the following ranges
  - Sensitivity (98.2% to 100%), specificity (81.6% to 89%)
  - PPV (90.5% to 93%), NPV (99%)
  - LR+ (9.20), LR- (0.00)
  - Prevalence of CAD (58% to 59.9%)
- The diagnostic accuracy of **stress SPECT compared with ICA** across sources had the following ranges
  - Sensitivity (83% to 85%), specificity (77% to 85%)
  - PPV (72% to 85%), NPV (79% to 85%)
  - LR+ (3.56 to 5.13), LR- (0.18 to 0.22)
  - Prevalence of CAD (41% to 50%)
- The diagnostic accuracy of **stress PET compared with ICA** across sources had the following ranges
  - Sensitivity (82% to 91%), specificity (82% to 91%)

  - PPV (93% to 96%), NPV (53% to 84%)
  - LR+ (4.97 to 8.89), LR- (0.11 to 0.21)
  - Prevalence of CAD (63% to 80%)
- The diagnostic accuracy of **stress echocardiography compared with ICA** across sources had the following ranges
  - Sensitivity (84% to 88%), specificity (72% to 89%)
  - PPV (85% to 93%), NPV (69% to 80%)
  - LR+ (3.08 to 8.35), LR- (0.13 to 0.21)
  - Prevalence of CAD (64% to 68%)

In addition to CCTA for anatomic imaging in particular, two systematic reviews[6,86] and one government report[100] describe diagnostic accuracy for the inclusion of FFRct to evaluate function. It is important to note that the government report was not a full systematic review, but a rapid response review that included two systematic reviews and one primary study.

For the diagnostic accuracy of FFRct in patients with suspected or known CAD in outpatient settings:

- The diagnostic accuracy of **FFRct compared with FFR via ICA** across sources had the following ranges
  - Sensitivity (84% to 91%), specificity (55% to 84%)
  - PPV (58% to 100%), NPV (0% to 90%)
  - LR+ (2.02 to 3.70), LR- (0.16 to 0.23)
  - Prevalence of CAD (32% to 100%)

Only one systematic review[114] reported on diagnostic accuracy across patients in an emergent setting. The patient population included those with suspected or known CAD, and the authors only reported sensitivity, specificity, positive and negative likelihood ratios. However, this study was done in patients with non-ST segment elevation myocardial infarction and without troponin, therefore the population is of lower risk of CAD. The prior ICER[184] study also included studies in emergency department settings but pooled all data across emergent and non-emergent settings. 3 prospective cohort studies[108,120,207] were identified from that report and data was abstracted.

For the diagnostic accuracy in patients with suspected or known CAD, presenting with or without ACS, or with possible ischemic chest pain in emergency departments:

- The diagnostic accuracy of **CCTA for anatomic imaging compared with ICA** across one systematic review and across three primary studies[108,120,207] from the prior ICER report had the following ranges
  - Sensitivity (93% to 100%), specificity (77% to 92%)
  - PPV (47% to 87%), NPV (91% to 100%)
  - LR+ (4.08 to 12.50), LR- (0.00 to 0.08)
  - Prevalence of CAD (NR)
  - The percentage of patients with a negative test that do have the disease (0% to 9%)
- The diagnostic accuracy of **stress SPECT compared with ICA** across sources had the following estimates

  - Sensitivity (85%), specificity (92%)
  - PPV (NR), NPV (NR)
  - LR+ (10.48), LR- (0.19)
  - Prevalence of CAD (NR)
- The diagnostic accuracy of **stress echocardiography compared with ICA** across sources had the following estimates
  - Sensitivity (75%), specificity (96%)
  - PPV (NR), NPV (NR)
  - LR+ (18.67), LR- (0.25)
  - Prevalence of CAD (NR)

In general, compared with FFR via ICA in the stress tests, sensitivity was similar or somewhat less while specificity was usually less than tests compared to the gold standard of ICA. Details are found in Tables 22-25.

Table 15. Summary of systematic review findings on diagnostic accuracy of coronary computed tomography angiography compared with invasive coronary angiography

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Coronary Computed Tomography Angiography (Radiation dose not specified)								
2016 AHRQ REPORT	Suspected CAD	98.2%	81.6%	90.5%	99.0%	NR	NR	59.9%
Coronary Computed Tomography Angiography (Low radiation dose)*								
2016 AHRQ REPORT	Suspected CAD	100%	89%	93%	99%	9.2	0.00	58%
Coronary Computed Tomography Angiography (≥50% stenosis)								
NICE 2016	Stable chest pain	96%	79%	84%†	97%†	4.57†	0.05†	NR
ICER 2008	Stable chest pain	98%	82%	89%†	97%†	5.44†	0.02†	59%
Haase 2019 Low‡	Stable chest pain	93.4%	84.4%	83.6%	93.7%	5.98	0.08	46.1%
Knuuti 2018 Low	Stable CAD (not acute coronary syndromes)	97%	78%	58% to 93%†	89% to 99%†	4.44	2.64	24.2% to 75.5
Coronary Computed Tomography Angiography (70% stenosis)								
NICE 2016	Stable chest pain	96%	72%	67%†	99%†	3.43†	0.06†	NR

AHRQ = Agency for Healthcare Research and Quality; CAD = coronary artery disease; ICER = Institute for Clinical and Economic Review; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NICE = National Institute for Health and Care Excellence; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

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

† Calculated from other values the authors provide.

‡ Reports on individual patient data.

Table 16. Summary of systematic review findings on diagnostic accuracy of coronary computed tomography angiography compared with computed tomography derived fractional flow reserve

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Coronary Computed Tomography Angiography (radiation dose NR)								
Pontone 2019 Low	Suspected or known CAD	93%	42%	62%	93%	1.72	0.17	NR
Coronary Computed Tomography Angiography (50% stenosis)								
Zhuang 2020 Low	Suspected or known CAD	88%	32%	55%	73%	1.37	0.23	NR
Coronary Computed Tomography Angiography (>50% stenosis)								
Gonzalez 2015 Low	Suspected or known CAD	92%	43%	57%	87%	1.64	0.19	45%

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

Table 17. Summary of systematic review findings on diagnostic accuracy of computed tomography (CCTA, FFRct) compared with fractional flow reserve via invasive coronary angiography

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Coronary Computed Tomography Angiography (≥50% Stenosis)								
Knuuti 2018 Low	Stable CAD (not acute coronary syndromes)	93%	53%	60% to 88%*	68% to 91%*	1.97	0.13	43.6% to 78.3%
Computed Tomography derived Fractional Flow Reserve (0.75 to 0.80)								
Gonzales 2015 Low†	Suspected or known CAD	90%	72%	70%	90%	3.70	0.16	42%
Computed Tomography derived Fractional Flow Reserve (<0.80)								
Agasthi 2018 Low	Suspected CAD	83%	72%	58% to 100%*	0% to 90%*	3.00	0.23	32% to 100%
Helfand 2019 High‡	Stable chest pain with suspected CAD§	84% to 85%	73% to 84%	NR	NR	NR	NR	NR
	Stable chest pain with suspected or known CAD**	84% to 86%	75% to 80%	NR	NR	NR	NR	NR

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
	Suspected CAD with at least 1 coronary stenosis of 40% to 90% on CCTA undergoing clinically indicated ICA with FFR††	91%	55%	58%*	89%*	2.02*	0.16*	41%

CAD = coronary artery disease; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.
* Calculated from other values the authors provide.
† Focused on HeartFlow technology.
‡ Study is not a full SR. Instead, it is a rapid response review.
§ SRs, focused on HeartFlow technology.
** SRs, focused on non-HeartFlow technology.
†† Single primary study, focused on HeartFlow technology.

Table 18. Summary of systematic review findings on diagnostic accuracy of CT myocardial perfusion imaging compared with invasive coronary angiography

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
CT myocardial perfusion (stenosis ≥50%)								
Sogaard 2016* Low	Suspected CAD	91%	77%	87%	83%	3.96†	0.12†	63%
NICE 2016	Stable chest pain	54%	100%	100%†	66%†	54.00†	0.47†	NR
CT myocardial perfusion (stenosis ≥70%)								
NICE 2016	Stable chest pain	66%	98%	96%†	80%†	33.00†	0.45†	NR

CAD = coronary artery disease; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NICE = National Institute for Health and Care Excellence; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.
* CT perfusion test is combined with CCTA (≥50% stenosis).
† Calculated from other values the authors provide.

Table 19. Summary of systematic review findings on diagnostic accuracy of CT myocardial perfusion imaging compared with computed tomography derived fractional flow reserve

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
CT myocardial perfusion (stenosis NR)								

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Pontone 2019 Low	Suspected or known CAD	79%	88%	84%	81%	5.15	0.26	63%
CT myocardial perfusion (stenosis >50%)								
Gonzalez 2015 Low	Suspected or known CAD	94%	77%	83%	92%	3.85	0.09	54%

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

Table 20. Summary of systematic review findings on diagnostic accuracy of stress nuclear testing (SPECT, PET) compared with invasive coronary angiography

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Single Photon Emission Computed Tomography (Radiation dose not specified)								
2016 AHRQ REPORT	Overall	83% to 85%	77% to 85%	79% to 85%	79% to 85%	3.56 to 5.13	0.18 to 0.22	50%
	Suspected CAD	83% to 84%	79% to 85%	72% to 85%	84%	3.88 to 5.01	0.19 to 0.21	41%
Single Photon Emission Computed Tomography (50% stenosis)								
NICE 2016	Stable chest pain	81%	78%	88%	65%	3.68	0.24	NR
Single Photon Emission Computed Tomography (>50% stenosis)								
Knuuti 2018 Low	Stable CAD (not acute coronary syndromes)	87%	70%	32% to 95%*	47% to 97%*	2.88	2.33	14.1% to 86%
Single Photon Emission Computed Tomography (70% stenosis)								
NICE 2016	Stable chest pain	76%	76%	86%*	56%*	3.17*	0.32*	NR
Positron Emission Tomography (Radiation dose not specified)								
2016 AHRQ REPORT	Overall	82% to 90%	86% to 88%	93% to 96%	53% to 84%	5.57 to 5.88	0.11 to 0.21	63% to 80%
	Suspected CAD	90% to 91%	82% to 91%	94%	75% to 84%	4.97 to 8.89	0.11	75%
Positron Emission Tomography (>50% stenosis)								

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Knuuti 2018 Low	Stable CAD (not acute coronary syndromes)	90%	85%	78% to 91%*	84% to 94%*	5.87	0.12	36.5% to 62.5%
Positron Emission Tomography (70% stenosis)								
NICE 2016	Stable chest pain	91%	86%	87%*	90%*	6.50*	0.10*	NR

AHRQ = Agency for Healthcare Research and Quality; CAD = coronary artery disease; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NICE = National Institute for Health and Care Excellence; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.
* Calculated from other values the authors provide.

Table 21. Summary of systematic review findings on diagnostic accuracy of nuclear stress testing (SPECT, PET) compared with computed tomography derived fractional flow reserve

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Single Photon Emission Computed Tomography (radiation dose NR)								
Pontone 2019 Low	Suspected or known CAD	71%	79%	75%	70%	2.94	0.42	NR
Positron Emission Tomography (radiation dose NR)								
Pontone 2019 Low	Suspected or known CAD	88%	86%	85%	88%	6.35	0.13	NR

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

Table 22. Summary of systematic review findings on diagnostic accuracy of nuclear stress testing (SPECT, PET) compared with fractional flow reserve via invasive coronary angiography

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Single Photon Emission Computed Tomography (>50% stenosis)								
Knuuti 2018 Low	Stable CAD (not acute coronary syndromes)	73%	83%	52% to 81%*	76% to 92%*	4.21	0.33	20% to 49.6%
ICER 2013	Suspected or known CAD	66% to 90%	50% to 100%	73% to 81%	58% to 91%	1.32 to 9.00*	0.10 to 0.68*	NR
Positron Emission Tomography (>50% stenosis)								

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Knuuti 2018 Low	Stable CAD (not acute coronary syndromes)	89%	85%	80% to 82%	91% to 92%	6.04	0.13	39.9% to 44.1%
ICER 2013	Suspected or known CAD	76% to 95%	83% to 91%	76% to 86%	83% to 97%	4.47 to 10.56*	0.05 to 0.29*	NR

CAD = coronary artery disease; ICER = Institute for Clinical and Economic Review; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.
* Calculated from other values the authors provide.

Table 23. Summary of systematic review findings on diagnostic accuracy of stress echocardiography compared with invasive coronary angiography

Author, year AMSTAR-2		Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Stress echocardiography (Stenosis NR)									
De Jong 2012 Low	Compared to ICA stenosis ≥50% to 75%	Suspected or known CAD	87%	72%	85%	73%	3.08	0.18	66%
	Compared to ICA Stenosis ≥50 stenosis	Suspected CAD	88%	89%	93%	80%	8.35	0.13	64%
2016 AHRQ REPORT		Overall	84% to 87%	72% to 77%	85% to 89%	69% to 73%	3.08 to 3.65	0.18 to 0.21	66% to 68%
		Suspected CAD	88%	89%	93%	80%	8.35	0.13	64%
Lapado 2013 Critically low		Suspected or known CAD	84%	77%	89%	69%	3.65	0.21	68%
Stress Echocardiography (50% stenosis)									
NICE 2016	Perfusion	Stable chest pain	84%	79%	88%*	71%*	4.00*	0.21*	NR
	Wall motion, vasodilators	Stable chest pain	77%	76%	93%*	97%*	3.21*	0.30*	NR
	Wall motion, heart rate modifiers	Stable chest pain	76%	80%	88%	62%	3.80	0.30	NR

Author, year AMSTAR-2		Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Stress Echocardiography (>50% stenosis)									
Knuuti 2018 Low		Stable CAD (not coronary syndromes)	85%	82%	72% to 98%*	36% to 91%*	4.67	2.95	35.1% to 90.8%
Stress Echocardiography, perfusion (70% stenosis)									
NICE 2016	Perfusion	Stable chest pain	90%	73%	74%*	55%*	3.33*	0.14*	NR
	Wall motion, vasodilators	Stable chest pain	64%	90%	91%*	66%*	6.40*	0.40*	NR
	Wall motion, heart rate modifier	Stable chest pain	75%	88%	90%*	84%*	6.25*	0.28*	NR

AHRQ = Agency for Healthcare Research and Quality; CAD = coronary artery disease; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NICE = National Institute for Health and Care Excellence; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.
* Calculated from other values the authors provide.

Table 24. Summary of systematic review findings on diagnostic accuracy of stress echocardiography compared with computed tomography derived fractional flow reserve

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Stress Echocardiography (Stenosis NR)								
Pontone 2019 Low	Suspected or known CAD	64%	84%	81%	70%	3.51	0.45	NR

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

Table 25. Summary of systematic review findings on diagnostic accuracy of non-invasive diagnostic tests (CCTA, SNI, stress echo) compared with invasive coronary angiography in Emergency Departments

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Coronary computed tomography angiography (Stenosis NR)								
Iannaconne 2019* Low	Suspected or known CAD	93%	90%	NR	NR	9.40	0.10	NR

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
ICER 2008†	Patients presenting to the ED with and without ACS, or with possible ischemic chest pain	94% to 100%	77% to 92%	47% to 87%	91% to 100%	4.08 to 12.5‡	0.0 to 0.08‡	NR
Single Photon Emission Computed Tomography (Stenosis NR)								
Iannaconne 2019* Low	Suspected or known CAD	85%	92%	NR	NR	10.48	0.19	NR
Stress echocardiography (Stenosis NR)								
Iannaconne 2019* Low	Suspected or known CAD	75%	96%	NR	NR	18.67	0.25	NR

CAD = coronary artery disease; ICER = Institute for Clinical and Economic Review; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

* Patient population were patients with non-ST segment elevation myocardial infarction (NSTEMI) and without troponin. Authors do not report prevalence of CAD, pretest likelihood, or true and false positives or negative.

† Abstracted from 3 primary studies included in this report.

‡ Calculated from values given by authors.

4.3 Results for Reliability

To provide a general overview of reliability of the included non-invasive tests, we performed a search of the literature to identify studies that included assessments of intra- and interobserver agreement using Cohen's Kappa. Cohen suggests that Kappa results be interpreted as follows: values ≤0 as indicating no agreement, 0.01 to 0.20 as none to slight agreement, 0.21 to 0.40 as fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as substantial, and 0.81 to 1.00 as almost perfect agreement.

Intraobserver reliability in CCTA ranged from substantial agreement to almost perfect agreement (k=0.72 to 0.96) in 3 studies.[137,205,258] Between observer reliability was investigated in six studies[31,90,109,137,205,258] and ranged from moderate agreement to almost perfect agreement (k=0.58 to 0.94). Intraobserver reliability was investigated in two studies[41,80] for FFRct and found fair to almost perfect agreement (k=0.40 to 0.97), but no studies were found on interobserver agreement. CT perfusion was only investigated in one study[43] and found interobserver reliability ranging from substantial to almost perfect agreement (k=0.72 to 0.86).

SPECT studies found almost perfect agreement across one intraobserver[70] and two interobserver studies[43,70] (k=0.96 and k=0.91 to 0.95 respectively). Similarly, one study[258] investigating PET found almost perfect agreement for both intra- and interobserver reliability (k=0.94 and k=0.82 respectively).

Reliability studies on stress echocardiography included both exercise and dobutamine for inducing stress. In general, three intraobserver studies[70,75,102] all found almost perfect agreement for stress echocardiography (k=0.81 to 0.90). Meanwhile, between observer reliability ranged from moderate to almost perfect agreement across 5 studies[70,74,75,102,130] (k=0.56 to 0.87).

Although ICA is commonly considered the gold standard for identifying CAD, there are well known limitations regarding variability, reliability, and image distortion in its use. Nevertheless, one study that we identified for CCTA also investigated the interobserver reliability of ICA and found substantial agreement between observers (k=0.79).[31]

Risk of bias was assessed using the following criteria: 1) Broad spectrum of persons with expected conditions, 2) Adequate methods description for replication, and 3) Blinded performance of tests/interpretations. A good-quality study includes all three criteria and drops one level for each violation. Our assessment found that study quality ranged from poor to good, with the majority of studies rated as good quality (Appendix E).

Table 26. Summary of intraobserver reliability studies for each test modality

Study, year Risk of Bias*	Test modality and criteria	Intraobserver Cohen's Kappa interpretation (k, 95% CI)
Computed Tomography (CCTA, FFRct)		
Lehman 2009 Good quality	CCTA (Stenosis NR)	Almost perfect agreement (k=0.95, 95% CI: NR)
Rinehart 2010 Good quality	CCTA (Stenosis NR)	Degree of stenosis: Almost perfect agreement (k=0.96, 95% CI: NR) Plaque classification: Almost perfect agreement (k=0.96, 95% CI: NR)
Williams 2017 Good quality	CCTA (>50% stenosis)	Substantial agreement (k=0.72, 95% CI: NR)
Ghaemian 2020 Moderate quality	FFRct (<0.80)	Whole population: Fair agreement (k=0.40, 95% CI: NR) True SPECT: Almost perfect agreement (k=0.97, 95% CI: NR)†
Collet 2018 Good quality	FFRct (<0.80)	Almost perfect agreement (k=0.82, 95% CI: 0.73 to 0.90) ‡
Stress Nuclear Imaging (SPECT, PET)		
Ferro 2007 Good quality	SPECT (Stenosis NR)	Almost perfect agreement (k=0.96, 95% CI: NR)
Williams 2017 Good quality	PET (Stenosis NR)	Almost perfect agreement (k=0.94, 95% CI: NR)
Stress Echocardiography		
Ferro 2007 Good quality	Dobutamine stress echo (Stenosis NR)	Almost perfect agreement (k=0.81, 95% CI: NR)
Hernandez-Gonzalez 2015 Moderate quality	Dobutamine stress echo (≥70% stenosis)	Almost perfect agreement (k=0.81, 95% CI: NR)
Gaibazzi 2010 Good quality	Wall motion stress echo (>70% stenosis)	Almost perfect agreement (k=0.90, 95% CI: NR)

CCTA = computed coronary tomography angiography; CI = confidence interval; DSE = dobutamine stress echocardiography; FFR = fractional flow reserve; FFRct = computed tomography derived fractional flow reserve; ICA = invasive coronary angiography; NR = not reported; PET = positron emission tomography; SPECT = single-photon emission computed tomography; WM = wall motion; WMS = wall motion scoring.

* Based on Risk of Bias for Diagnostic Reliability Studies (Appendix D). The three criteria include 1) Broad spectrum of persons with expected conditions, 2) Adequate methods description for replication, and 3) Blinded performance of tests/interpretations. A good-quality study includes all three criteria, and drops one level for each violation.

† Whole population = concordance between FFR and SPECT in patient population as a whole; True SPECT = concordance between FFR and SPECT in patients in whom SPECT was truly positive and truly negative.

‡ Compares agreement concerning recommendation of revascularization strategy between FFRct and ICA

Table 27. Summary of Interobserver reliability studies for each test modality

Study (Year) Risk of Bias*	Test modality and criteria	Interobserver Cohen's Kappa interpretation (95% CI)
Computed Tomography (CCTA, CT perfusion)		
Hoffman 2012 Poor quality	CCTA (Stenosis NR)	Almost perfect agreement (k=0.94, 95% CI: NR)
Lehman 2009 Good quality	CCTA (Stenosis NR)	Almost perfect agreement (k=0.93, 95% CI: NR)
Rinehart 2010 Good quality	CCTA (Stenosis NR)	Degree of Stenosis: Almost perfect agreement (k=0.90, 95% CI: NR) Plaque classification: Almost perfect agreement (k=0.88, 95% CI: NR)
Williams 2017 Good quality	CCTA (>50% stenosis)	Substantial agreement (k=0.77, 95% CI: NR)
Butler 2007 Good quality	CCTA (>50% stenosis)	Substantial agreement (k=0.77, 95% CI: NR)
Gueret 2013 Good quality	CCTA (≥50% stenosis)	Moderate agreement (k=0.58, 95% CI: 0.29 to 0.88)
Cury 2015 Good quality	CT Perfusion (<50% or ≥50% and 70% or ≥70%)	Reversible perfusion defects† Agreement between observers 1 and 2: Substantial agreement (k=0.77, 95% CI: 0.69 to 0.85) Agreement between observers 1 and 3: Almost perfect agreement (k=0.84, 95% CI: 0.77 to 0.91) Agreement between observers 2 and 3: Substantial agreement (k=0.80, 95% CI: 0.72 to 0.88) Fixed perfusion defects‡ Agreement between observers 1 and 2: Substantial agreement (k=0.72, 95% CI: 0.63 to 0.81) Agreement between observers 1 and 3: Almost perfect agreement (k=0.86, 95% CI: 0.79 to 0.92) Agreement between observers 2 and 3: Substantial agreement (k=0.74, 95% CI: 0.66 to 0.83)
Stress Nuclear Imaging (SPECT, PET)		
Ferro 2007 Good quality	SPECT (Stenosis NR)	Almost perfect agreement (k=0.92, 95% CI: NR)
Cury 2015 Good quality	SPECT (<50% or ≥50% and 70% or ≥70%)	Agreement between observers 1 and 2: Almost perfect agreement (k=0.92, 95% CI: 0.86 to 0.97) Agreement between observers 1 and 3: Almost perfect agreement (k=0.91, 95% CI: 0.85 to 0.96) Agreement between observers 2 and 3: Almost perfect agreement (k=0.95, 95% CI: 0.93 to 1.00)
Williams 2017 Good quality	PET (Stenosis NR)	Almost perfect agreement (k=0.82, 95% CI: NR)
Stress Echocardiography		
Khan 2017 Poor quality	Stress echo (Stenosis NR)	Rest: Almost perfect agreement (k=0.87, 95% CI: 0.75 to 0.96) Stress: Substantial agreement (k=0.70, 95% CI: 0.60 to 0.79)
Ferro 2007	Dobutamine stress echo	Moderate agreement (k=0.56, 95% CI: NR)

Study (Year) Risk of Bias*	Test modality and criteria	Interobserver Cohen's Kappa interpretation (95% CI)
Good quality	(Stenosis NR)	
Hernandez-Gonzalez 2015 Moderate quality	Dobutamine stress echo (≥70% stenosis)	Almost perfect agreement (k=0.81, 95% CI: NR)
Gaibazzi 2013 Good quality	Wall motion stress echo (Stenosis NR)	Almost perfect agreement (k=0.86, 95% CI: NR)
Gaibazzi 2010 Good quality	Wall motion stress echo (>70% stenosis)	Substantial agreement (k=0.80, 95% CI: NR)
Invasive Coronary Angiography		
Butler 2007 Good quality	ICA (>50% stenosis)	Substantial agreement (k=0.79, 95% CI: NR)

CCTA = computed coronary tomography angiography; CI = confidence interval; DSE = dobutamine stress echocardiography; FDG = F-18-fluoro-2-deoxyglucose; FFR = fractional flow reserve; FFRct = computed tomography derived fractional flow reserve; ICA = invasive coronary angiography; IHP = International Harmonization Project; NR = not reported; PET = positron emission tomography; PET-CT = positron emission tomography-computed tomography; SPECT = single-photon emission computed tomography; WM = wall motion; WMS = wall motion scoring.

* Based on Risk of Bias for Diagnostic Reliability Studies (Appendix D). The three criteria include 1) Broad spectrum of persons with expected conditions, 2) Adequate methods description for replication, and 3) Blinded performance of tests/interpretations. A good-quality study includes all three criteria, and drops one level for each violation.

† The number of reversible defects was calculated as the number of segments with positive differences (stress score rest score) for segments with a stress score >1. A subject was determined to be ischemic if ≥2 segments had reversible defects according to the median count across the 3 readers.

‡ The segment was considered fixed if the segment was scored >1 and was equal at both rest and stress. A subject was determined to have the presence of fixed defects if ≥1 segment had a fixed defect according to the median count across the 3 readers.

5 Key Questions Results Overview

5.1 Number of studies retained

From 15,443 unique citations identified via systematic data base searching, 81 studies across 112 publications were retained (Figure 3). A total of 36 studies (in 66 publications) (35 RCTs and 1 prospective comparative cohort)[5,17,36,37,47,48,52,57-60,83-85,88,91,96,109,111,117,126,135,138-146,148,149,151,153,159-161,163,168,171,175,176,180,186,187,189,192,204,209-211,215,217,218,220,223,237,238,241,245,246,248,256,257,262] comprised the primary evidence base for Key Questions 1–4 and an additional 31 studies (2 SRs and 29 nonrandomized observational studies)[4,13,15,20,23,24,33,45,64,66,69,72,76,77,81,87,119,122,124,125,134,155,158,164-166,181,191,193,200,229] provided supplemental data on safety (Key Question 3; see Appendix Tables O23-O25 for details). For cost-effectiveness (Key Question 5), 14 studies across 15 publications (3 systematic reviews and 11 formal economic analyses) were included.[8,26,27,82,91,116,123,136,147,162,196,197,243,249,263]

5.1.1 Primary evidence base for Key Questions 1–4

A total of 35 trials (in 64 publications) [5,17,36,37,47,48,52,58,59,83-85,88,91,96,109,111,117,126,135,138-146,148,149,151,153,159-161,163,168,171,175,176,180,186,187,189,192,204,209-211,215,217,218,220,223,237,238,241,245,246,248,256,257,262] and one prospective comparative cohort study (in 2 publications)[57,60] that met inclusion criteria were identified and comprise the primary the evidence base for evaluation of efficacy and safety in this report. The bulk of the new trials evaluated CCTA. Most trials were considered fair (17 RCTs) with 11 considered good and seven considered poor quality (see Appendix E for details).

Although we sought studies in the three symptomatic populations of interest (i.e., patients with unknown but suspected CAD, those with known/established CAD and those with suspected ACS), only 1 trial (which evaluated PET) was specifically in patients with known CAD.[189] Populations in 13 trials[36,52,59,88,126,153,163,209,211,215,223,238,262] and one prospective comparative cohort[60] were predominately (≥80%) those with unknown/suspected CAD presenting to in an outpatient setting and are described as stable outpatients in the results. Five trials enrolled a mixed population of known and suspected CAD.[48,117,168,210,220] Sixteen trials were in patients presenting acutely to the ED or similar setting with suspected ACS (unstable angina or NSTEMI).[37,47,84,85,96,109,138,140,142,144,145,161,171,180,192,248] Studies in patients with STEMI were excluded. There was heterogeneity across trials regarding how pre-test risk was determined and reported. Given this heterogeneity it was not possible to stratify results by this variable. Appendix M provides information as reported by trial authors, and patient and study characteristics can be found in Appendix Q.

Table 28 below provides an overview of the included studies by test and comparator as well as population.

Table 28. Overview of included studies comprising the primary evidence base for Key Questions 1–4 arranged by test and comparator as well as population of interest.

Test	Comparator	Population					Total
		Stable, OP			Acute, ED/similar setting		
		Suspected CAD only	Mixed suspected or known CAD	Known CAD	Suspected ACS only	Mixed suspected or known CAD	
CCTA	**Any functional testing**	*Low to intermediate pre-test risk:* 1. Douglas 2015 (PROMISE)[59]			*Low pre-test risk:* 1. Dedic 2016 (BEACON)[47] *Low to intermediate pretest risk:* 2. Litt 2012 (ACRIN-PA)[145] 3. Linde 2013 (CATCH)[144] 4. Miller 2011[161] *Intermediate pre-test risk:* 5. Hoffman 2012 (ROMICAT-II)[109] *Mixed* pretest risk:* 6. Chang 2008[37]		**7 RCTs**
	SPECT	*Intermediate pre-test risk:* 1. Karthikeyan 2017 (IAEA-SPECT/CTA)[126] *Intermediate to high pre-test risk:* *2.* Min *2012*[163] *Pre-test risk NR:* 3. Stillman 2020 (RESCUE)[238]			*Low pre-test risk:* 1. Goldstein 2011 (CT-STAT)[84] 2. Goldstein 2007[85] *Low to intermediate pre-test risk* 3. Nabi 2016[171] *Intermediate pre-test risk:* 4. Levsky 2015 (PROSPECT)[140]		**7 RCTs**
	Stress Echo				*Low to intermediate pre-test risk* 1. Levsky 2018[138] 2. Pineiro-Portela 2021[192] *Pre-test risk NR* 3. Uretsky 2017 (PERFECT)[248]		**3 RCTs**
	ETT ECG	*Mixed* pre-test risk* 1. McKavanagh 2015 (CAPP)[153] *Pretest risk NR:* 2. SCOT-HEART Investigators 2015 (SCOT-HEART)[215]†			*Low to intermediate pre-test risk:* 1. Hamilton-Craig 2014 (CT-COMPARE)[96]		**3 RCTs**
	ICA	*Intermediate pre-test risk:* 1. Dewey 2016 (CAD-Man)[52] 2. Chang 2019 (CONSERVE)[36]					**2 RCTs**
	Any comparator	**8 RCTs**	**-----**	**-----**	**14 RCTs**	**-----**	**22 RCTs**

CCTA FFR	**Any functional testing**	*Intermediate pre-test risk* 1. Douglas 2015 (PLATFORM)[60] [Pro observational]					**1 pro CC**
	ICA						**1 pro CC**
	Any comparator	**1 prospective CC**	-----	-----	-----	-----	**1 pro CC**
SPECT	**Stress Echo**		1. Sharples 2007 (CeCaT)[220]			1. Salame 2018[210]	**2 RCTs**
	ETT ECG	*Intermediate pre-test risk* 1. Shaw 2011 (WOMEN)[223] *Mixed* pretest risk:* 2. Sabharwal 2007 [209]					**2 RCTs**
	NICE guidelines-directed care‡	*Intermediate pre-test risk* 1. Greenwood 2016 (CE-MARC 2)[88]					**1 RCT**
	Clinical assessment only§				*Mixed* pre-test risk* 1. Lim 2013[142]		**1 RCT**
	ICA		1. Sharples 2007 (CeCaT)[220]				**1 RCT**
	Any comparator	**3 RCTs**	**1 RCT**	-----	**1 RCT**	**1 RCT**	**6 RCTs**
STRESS ECHO	**ETT ECG**	*Mixed* pre-test risk* 1. Zacharias 2017[262] *Pretest risk NR* 2. Sanfilippo 2005[211]			*Low pre-test risk* 1. Nucifora 2009 (ASSENCE)[180]	1. Jeetley 2006[117] 2. Desideri 2005 (COSTAMI-II)[48]	**5 RCTs**
	"Standard care"**				*Low pre-test risk* 1. Nucifora 2009 (ASSENCE)[180]		**1 RCT**
	ICA		1. Sharples 2007 (CECaT)[220]				**1 RCT**
	Any comparator	**2 RCTs**	**1 RCT**	-----	**1 RCT**	**2 RCTs**	**6 RCTs**
PET	**SPECT**		1. Mullani 2000[168]	1. Patel 2019[189]			**2 RCTs**
TOTAL		**13 RCTs** **1 prospective CC**	**2 RCTs**	**1 RCT**	**16 RCTs**	**3 RCTs**	**35 RCTs** **1 pro CC**

CCTA = coronary computed tomography angiography; ETT ECG = exercise treadmill test with electrocardiography; FFR = fractional flow reserve; ICA = invasive coronary angiography; PET = positron emission tomography; Pro CC = prospective comparative cohort; RCT = randomized controlled trial; SPECT = single photon emission computed tomography; Stress Echo = stress echocardigraphy

* **McKavanagh 2015 (CAPP)**: Low risk: 43%; Intermediate risk: 24%; High risk: 34%.
Sabharwal 2007: Low risk: 16%; Intermediate risk: 61%; High risk: 23%.

Chang 2008: Low risk: 37%; Intermediate risk: 42%; High risk: 21%.
Lim 2013: unclear distribution
Zacharias 2017: Low risk: 41%; Intermediate risk: 34%; High risk: 25%.

† 85% of patients in the CCTA arm also received ETT ECG so this is not a true CCTA vs. ETT ECG comparison.

‡ From Supplemental material, CE-MARC 2 trial: "In essence, the guidelines recommend invasive angiography as the most cost-effective first test if the likelihood of CHD is 61-90%, non-invasive functional testing (SPECT, stress echocardiography or stress CMR) if the likelihood of CHD is 30-60%, CT scanning (with 64 slices or above) if the likelihood of CHD is 10-29% or no further testing if the likelihood of CHD is low (<10%)."

§ 6-hour observation period followed by hospital admission if deemed (by ED physician) high to intermediate risk for ACS (by the ED physician) or discharge (discharged patients followed-up at the cardiology clinic within 2 weeks). Further investigations (i.e., ICA or non-invasive cardiac function testing—including stress echocardiography, SMPI, or exercise ECG testing) performed at discretion of the attending cardiologist either during index hospitalization or on an outpatient basis (32% had MPI or stress echo; 24% had stress ECG only; 11% had ICA).

****** Hospitalized until a positive or negative diagnosis was reached according to local protocols without imposing any time constraints on investigators. The final diagnosis was achieved using clinical judgment only without performing additional diagnostic examinations in 39 cases (71%), using stress echo in 6 (11%), using EET in 7 (13%), and using coronary angiography in 3 (5%).

A total of 22 trials across 46 publications evaluated CCTA (see Appendix Table O34 for a list of the index trial and its affiliated publications). Twenty trials compared CCTA with functional testing.[59,126,153,163,215,238] Of these, six trials evaluated stable patients with suspected CAD[59,126,153,163,215,238] and 14 trials evaluated patients with suspected ACS.[37,47,84,85,96,109,138,140,144,145,161,171,192,248] Two RCTs compared CCTA versus direct referral to ICA in patients with suspected CAD (known CAD was an exclusion criteria)[36,52] One prospective nonrandomized comparative cohort compared CCTA plus Fractional Flow Reserve (FFR) versus any non-invasive testing and versus ICA in patients with suspected CAD treated on an outpatient basis.[57,60] Of the 22 RCTs, seven were considered good quality[47,52,59,84,126,215,238], 12 fair quality[36,37,96,109,138,140,144,145,153,171,192,248] and three poor quality[85,161,163]; the prospective comparative cohort was considered good quality[57,60] (see Appendix E for details).

A total of six trials evaluated SPECT. Two trials compared SPECT imaging with stress echocardiography in mixed populations of patients with suspected or known CAD, one in stable and one in acute patients.[210,220,241] Two trials compared SPECT with exercise ECG in stable outpatients with suspected CAD (known CAD was an exclusion criteria).[209,223] One trial compared SPECT imaging versus clinical assessment only in acute patients with suspected ACS presenting to the ED.[142]

One trial compared SPECT with NICE guideline-directed care in stable outpatients with suspected CAD.[88] Lately, one trial compared SPECT with ICA in stable patients with suspected or known CAD.[220,241] This latter trial also compared SPECT with exercise ECG. Of the six RCTs, two were considered good quality[88,220,241] and four fair quality[142,209,210,223] (see Appendix E for details).

A total of six, primarily older trials (2009 or earlier) evaluated stress echocardiography. Five trials compared stress echocardiography with exercise ECG, two in stable outpatients with suspected CAD (known CAD was an exclusion criteria)[91,211,262] and three in patients with acute symptoms presenting to the ED or hospital[48,117,180]. One trial compared stress echocardiography with "standard care" in low-risk patients with suspected ACS presenting to the ED.[180] One trial compared stress echocardiography with direct referral to ICA in stable patients with suspected or known CAD.[220,241] One of these trials included both an exercise ECG and a standard care comparison arm.[180] Of the six RCTs, two were considered good quality[91,220,241,262], one fair quality[48] and three poor quality[117,180,211] (see Appendix E for details).

A total of two trials evaluated PET and both compared PET with SPECT in outpatient settings. One poor-quality trial included stable patients with a mixed of suspected or known CAD[168] and the second good-quality trial included stable patients with known CAD presenting with new or worsening symptoms.[189]

See Appendix E for study quality details.

5.1.2 Evidence base for Key Question 5

In addition to the trials evaluating efficacy and safety, a total of three systematic reviews[243,249,263] and 11 primary studies were included that formally evaluated cost-effectiveness. Eight of the studies (in nine publications) were in stable outpatients with suspected CAD,[8,26,27,91,116,123,136,147,162] and three were in patients with suspected ACS.[82,196,197] Formal economic studies identified for inclusion primarily

compared combinations of testing strategies involving CCTA, stress nuclear imaging (primarily SPECT), stress echocardiography, exercise ECG treadmill testing and invasive coronary angiography, with only few directly comparing one specific test to another. Given the complexity of interpreting these studies, all cost-effectiveness data is summarized under section 6.1.5 under the CCTA heading. Across the studies, scores on the Quality of Health Economic Studies (QHES), the instrument used to systematically assess the quality of each study, ranged from 50 to 94 out of 100 (See Appendix E for details).

5.2 Comparison with the 2008 and 2013 reports

CCTA

The 2008 review of CCTA primarily focused on diagnostic accuracy (34 for the 41 included studies) for 64 slice or higher resolution equipment and most included patient already scheduled for ICA. A variety of scenarios were modeled for clinical impact and cost-effectiveness of CCTA related to CAD prevalence. Only one RCT[85] measured the impact of CCTA on patient outcomes was identified. The report included patients with acute chest pain presenting in an ED setting (7 studies, total N=496) and patients with stable chest pain at low to intermediate CAD risk presenting to outpatient settings (34 studies, total N 3349, CAD prevalence range 2–40%); most reported on diagnostic accuracy. Approximately two-thirds of studies excluded patients with known CAD or revascularization.

Primary findings from the 2008 report include:

- Based on ICER's modeling, Integrated Evidence Rating method and assuming a CCTA reimbursed price of $466:
    - For the triage of patients with acute chest pain at low to intermediate risk of ACS in an ED setting, CCTA was considered to be of comparative clinical effectiveness versus usually care/other diagnostic strategies and of high value based on their economic modeling.
    - In outpatients with or without signs and symptoms of unstable chest pain and at low to intermediate risk of significant CAD, the comparative clinical effectiveness of CCTA was rated as "unproven but with evidence of potential net benefit" (limited confidence of small or moderate-large net health benefit) and reasonable or comparable value.
- CCTA was considered highly sensitive with moderately high specificity (See Executive Summary and other tables in this report).
- Data on clinical outcomes and decision making not synthesized across studies; all but one study was observational.
- For triage of ED patients, their models suggested that ICA may be reduced if CCTA were to be employed compared with usual care.
- Regarding safety, CCTA was considered safe with risks similar to other tests employing contrast media. A range of CCTA-related radiation exposure values was reported (2 mSv to 14 mSv). As noted, small but definite risks may exist related to radiation exposure. Incidental/extra cardiac findings requiring further evaluation was reported to range from 5 to 20% of patients. Authors note the need to consider incidental findings in economic analyses.

Comparison with this update:

Since 2008, 19 additional RCTs (43 publications, total N >20,000 patients) comparing CCTA with functional testing have been published and are included in this re-review and constitute the primary evidence base for CCTA effectiveness and safety. This update reports on an expanded evidence base of higher quality studies. Thus, this update focused on the impact of CCTA on clinical outcomes and decision making with information regarding diagnostic accuracy summarized for contes making direct comparison to the 2008 report challenging

- In general, for CCTA compared with functional imaging in particular, there were no clear differences in clinical outcomes (MI, all-cause mortality), use of additional testing or hospitalization for patients presenting to the ED or for stable outpatients. (See Executive Summary and full report for details).
- In contrast to modeling done in the 2008 report, data synthesized across more recent RCTs suggests that ICA is more common (as is PCI) with CCTA versus functional imaging
- Safety findings in this update are overall consistent with the 2008 report. Continued improvement in methods for reducing test-related radiation exposure are noted.
- Definitive conclusions for cost-effectiveness of CCTA specifically from published included studies were not possible.

Cardiac nuclear imaging

The key questions for 2013 review of cardiac nuclear imaging differed from this review evaluation and the prior review included screening of asymptomatic patients. The review included 34 studies, 26 of which evaluated clinical outcomes. Nine studies were comparative cohort studies comparing different protocols and 12 were case series. The 2013 report included patients with known CAD, including asymptomatic patients, who receive nuclear imaging test for prognostic purposes such as risk stratification, treatment selection or follow-up monitoring. Most studies were in "mixed" populations which included symptomatic and asymptomatic patients, those with suspected and known CAD. Most studies of symptomatic patients were in higher risk patients.

Primary findings of the 2013 report relevant to this update:

- For diagnostic accuracy, the report compared PET and SPECT with ICA-derived fractional flow reserve and summarized accuracy data from systematic reviews for the comparison with ICA. (See report and Executive Summary Tables).
- Overall, based on ICER's modeling, Integrated Evidence Rating method for symptomatic patients at low to intermediate CAD risk,
    - Clinical effectiveness of SPECT was considered to be comparable or better versus ETT and based on HCA payment schedules, was more costly as an initial test, but that a 2-stage strategy of ETT followed by SPECT may provide cost savings but the comparative value was considered to be low.
    - SPECT and stress echo were considered to provide similar diagnostic and prognostic performance and SPECT was rated as "reasonable/comparable" for both clinical effectiveness and value.
    - In symptomatic patients with known CAD, SPECT and stress echo were considered comparable in clinical effectiveness and they expected it to be of "reasonable/comparable" value based on one RCT. Evidence comparing SPECT with ETT was considered to be insufficient as no studies were identified.

    - SPECT and PET were considered to be safe, but lack of comparative effectiveness evidence was noted. AEs were generally considered to be insignificant and due to exercise or pharmacologic stressors. Effective radiation does for SPECT (7–30 mSv) and PET (2–14 mSV) were reported.
- Evidence for PET was considered to be insufficient for all populations

- Evidence related to differential effectiveness or safety for key subgroups was considered insufficient.

Comparison with this update:

Our update focuses on the clinical impact of stress nuclear imaging (SPECT and PET).

- This update does not include asymptomatic patients based on clinical input at the time of topic development, nor does it include patients at high CAD risk or studies of prognosis.
- A total of six RCTs (including three from the prior report) for SPECT and two RCTs for PET (including one from the previous report. RCTs comparing SPECT with NICE guideline directed care and clinical assessment where part of this update as was one RCT comparing it with ICA which were not part of the 2013 report. (Please see full report and executive summary)
- For SPECT compared with other functional test (ETT, stress echo), there were no differences in all-cause mortality, ICA referral, hospitalization, subsequent ED visits (SOE low for all) or revascularization (SOE Moderate). Findings and conclusions regarding safety are similar to the prior report.
- For PET, was insufficient for all clinical outcomes. There was no difference in ICA or revascularization between PET and SPECT based on the newly identified RCT in patients with known CAD with new or worsening symptoms (SOE Low).
- Definitive conclusions for cost-effectiveness of CCTA specifically from published included studies were not possible.

Given that stress echocardiography is an established modality for evaluating cardiac function, based on clinical input it is included in this HTA.

6 Coronary Computed Tomography Angiography (CCTA) Results

6.1 CCTA versus Any Functional Testing

A total of 20 trials comparing CCTA with functional testing that met inclusion criteria were identified.[59,126,153,163,215,238] Six trials evaluated stable patients with suspected CAD[59,126,153,163,215,238] and 14 trials evaluated patients with suspected ACS.[37,47,84,85,96,109,138,140,144,145,161,171,192,248]

Since studies of patient with STEMI were excluded, ACS for included studies pertains to patients with unstable angina or NSTEMI as described in the studies. Some studies focused on patients with normal ECG and negative troponins. No studies specifically in patients with known CAD were identified.

CCTA vs. functional testing in stable patients with suspected CAD

Six randomized control trials (across 23 publications)[5,58,59,115,126,135,146,148,149,151,153,163,175,176,186,187,215,217,218,237,238,256,257] compared CCTA with functional testing in patients with suspected CAD in the outpatient setting. (See Appendix Q for details). All trials used a 64-slice (or higher) CT scanner for CCTA imaging and four[153,163,215,238] reported the use of iodinated contrast agents. Two trials[153,215] included CACS imaging as part of their CCTA protocol and three trials[59,163,238] did not. In one trial,[126] 3% of patients randomized to the CCTA arm received CACS. Specific functional tests included SPECT in three trials [126,163,238](across 4 publications, N=1,533), exercise ECG in two trials[153,215] (across 7 publications, N=4,646), and any functional testing in one trial[59] (across 12 publications, N=10,003). In the latter trial, most patients (63%) underwent nuclear stress testing as their index test, though patients could have received CACS, stress echocardiography, exercise ECG, ICA, or no testing at index visit. In one trial, the SCOT-HEART trial,[215] 85% of *all* patients in the CCTA arm had exercise treadmill tests (ETT) (as standard care) and the function testing arm was predominately ETT making this trial more of an adjunctive comparison.

Across all six trials, sample sizes ranged from 180 to 10,003 (total N=16,182). Mean patient age ranged from 57 to 61 years and the proportion of females ranged from 44% to 53%. Less than a third of participants were non-white (range, 22% to 29%) across the three trials reporting race.[59,126,238] Five trials specifically excluded patients with known CAD[59,126,153,163,238] and four trials excluded patients with prior revascularizations.[59,126,163,238] Patients' pre-test risk for CAD was low to intermediate one trial,[59] intermediate in one trial,[126] intermediate to high in one trial,[163] mixed in two trials,[153,215] and not reported in one trial.[238] Across all six trials, the proportion of patients reporting chest pain ranged from 73% to 100% (four trials reported on the specific sub-type of chest pain: typical [range, 12% to 35%] atypical [7% to 78%] and non-anginal [11% to 40%][59,153,163,215]); hypertension, from 31% to 65%; diabetes, from 11% to 28%; and smoking (past or current), from 15% to 53%. None of the trials reported on the proportion of patients with unstable angina. The proportion of patients presenting with dyspnea was reported by two trials (range, 10% to 15%)[59,126] and hyperlipidemia by three trials (range, 57% to 68%).[59,126,163] Duration of follow-up ranged from 2 months to 5 years. See Appendix Q for details.

Three trials were conducted in the United States,[59,163,238] two trials in the United Kingdom,[153,215] and one trial in multiple countries (Brazil, Czech Republic, India, Mexico, Slovenia, and Turkey).[126] Investigators

received funding from the government in four trials,[153,215,238] industry in one trial,[238] and an international organization in one trial.[126]

Four trials were rated good quality,[59,126,215,238] one fair quality,[153] and one poor quality.[163] The major methodological limitations in the fair-quality trial were unclear allocation concealment methods and unclear blinding of outcome assessors. In the poor-quality trial, limitations included unclear randomization and allocation concealment methods, failure to blind outcomes assessors, differences in key CAD risk factors at baseline between groups, it was unclear if follow-up times were comparable between groups.

CCTA vs. functional testing among patients with suspected ACS

Fourteen randomized control trials[37,47,84,85,96,109,138,140,144,145,161,171,192,248] (across 21 publications) compared CCTA with functional testing in patients with suspected ACS. (See Appendix Q for details). Ten trials took place in the Emergency Department,[37,47,84,85,96,109,138,145,161,248] three trials in the inpatient setting,[140,171,192] and one trial in the outpatient setting.[144] All trials used a 64-slice (or higher) CT scanner for CCTA imaging and nine reported the use of iodinated contrast agents.[37,84,85,96,109,140,171,192,248] Seven trials[84,85,109,140,145,161,171] included CACS imaging as part of their CCTA protocol and six trials[37,47,96,138,144,192] did not. In one trial,[248] 1% of patients randomized to the CCTA arm received CACS. Specific functional tests included SPECT in four trials[84,85,140,171] (across 5 publications, N=1,944), stress echocardiography in three trials[138,192,248] (across 4 publications, N=1,014), exercise ECG in one trial (across 1 publication, N=562),[96] and any functional testing in six trials[37,47,109,144,145,161] (across 11 publications, N=3,818).

Across all 14 trials, sample sizes ranged from 60 to 1,392 (total N=7,338). Mean patient age ranged from 49 to 64 years and the proportion of females ranged from 39% to 63%. A large majority of the patients identified as non-white (range, 33% to 95%) across the 7 trials reporting race.[109,138,140,145,161,171,248] Eight trials specifically excluded patients with known CAD,[85,96,109,138,140,161,171,248] and in two trials, 14% and 15% of patients had known CAD.[37,144] The remaining four trials did not report on patient's CAD status.[47,84,145,192] Two trials reported excluding patients with prior revascularizations[109,161] and one trial reported excluding patients with prior MI.[109] In two trials, 1% of patients had a prior MI.[84,145] The remaining trials did not report on patients' history of MI or revascularizations. Patients' pre-test risk for CAD was very low to low in one trial,[85] low in one trial,[47] low to intermediate in eight trials,[84,96,138,144,145,161,171,192] intermediate in two trials,[109,140] mixed in one trial,[37] and not reported in one trial.[248] In the trial including patients with varied risk statuses, 37% were low risk, 42% were intermediate risk, and 21% high risk.[37] All patients in all trials reported having chest pain (four trials reported on the specific sub-type of chest pain; typical [range, 12% to 90%] atypical [10% to 39%] and non-anginal [2% to 49%][109,140,144,192]). One trial reported that 1% of patients had unstable angina.[84] Two trials reported the proportion of patients with dyspnea (range, 2% to 49%),[109,248] 13 trials reported the proportion of patients with hypertension (range, 17% to 72%),[37,47,84,85,96,109,138,140,144,145,171,192,248] 12 trials reported the proportion of patients with diabetes (range, 6% to 32%),[37,84,85,96,109,138,140,144,145,171,192,248] 11 trials reported the proportion of patients with hyperlipidemia (range, 25% to 52%),[37,84,85,96,109,138,140,144,145,171,248] and 13 trials reported the proportion of smokers (past or current) (range, 14% to 49%).[37,47,84,85,96,109,138,140,144,145,171,192,248] Duration of follow-up ranged from 1 month to 4.7 years.

Nine trials were conducted in the United States,[84,85,109,138,140,145,161,171,248] one trial in Australia,[96] one trial in Denmark,[144] one trial in the Netherlands,[47] one trial in South Korea,[37] and one trial in Spain.[192] Investigators received funding from the government in four trials,[47,109,145,161] industry in two trials,[84,85] and non-profit foundations in four trials.[96,138,140,144] One trial reported receiving no funding[248] and three trials provided no information on funding.[37,171,192]

Two trials were rated good quality,[47,84] 10 trials were rated fair quality,[37,109,138,140,144,145,171,192,248] and two were rated poor quality.[85,161] The major methodological limitations in the fair-quality trials were unclear randomization and allocation concealment methods and failure to blind outcomes assessors. Other methodological shortcomings in the poor-quality trials included difference in key CAD risk factors between groups at baseline which were not controlled for and no prespecified definition for a positive test in one trial.

6.1.1 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

6.1.1.1 Summary of results for primary outcomes

There were 17 RCTs comparing CCTA with functional testing, six RCTs[59,126,153,163,215,238] in stable patients with suspected CAD and 11 RCTs (12 publications)[37,47,84,85,96,109,111,138,143,145,192,248] in patients with suspected ACS that reported primary clinical outcomes. Functional testing included imaging tests (stress nuclear, stress echocardiography and ETT. Given the limitations of ETT as a functional test, sensitivity analyses comparing CCTA with functional imaging tests only were conducted. There was no statistical interaction between the patient populations for any outcome.

Across studies that include stable patients with suspected CAD and patients with suspected ACS presenting to an emergency department or similar setting:

- There is no clear difference in the frequency of MI between CCTA and functional imaging tests (SOE Moderate).
    - Three smaller RCTs, one in stable patients and two in those with suspected ACS, reported no MI in either testing arm.
    - CCTA was associated with lower MI risk compared with functional testing based on pooled estimates across the 14 remaining RCTs (14 RCTs, pooled RR 0.70, 95% CI 0.56 to 0.89, I^2=0%), however, the RD (0.4, 95% CI 0.1 to 0.8 per 100 patients) was small. The association was no longer clearly significant following exclusion of one RCT in stable patients with suspected CAD in which 85% of all patients had ETT in addition to CCTA (13 RCTs, pooled RR 0.75, 95% CI 0.57 to 0.99, I^2=0). This pattern was seen across RCTs of stable patients when the one trial was excluded. Across 10 RCTs in patients with suspected ACS, there was no difference in the frequency of MI between CCTA and functional testing at any time.
- There was no association between CCTA and reduction in all-cause mortality compared with functional testing (SOE Moderate).
    - Six RCTs reported no mortality in either testing arm (1 RCT in stable patients, 5 RCTs in suspected ACS patients).

  - There was no difference in all-cause mortality between CCTA and functional testing across the remaining 11 RCTs (pooled RR 0.99 95% CI 0.40 to 2.68, I^2=0%). There was also no difference in all-cause mortality when the populations were considered separately.
- Cardiac death was rare in both patient populations, with six total cardiac deaths reported in patients receiving CCTA and 13 reported in patients receiving functional testing (SOE Insufficient).
- It is possible that smaller trials in particular may have been underpowered to detect differences in MI, all-cause mortality, and cardiac death between CCTA and functional testing given that many trials enrolled patients with low or low to intermediate pre-test risk.

Detailed results

6.1.1.2 Myocardial infarction

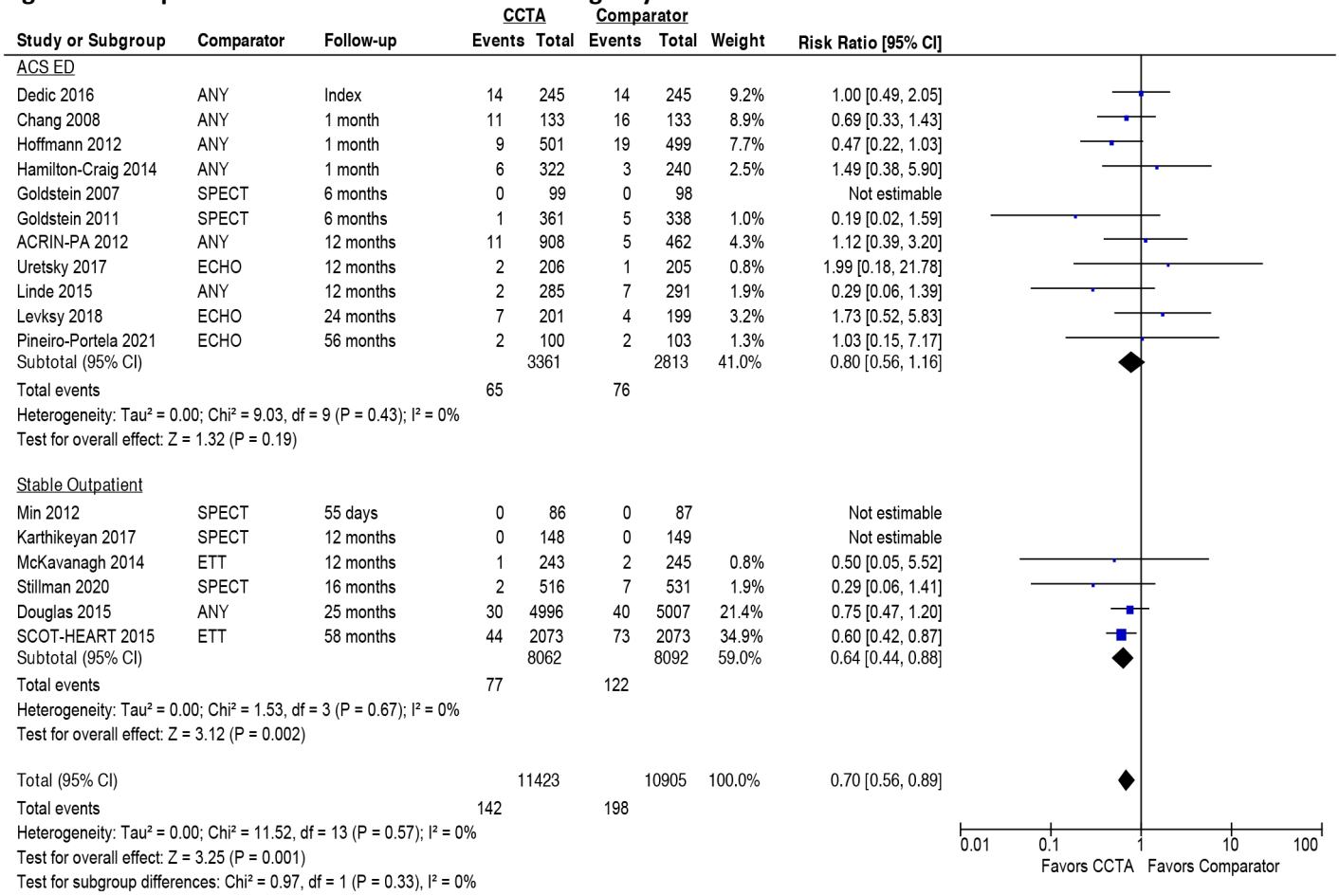
Across populations, 17 RCTs (N=22,238) reported on myocardial infarction; six RCTs[59,126,153,163,215,238] were in stable patients with suspected CAD and 11 RCTs (12 publications)[37,47,84,85,96,109,111,138,143,145,192,248] were in patients with suspected ACS presenting to an emergency department or similar setting. Across trials, the cumulative incidence of MI was 1.5 per 100 patients, with 3 smaller trials (N=667), two in the stable, suspected CAD population[126,163] and one in the suspected ACS population[85], reporting no MI in either testing arm. CCTA was associated with CCTA was associated with lower MI risk compared with functional testing based on pooled estimates across the 14 remaining RCTs (14 RCTs, pooled RR 0.70, 95% CI 0.56 to 0.89, I^2=0%)[37,47,59,84,96,109,111,143,145,153,192,215,238,248] however the RD (0.4, 95% CI 0.1 to 0.8 per 100 patients, I^2=19%) was small. Only one RCT (SCOT-HEART)[215] in a population of stable patients with suspected CAD at intermediate pre-test risk reported a statistically significant decrease in MI favoring CCTA over ETT. However, 85% of *all* patients had ETT (as standard care) and the function testing arm was predominately ETT in this trial, raising concern regarding substantial clinical heterogeneity compared with other RCTs where stress echocardiography and SPECT were more common in the functional testing arm. Exclusion of this trial did not impact statistical heterogeneity, (no change in I^2) however, the confidence interval for the pooled estimate across the remaining RCTs the null value of 1.0 suggesting no clear association between CCTA and reduced MI (13 RCTs RR 0.75, 95% CI 0.57 to 0.99). Exclusion of two poor-quality studies[85,163] did not affect pooled estimates as both had reported that no MI occurred (Figure 4, Table 29). There was no statistical interaction between the stable and suspected ACS populations (p = 0.23).

In stable outpatients with suspected CAD, MI was evaluated in six RCTs (N= 16,154)[59,126,153,163,215,238] comparing CCTA with functional testing in stable outpatients. Two smaller RCTs, one poor-quality (N= 173) with 55 days follow-up[163] in intermediate to high-risk patients and one good-quality RCT (N = 297)[126] in intermediate risk patients reported no MI in either testing arm. Four RCTs reported occurrence of MI. CCTA was associated with lower risk of MI compared with functional testing across six RCTs reporting various lengths of follow-up (4 RCTs, pooled RR 0.64, 95% CI 0.44 to 0.87, I^2=0%)[59,153,215,238] after testing in stable outpatients

suspected of CAD across time frames ranging from 12 to 58 months. The risk difference was small however across trials (pooled RD 1, 95% CI –1 to 0 per 100 people I^2=42%). Only one RCT (SCOT-HEART)[215] in a population that appears to have enrolled patients at intermediate pre-test risk of CAD reported a statistically significant decrease in MI favoring CCTA over ETT, however 85% of *all* patients had ETT and the function testing arm was predominately ETT (as standard care) in this trial, raising concern regarding substantial clinical heterogeneity compared with other RCTs where stress echocardiography and SPECT were more common in the functional testing arms. Exclusion of this trial did not impact statistical heterogeneity, (no change in I^2) however. The impact of the longer follow-up time (58 months) than reported for other trials is unknown. Results were no longer statistically significant based on sensitivity analysis excluding the SCOT-HEART trial (3 RCTs, pooled RR 0.69, 95% CI 0.27 to 1.14 I^2=0%).[59,153,238]

In patients with suspected ACS *presenting to an emergency room or similar acute care setting*, seven trials evaluated MI at or shortly after index visits (N=4584).[37,47,85,96,109,145] There was no difference in MI frequency between CCTA and functional testing at time of index testing (6 trials, pooled RR 0.8, 95% CI 0.53 to 1.19, I^2=21.6%). One smaller (N= 197) poor-quality trial in very low risk patients reported no MI occurred in either testing arm.[85] At 1 to 6.5 months, there were also seven trials that reported on MI.[37,84,85,96,109,144,145] No MI was reported for any testing arm when CCTA was compared with either SPECT (two RCTs)[84,85] or ETT (one RCT)[96]. Across the four other trials of CCTA versus any type of functional test the difference between tests on the occurrence of MI failed to reach statistical significance (4 trials, pooled 0.28, 95% CI 0.07 to 1.09 I^2= 0%). Similarly at time frames ≥12 months, there was no difference in MI between CCTA and functional testing (5 trials, pooled RR 1.22 (95% CI 0.51 to 2.74 I^2=0%)[111,138,143,192,248] There was little or no statistical heterogeneity in the analyses. In some trials, patients were only randomized to index testing after normal ECG and normal serum biomarkers were obtained and/or the tests were performed after the time of the index visits.

Figure 4. Comparison of CCTA and functional testing: Myocardial infarction



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

Table 29. Summary of effect estimates including sensitivity analyses for CCTA versus functional testing across studies in patients with suspected CAD who are stable and patients with suspected ACS

Outcome Analysis # RCTs (N=) reporting	Risk CCTA vs. Functional (per 100 persons)*	Pooled estimates Number RCTs (N) for pooled RR RR, 95% CI, I^2 RD, 95% CI, per 100†, I^2	Interaction: Suspected ACS, Stable suspected CAD p-value
MI‡			
Primary analysis 17 RCTs (N=22,328)	1.2 vs. 1.8	14 RCTs (N=21,661) RR 0.70, 95% CI 0.56 to 0.89, I^2=0% RD 0.4, 95% CI 0.1 to 0.8 per 100, I^2=19%*	0.23
Exclude SCOT-HEART	1.0 vs. 1.4	13 RCTs (N =17,515)	0.623

Outcome Analysis # RCTs (N=) reporting	Risk CCTA vs. Functional (per 100 persons)*	Pooled estimates Number RCTs (N) for pooled RR RR, 95% CI, I^2 RD, 95% CI, per 100†, I^2	Interaction: Suspected ACS, Stable suspected CAD p-value
16 RCTs (N=18,182)		RR 0.75, 95% CI 0.57 to 0.99, I^2=0% RD 0.3, 95% CI 0 to 0.5 per 100, I^2=0%	
Exclude ETT as comparator 14 RCTs (N=17,132)	1.0 vs. 1.4	11 RCTs (N=16,465) RR 0.74, 95% CI 0.55 to 0.98, I^2=0%	0.660
Exclude poor RCTs 15 RCTs (N=21,958)	1.3 vs. 1.8	14 RCTs (N=21,661) RR 0.70, 95% CI 0.56 to 0.89, I^2=0% RD 0.5, 95% CI 0.1 to 0.9 per 100, I^2=28%	0.345
All-cause mortality§			
Primary analysis 17 RCTs (N=21,680)	1.2 vs. 1.3	11 RCTs (N=18,935) RR 0.99, 95% CI 0.40 to 2.68, I^2=0% NS, no RD	0.985
Exclude SCOT-HEART 16 RCTs (N=18,902)	1.0 vs. 1.1	Pooled 10 RCTs (N=17,534) RR 1.00, 95% CI 0.69 to 1.00, I^2=0% NS, no RD	0.985
Exclude poor RCTs 15 RCTs (N= 21,680)	1.2 vs. 1.3	Pooled 11 RCTs (N=21,310) RR 1.00, 95% CI 0.77 to 1.30, I^2=0% NS, no RD	0.984
ICA			
Primary analysis 19 RCTS (N=22,335)	14.4 vs. 12.0	RR 1.25, 95% CI 1.09 to 1.47, I^2=67% RD 2.7, 95% CI 1 to 4 per 100, I^2=59%	0.922
Exclude SCOT-HEART 18 RCTs (N=18,1888)	12.3 vs. 9.1	RR 1.31, 95% CI 1.12 to 1.51, I^2=45% RD 3, 95% CI 1.3 to 4.7 per 100, I^2=55%	0.578
Exclude poor RCTs 16 RCTs (N=21,904)	14.2 vs. 12.0	RR 1.25, 95% CI 1.07 to 1.45, I^2= 72% RD 2.6, 95% CI 0.9 to 4.4 per 100, I^2= 65%	0.887
Exclude outlier** 18 RCTs (N=21,923)	14.5 vs. 12.1	RR 1.23, 95% CI 1.07 to 1.41, I^2=64.6% RD 2.3, 95% CI 0.08 to 4.3 per 100, I^2= 51%	0.885
Exclude ETT as comparator RCTs (N=17,138)	12.0 vs. 8.8	RR 1.28, 95% CI 1.07 to 1.51, I^2= 49% NS, no RD	0.120
Any additional NIT			
Primary analysis 17 RCTs (N=11,595)	7.2 vs. 7.6	RR 0.82, 95% CI 0.53 to 1.28, I^2=83% NS, no RD	0.37
Exclude SCOT-HEART 16 RCTs (N=7,449)	10.9 vs. 12.0	RR 0.82, 95% CI 0.52 to 1.32, I^2= 83% NS, no RD	0.333
Exclude poor RCTs 14 RCTs (N=11,165)	7.3 vs. 7.4	RR 0.92, 95% CI 0.56 to 1.54 I^2=85% NS, no RD	0.491

Outcome Analysis # RCTs (N=) reporting	Risk CCTA vs. Functional (per 100 persons)*	Pooled estimates Number RCTs (N) for pooled RR RR, 95% CI, I^2 RD, 95% CI, per 100†, I^2	Interaction: Suspected ACS, Stable suspected CAD p-value
Exclude outliers†† 15 RCTs (N=10,841)	7.4 vs. 6.7	RR 0.94, 95% CI 0.68 to 1.25, I^2=69% NS, no RD	0.449
Any revascularization			
Primary analysis 19 RCTs (N=23,124)	9.5 vs. 7.1	RR 1.52, 95% CI 1.26 to 1.90 I^2=66% RD 2.4, 95% CI 1.4 to 3.3 per 100, I^2=46%	0.779
Exclude SCOT-HEART 18 RCTs (N=18,978)	6.2 vs. 3.6	RR 1.63, 95% CI 1.33 to 1.98, I^2=31% RD 2.4, 95% CI 1.4 to 3.5 per 100, I^2=51%	0.391
Exclude poor RCTs 16 RCTs (N=22,694)	9.5 vs. 7.2	RR 1.48, 95% CI 1.22 to 1.83, I^2=68% RD 2.2, 95% CI 1.2 to 3.2 per 100, I^2=51%	0.839
Exclude ETT as comparator 16 RCTs (N=17,280)	6.0 vs. 3.6	RR 1.53, 95% CI 1.20 to 1.94, I^2=23%	0.583
PCI			
Primary analysis 12 RCTs (N=18,960)	8.2 vs. 6.0	RR 1.63, 95% CI 1.22 to 2.35, I^2=74% RD 2.4, 95% CI 1.3 to 3.6 per 100, I^2=51%	0.946
Exclude SCOT-HEART 11 RCTs (N=14,814)	5.1 vs. 2.6	RR 1.89, 95% CI 1.38 to 2.43, I^2=36% RD 2.6 95% CI 1.3 to 4.0 per 100, I^2=55%	0.431
Exclude poor RCTs 10 RCTs (N=18,703)	8.3 vs. 6.1	RR 1.60, 95% CI 1.18 to 2.30, I^2=78% RD 2.4, 95% CI 1.1 to 3.7 per 100, I^2=60%	0.961
Exclude outlier** 11 RCTs (N=18,549)	8.3 vs. 6.1	RR 1.58, 95% CI 1.18 to 2.22, I^2=73% RD 2.1, 95% CI 1.0 to 3.2 per 100, I^2=60%	0.906
Exclude ETT as comparator 9 RCTs (N=13,854)	4.9 vs. 2.5	RR 1.68, 95% CI 1.09 to 2.45, I^2=28%	0.46

ACS = acute coronary syndrome; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ETT = exercise treadmill test; ICA = invasive coronary angiography; MI = myocardial infarction; NA = not applicable; NIT = noninvasive testing; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio.

*Absolute risk estimates and risk differences (RD) include RCTs reporting no events in either arm for MI and no events for all-cause mortality in the denominator.

†Reported only if association observed (i.e., RR is statistically significant).

‡Pooled estimates for RR do not include 3 RCTs (N=667) in which no MI occurred in either arm as RR is not estimable.

§Pooled estimates for RR do not include 6 RCTs (N=2746) in which no deaths occurred in either arm as RR is not estimable; 11 RCTS reported one or more deaths and were pooled.

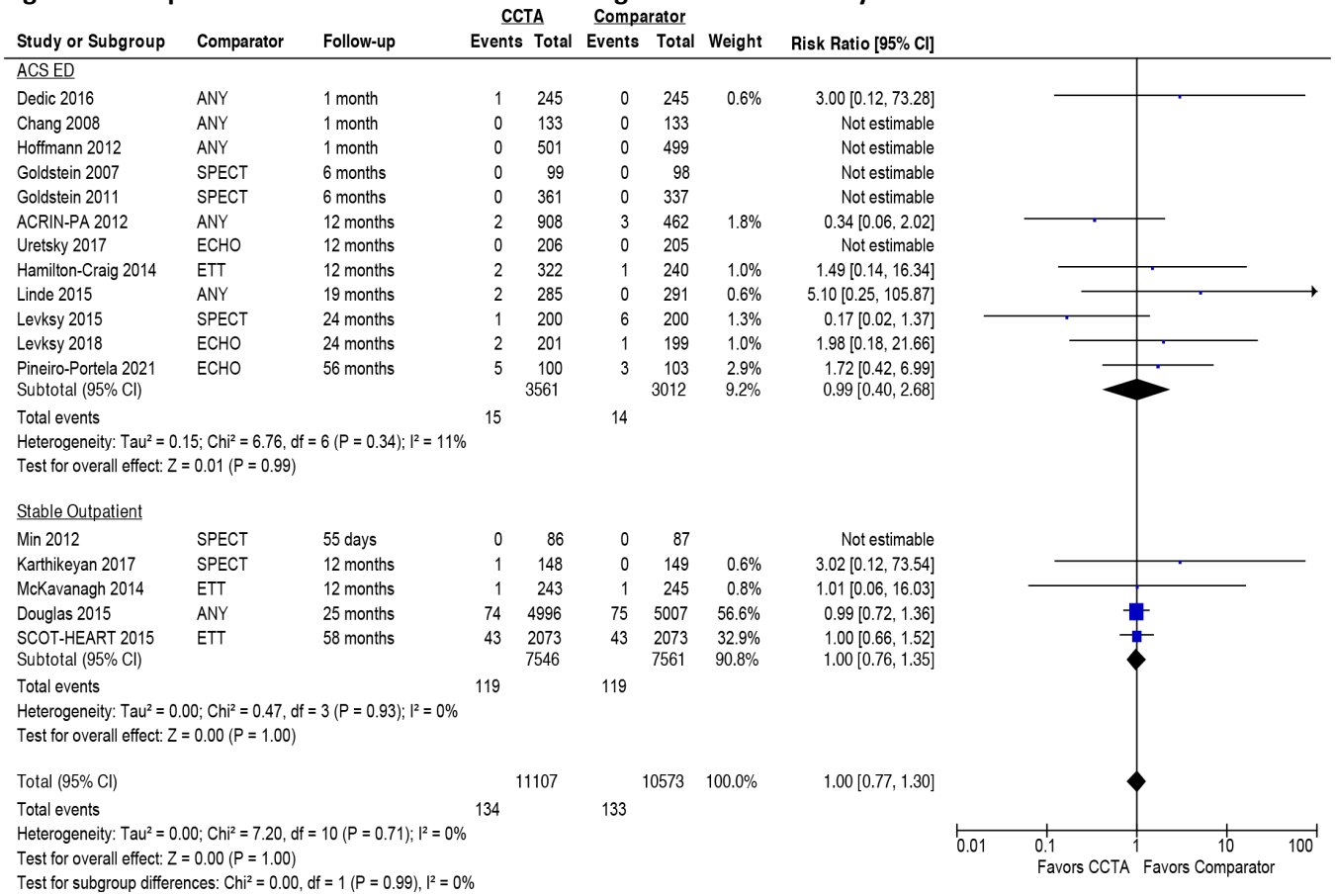
**Uretsky 2017

††McKavanagh 2015, Chang 2008

6.1.1.3 All-cause mortality and cardiac mortality

Across populations, seventeen RCTs (N= 21,680) reported on all-cause mortality; five RCTs[59,126,153,163,215] were in stable patients with suspected CAD and 12 were in patients with suspected ACS.[37,47,84,85,96,109,111,138,140,143,145,192,248] Across trials, the cumulative incidence of all-cause mortality was 1.3 per 100 patients. There was no difference in all-cause mortality between CCTA and functional testing (1.2 versus 1.3 per 100 patients). No mortality was observed in six trials (n=2746) including one RCT in stable patients[163] and five RCTs in patients with suspected ACS.[84,85] Across the remaining 11 RCTs reporting events (N=18,935), there was no association between CCTA and mortality compared with functional testing (11 RCTs, pooled RR 0.99 95% CI 0.40 to 2.68, I^2=0%). Figure 5. Exclusion of SCOT-HEART or poor-quality RCTS did not impact effect size estimates, heterogeneity or conclusions (Table 29). There was no statistical interaction between the stable and suspected ACS populations (p=0.985).

Figure 5. Comparison of CCTA and functional testing: All-cause mortality



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

Evidence was insufficient to draw conclusions regarding the impact of CCTA versus functional testing on cardiac mortality. The pre-test CAD probability across most studies was low to intermediate and cardiac

death was rare; studies may not have been adequately powered to detect cardiac death. Cardiac mortality was evaluated in 13 RCTs, four RCTs in stable patients[153,163,238] (N=5854) and nine RCTs in patients with suspected ACS (N= 5793).[84,85,96,109,111,138,143,145,171,248] Ten RCTs reported no cardiac deaths in either testing arm. Individual study sample sizes ranged from N=173 to N=4146.

Across populations, six cardiac deaths in those receiving CCTA and 13 in those receiving functional testing were observed in three RCTs.[111,143,215] In stable patients, cardiac death occurred in 0.24% (5/2073) CCTA patients and 0.28% (12/2073) of ETT patients RR 0.42, 95% CI 0.15 to 1.18) in one RCT.[215] In patients with suspected ACS, across two RCTs (N= 1942), only two cardiac deaths were reported, one in each study arm (RR 0.72, 95% CI 0.04 to 13.3) in each trial.[111,143]

> ***In stable outpatients with suspected CAD,*** there were no differences between CCTA and functional testing in in all-cause mortality across five individual trials (N= 15,107)[59,126,153,163,215] from 55 days up to 58 months after testing. No mortality was seen in either testing arm in one smaller (N= 173) poor-quality trial.[163] Across trials in which death occurred, there was no difference between CCTA and functional testing (4 trials, pooled RR 1.0, 95% CI 0.76 to 1.3, I^2=0%)[59,126,153,215]. Exclusion of the SCOT-HEART comparing CCTA with ETT did not change the effect estimate, statistical heterogeneity or conclusions. (3 trials, RR 1.0, 95% CI 0.61 to 1.89, I^2=0%).[59,126,153,163] One trial also comparing CCTA with ETT in a mixed risk population (N= 488) (McKavanagh) in which 38% of patients were at higher risk reported only one death in each arm.
>
> Four RCTs (N= 5854)[153,163,215,238] reported on cardiac death. Three reported that no cardiac deaths occurred in either testing arm; there was no difference between CCTA (0.2%, 5/2073) and ETT (0.58% 12/2073), in the one RCT in which cardiac death occurred RR 0.42, 95% CI 0.15 to 1.18). To the extent that cardiac death is rare in these populations, individual studies may have been underpowered to detect cardiac death or differences in cardiac death.
>
> ***In patients with suspected ACS*** *presenting to an emergency room or similar acute care setting,* there was no difference in all-cause mortality across 13 RCTs (N= 7941)[37,47,84,85,96,109,111,138,140,143,145,192,248] comparing CCTA to functional tests and time frames ranging from one-month post ED/observational unit discharge to 56 months. No deaths were observed in six[37,84,85,109,145,248] of the 13 trials (N= XXX) . Across the seven trials reporting one or more deaths, there was no different between testing arms (pooled RR 1.0, 95% CI 0.40 to 2.69, I^2= 11%).[47,96,111,138,140,143,192]
>
> There was no difference in cardiac mortality across 10 RCTs (N=7163)[84,85,96,109,111,138,140,143,145,248] comparing CCTA to functional tests and time frames ranging from one-month post ED/observational unit discharge to 56 months. Eight of the trials found no cardiac mortality. Across the two other trials, no difference was seen between testing arms, RR 0.72, 95CI 0.4 to 13.3 I^2= 0%. Pre-test risk in patient populations across studies were most generally low[47,84] or low to intermediate[96,138,144,145,161,171,192], with one reporting very low pre-test probability.[85] Two trials focused on patient with intermediate risk.[109,140] To the extent that cardiac death is rare in these populations, individual studies may have been underpowered to detect cardiac death or differences in cardiac death.

6.1.1.4 Other clinical outcomes

See Appendix O for summary tables.

Acute coronary syndrome, unstable angina (Appendix O, Tables O29 and O30)

No trials in stable outpatients reported on the frequency of ACS. Across five trials in *patients with suspected ACS*[37,47,96,109,111,143-145], there was no difference between CCTA and functional testing in the cumulative frequency ACS (as defined by the authors). There was no difference between testing arms in the cumulative frequency of unstable angina (UA) across nine RCTs, one in stable outpatients[153] and eight in patients with suspected ACS[37,47,84,85,96,109,143,144,248]. One RCT, in stable outpatients, reported that at 12 months there was no difference in UA between testing arms at 12 months, but more CCTA patients had UA at a median of 25 months compared with functional testing (1.2% vs. 0.8%, p=0.045).

Nonfatal stroke, cardiac arrest, continued chest pain, recurrent ischemia

Across populations, stroke and cardiac arrest were rare, occurring in ≤ 1% of any testing arm. No differences in cumulative frequency of these was see between testing arms were reported at any time frame. Five RCTs reported on nonfatal stroke,[59,138-140,175,215,238] one RCT reported on cardiac arrest[138,139], Many trials may have been underpowered to detect these events or evaluate differences between arms.

The cumulative frequency of continued chest pain varied substantially across trials (0.8% to 28%).

> ***In stable outpatients***, CCTA was associated with lower frequency of revisit to the ED with chest pain compared with ETT in one RCT (0.8 vs 6.9%) within 12 months[153], but a second larger RCT[175] reported no difference (3.7% vs. 3.3%) at a median of 1.7 years.
>
> ***In patients with suspected ACS***, across four RCTs[85,143,144,171,192] there were no difference between testing arms in the cumulative frequency of continued or recurrent chest pain at any time frame, however one RCT reported that CCTA was associated with a higher frequency compared with stress echocardiography (28% vs. 19%) at one month.[138] There was no difference between CCTA and SPECT in the cumulative frequency of recurrent ischemia in one trial of stable outpatients.[126] One RCT in patients with suspected ACS reported that recurrent ischemia occurred in 10% of those who had functional testing but no data for the CCTA arm were provided.[143,144]

Composite outcomes (MACE)

Across populations composite outcomes (MACE) were the primary endpoint(s) in many trials. Components of the composites varied across trials and within trials, different combinations of components were used. The PROMISE trial[59] reported on four different composite outcomes in stable outpatients. Appendix O, Table O31 summarizes the findings for the composites. In general, across trials, there were no statistically significant differences between CCTA and functional testing for various composite outcomes in stable outpatients or in patients with suspected ACS. There were two exceptions. The PROMISE trial[59] reported a marginally insignificant association between CCTA and

slightly lower occurrence of their primary MACE (which included all-cause mortality, nonfatal MI, hospitalization for UA, or major procedural complication) plus catheterization showing no obstructive CAD at 12 months, based on adjusted hazard ratios, but the risk differences were small (RD –0.4 per 100 patients). Their composite of mortality or nonfatal MI was similarly marginally insignificant with a small RD. The SCOT-HEART trial[175,215] compared CCTA with ETT (although 85% of CCTA patients also receive ETT). CCTA was associated with reduction of both composite outcomes evaluated.

Health status (Seattle Angina Questionnaire)

Four RCTs[59,153,163,256], ***all in stable outpatients*** administered the Seattle Angina Questionnaire (SAQ). The SAQ scores range from 0 to 100 and assess the following domains: Physical Limitation (9 items), Angina Stability (1 item), Angina Frequency (2 items), Treatment Satisfaction (4 items), and Quality of Life(QOL) (3 items). For the QOL domain (scale 0–100) higher scores indicate increased QOL, fewer symptoms and better health status. None of the RCTs in patients with suspected ACS reported on this outcome. There were no differences between CCTA and functional tests for the physical limitation or treatment satisfaction domains in any RCT. Results across trials for the other domains were inconsistent with only one or two of the four RCTs finding an association with the testing strategy. Results for the remaining domains are summarized as follows:

- Anginal stability: In three RCTs, there was no difference between testing groups on this domain at any time frame[59,163,215]; one RCT reported that CCTA was associated with less angina at 3 and 12 months.[153]
- Anginal frequency: Three trials reported no difference between testing groups for this domain at any time frame.[59,163,215] One RCT reported that CCTA was associated with less frequent angina at 6 months, but there was no difference at six weeks from index testing compared with ETT.[256]
- QOL: Two RCTs, including the largest (PROMISE) reported no difference in the QOL domain at any time frame.[59,163] One RCT reported that CCTA was associated with improved QOL at 6 months but not at 6 weeks[256]; another reported an association between CCTA and improved QOL at both 3 and 12 months.[153]

6.1.2 Key Question 2: Clinical decision making

6.1.2.1 Summary of results

The majority of RCTs comparing CCTA with functional testing which reported one or more of the following outcomes in either stable patients with suspected CAD or patients presenting emergently with suspected ACS: Referral for ICA (19 RCTs, N=22,335), any additional noninvasive testing (17 RCTs, N=11,595), referral for any revascularization (19 RCTs, N=23,124) and referral for PCI specifically (12 RCTs, N=18,960). There was no statistical interaction between the patient populations for any outcome.

Summary of results across populations

Across studies that include stable patients with suspected CAD and patients with suspected ACS presenting to an emergency department or similar setting:

- **ICA referral:** CCTA was associated with more frequent ICA referral compared with functional testing (19 RCTs, 14.4 vs. 12 per 100 patients, pooled RR 1.25, 95% CI 1.09 to 1.47, I^2=67%, RD 2.7, 95% CI 1 to 4 per 100, I^2=59%) (SOE Moderate).
    - **In stable outpatients**, ICA referral was more frequent following CCTA), but the association bordered the null and there was substantial heterogeneity. However, exclusion of SCOT-HEART increased the effect size and strengthen the association between CCTA and ICA referral compared with functional testing and substantially reduced the heterogeneity (4 RCTS pooled RR 1.57, 95% CI 1.21 to 1.65, I^2=0%, RD 4.1, 95% CI 3.0 to 5.2 per 100 patients).
    - **In patients with suspected ACS**, ICA referral (cumulative) was also more frequent following CCTA compared with functional testing but was less than the frequency seen in stable outpatients. Referral for ICA was highest at the index evaluation.
- **Referral for any additional noninvasive testing** was not different between CCTA and functional testing groups across populations (17 RCTs, 7.2 versus 7.6 per 100, pooled RR 0.82, 95% CI 0.53 to 1.28, I^2=83%) (SOE Low) or when populations were considered individually. Type of additional testing was inconsistently reported but appears to be primarily stress imaging.
- **Revascularization:** CCTA was associated with more frequent revascularization (9.5 per 100 patients) compared with functional testing (7.1 per 100 patients), 19 RCTs, pooled RR 1.52, 95% CI 1.26 to 1.90 I^2=66%, RD 2.4, 95% CI 1.4 to 3.3 per 100) (SOE Moderate). Again, this was also true when the populations were considered individually.
- **PCI for revascularization:** CCTA was associate with higher frequency of PCI as a revascularization procedure compared with functional testing (12 RCTs, 8.2 vs. 6.0 per 100 patients, pooled RR 1.63, 95% CI 1.22 to 2.35, I^2=74%, RD 2.4, 95% CI 1.3 to 3.6 per 100 patients) across populations (SOE Moderate).
    - In stable outpatients with suspected CAD, PCI was more common with CCTA, but the association failed to reach statistical significance (pooler RR 1.16, 95% CI 0.96 to 2.99).
    - In patients with suspected ACS the association between CCTA and PCI was seen at index testing but there was no difference between CCTA and functional testing at 1 to 6.5 months or ≥ 12 months.
- **Hospitalization**:
    - **In stable outpatients t**here was no difference in hospitalization between CCTA and functional testing across 4 RCTs (SOE Moderate).
    - **In patients with suspected ACS**,
        - At index testing, across comparators with CCTA there is substantial heterogeneity and results are mixed. While 4 RCTs comparing CCTA with any functional test suggest that hospitalization is less common with CCTA, large studies of CCTA vs echo and SPECT suggest that hospitalization may be more with CCTA (SOE Insufficient).
        - There was no difference in hospitalization between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months after index testing (9 RCTs, 3.0 vs. 3.9 per 100 patients, pooled RR 0.76, 95% CI 0.49 to 1.1, I^2=18%) (SOE High). Similarly, there was no difference between testing arms at ≥12

months (6 RCTs 14.9 vs. 17.4 per 100 patients, pooled RR 0.90, 95% CI 0.77 to 1.03, I^2=0%) (SOE High).

- **Subsequent ED visits:** In patients with suspected ACS there was no difference in emergency department visits after index testing between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months (7 RCTs, pooled RR 0.84, 95% CI 0.66 to 1.06, I^2=0%) or at ≥12 months (5 RCTs, pooled RR 1.06, 95% CI 0.93 to 1.56, I^2=16%) (SOE High for both time frames).

Medication: CCTA was not consistently associated with initiation of, discontinuation of or changes in medications and results for many mediations were mixed. Evidence is insufficient to draw firm conclusions about the impact of testing on medication use (SOE insufficient).

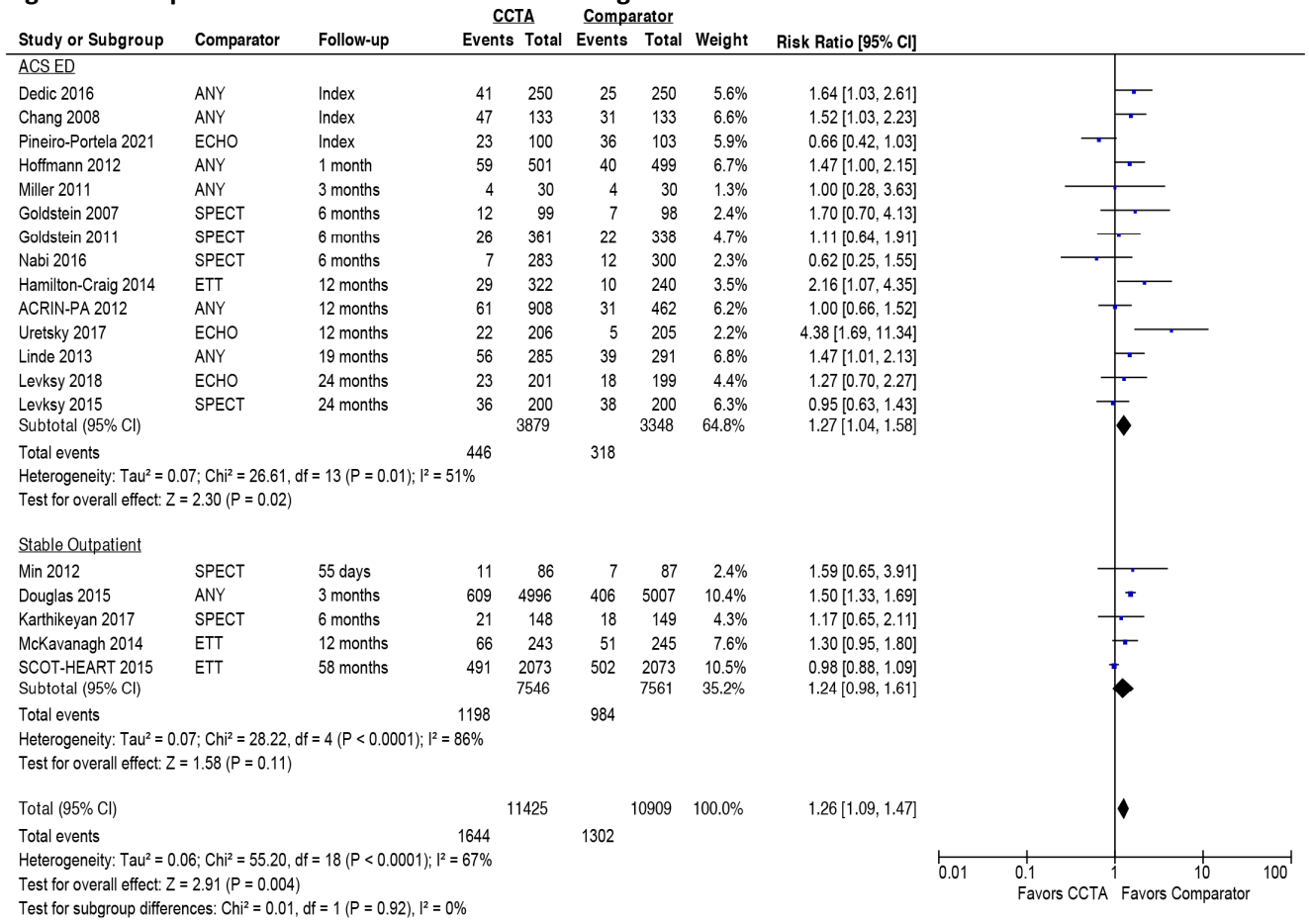
Detailed results

6.1.2.2 Additional testing (ICA, other noninvasive testing)

Referral for ICA was reported in 19 RCTs, of which 14 were in patients with suspected ACS [37,47,84,85,96,111,138,140,143,145,161,171,192,248] and five were in stable patients with suspected CAD.[59,126,153,163,215] Five RCTs were considered good quality,[47,59,84,126,215] three were considered poor [85,161,163] and the remaining 10 were considered fair.[37,96,109,111,138,140,143,145,153,171,192,248]

Across populations, CCTA was associated with higher frequency of ICA referral (14.4 per 100 patients) compared with functional testing (12 per 100 patients) across 19 RCTs (pooled RR 1.25, 95% CI 1.09 to 1.47, I^2=67%, RD 2.7, 95% CI 1 to 4 per 100, I^2=59%). (Figure 6) There was no statistical interaction between the stable and suspected ACS populations (p= 922). Exclusion of the SCOT-HEART trial[215] had no substantial impact on effect size or conclusions but did decrease heterogeneity from I^2 of 67% to 45%. Effect sizes and heterogeneity were similar following exclusion of three poor-quality trials[85,161,163] and exclusion of one outlier trial.[248] (Table 29)

Figure 6. Comparison of CCTA and functional testing: ICA referral



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; ICA = invasive coronary angiography; SPECT = single photon emission computed tomography.

In stable outpatients with suspected CAD, ICA referral was more frequent following CCTA, compared with functional testing (15.9 vs. 13.0 per 100), but the association bordered the null and there was substantial heterogeneity (5 RCTs, pooled RR 1.24, 95% CI 1.00 to 1.61, I^2=86, RD 2.0, 95% CI –0.3 to 5.8 per 100 patients).[59,126,153,163,215] Exclusion of one poor-quality trial[163] had no impact on effect size, the association or heterogeneity (4 RCTs, 1.23, 95% CI 0.94 to 1.6, I^2=89%). However, exclusion of SCOT-HEART[215] increased the effect size and strengthen the association between CCTA and ICA referral and substantially reduced the heterogeneity (4 RCTS pooled RR 1.57, 95% CI 1.21 to 1.65, I^2=0%, RD 4.1, 95% CI 3.0 to 5.2 per 100 patients).

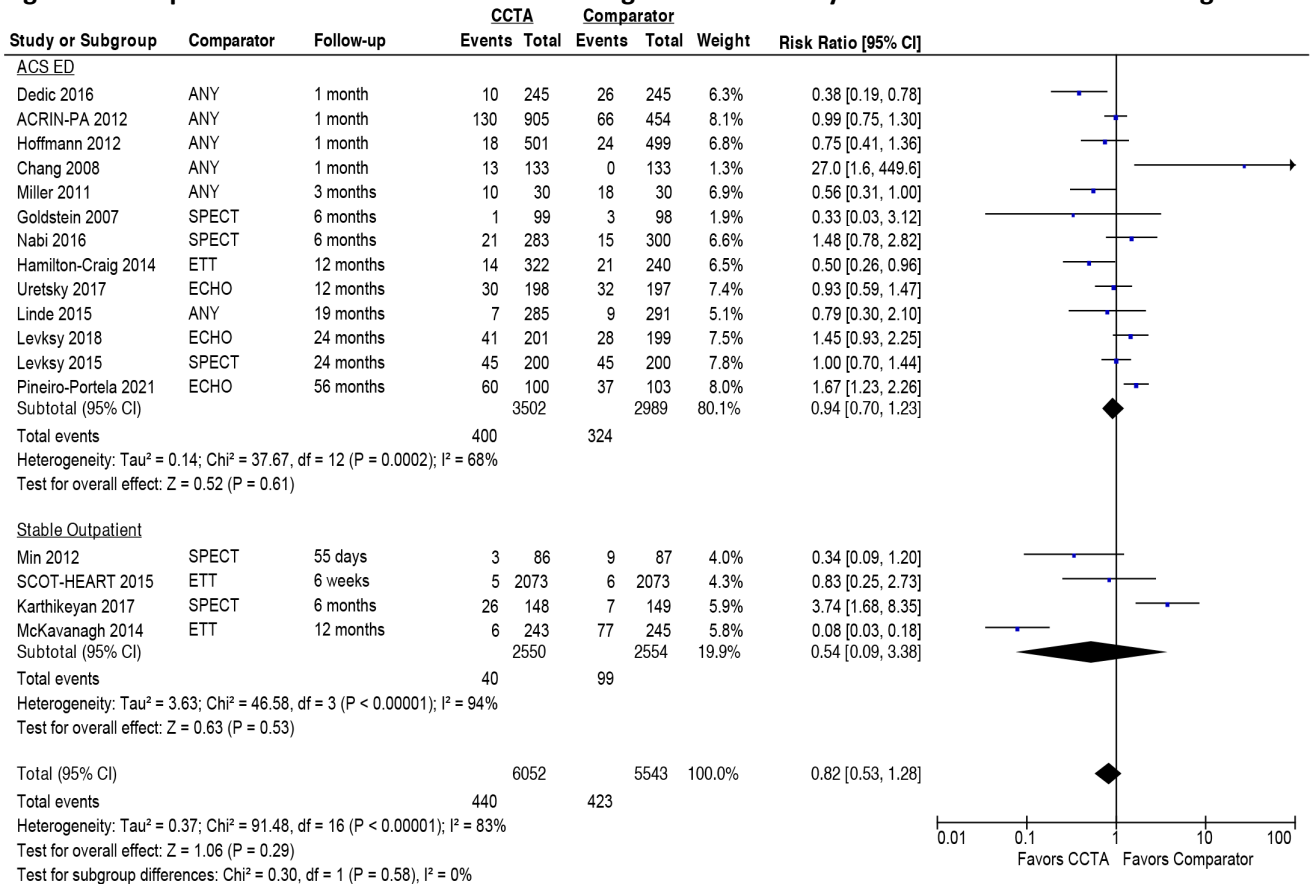
In patients with suspected ACS *presenting to an emergency room or similar setting,* ICA referral (cumulative) was also more frequent following CCTA compared with functional testing, (11.5 vs. 9.5 per 100 patients, 14 RCTS pooled RR 1.27, 95% CI 1.04 to 1.58, I^2= 51%, RD 2.8, 95%VI 0.6 to 5.0 per 100 patients),[37,47,84,85,96,109,111,138,140,143,145,161,171,192,248] but was less than the frequency seen in stable outpatients. Exclusion of two poor-quality trials[85,161] did not impact effect estimates

and slightly increased heterogeneity (12 RCTs, pooled RR 1.26, 95% CI 1.01 to 1.60, I^2= 58%). Referral for ICA was highest at the index evaluation (10.6 and 10.7 per 100 patients) and ≥12 months (6.5 vs. 5.5 per 100 patients) for CCTA and functional testing respectively with only 1.4 vs. 1.6 per 100 patients receiving ICA between 1 and 6.5 months. Pooled estimates at individual time frames however were not statistically significant; Index evaluation (8 RCTs, pooled RR 1.11, 95% CI 0.87 to 1.48),[37,47,84,85,109,144,145,192] 1 to 6.5 months (7 RCTs pooled RR 0.96, 95% CI 0.57 to 1.67),[47,84,85,109,145,161,171] ≥12 months (6 RCTS, pooled RR 1.45, 95% CI 0.87 to 2.69).[96,111,138,140,143,248] Exclusion of one outlying trial[248] for the ≥12-month time frame, slightly decreased effect size (3 RCTs, pooled RR 1.34, 95% CI 0.76 to 2.54) but did not change conclusions.

Referral for any additional noninvasive testing was reported in 17 RCTs (N=11,595), of which four were in stable patients[126,153,163,215] and 13 were in patients with suspected ACS.[37,47,84,85,96,109,111,138,140,143,145,161,192,248]

Across populations referral for additional noninvasive testing was not different between CCTA and functional testing groups (7.2 versus 7.6 per 100, pooled RR 0.82, 95% CI 0.53 to 1.28, I^2=83%), however substantial heterogeneity was noted. (Figure 7) Exclusion of two outlier RCTS resulted in a slight increase in the pooled RR (15 RCTS RR 0.94, 95% CI 0.68 to 1.25, I^2=69.3%) and reduced heterogeneity, but conclusions of no association did not change. Exclusion of three poor-quality trials[85,161,163] also resulted in the same slight increase in effect size but heterogeneity was similar. Exclusion of SCOT-HEART, in which 85% of patients received ETT, did not impact effect size, heterogeneity, or conclusions across the populations. Exclusion of two outliers[37,153] resulted in a larger effect size and reduced heterogeneity (15 RCTS, pooled RR 0.94, 95% CI 0.68 to 1.25 I^2=69%) but no difference in conclusions. (Table 29)

Figure 7. Comparison of CCTA and functional testing: Referral for any additional noninvasive testing



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

In stable outpatients with suspected CAD, there was no association between CCTA and referral for any additional noninvasive testing (4 RCTs, pooled RR 0.54, 95% CI 0.09 to 3.38, I^2=94%), but heterogeneity was substantial. Exclusion of one poor-quality RCT[163] slightly increased the effect size and exclusion SCOT-HEART decreased the effect size estimate, but neither of these exclusions impacted heterogeneity or conclusions. Exclusion of an outlier trial[153] resulted in a higher effect estimate and decreased heterogeneity, however the conclusion of no association remained.

Referral for additional stress imaging specifically in general and stress imaging that involved additional radiation was rarely described across trials. The evidence is sparse and conflicting and may be related to the comparator for CCTA. CTTA was associated with referral for additional stress imaging within 6 months of initial evaluation in one small good-quality RCT (RR 3.60, 95% CI 1.6 to 8.1)[126] compared with SPECT (16.9 vs. 4.7 per 100 patients, RD 11, 95% CI 4 to 18 per 100). Stress imaging involving radiation was done 23 of the 25 patients in the CCTA group (15.5 per 100 patients in the group) and in all seven patients in the SPECT group. At ≥12 months one

trial reported that CCTA was associated with less frequent referral for stress imaging compared with ETT (RR 0.08, 95% CI 0.03 to 0.18, RD –29, 95% CI –35 to –22).[153] All six patients in the CCTA group received additional stress imaging involving radiation as did 76 of the 77 patients in the ETT group (31 per 100 patients in the ETT group). Another larger trial which compared CCTA to ETT reported no association between CCTA and use of additional noninvasive testing (RR, 0.83, 95% CI 0.25 to 2.73).[215] This may in part be due to use of ETT across 85% of the enrolled patients in this trial. Authors do not report whether additional stress imaging involved radiation. (APPENDIX P)

In patients with suspected ACS *presenting to an emergent setting,* again, no association between CCTA and additional noninvasive testing was observed (13 RCTS, pooled RR 0.94, 95% CI 0.69 to 1.23, I^2=68%). Exclusion of an outlier trial[37] or two poor-quality trials[85,161] did not change effect size, heterogeneity, or conclusions. Similarly, no differences in referral for any additional noninvasive testing between testing groups was seen at < 6 months after index testing (7 RCTs, pooled RR 0.82, 95% CI 0.51 to 1.41)[37,47,85,109,145,161,171] or ≥12 months (7 RCTs, pooled RR 1.05, 95% CI 0.74 to 1.39.[96,111,138,140,143,192,248] Removal of one outlying trial[37] at the < 6 month time frame slightly increased effect size, but did not change conclusions.

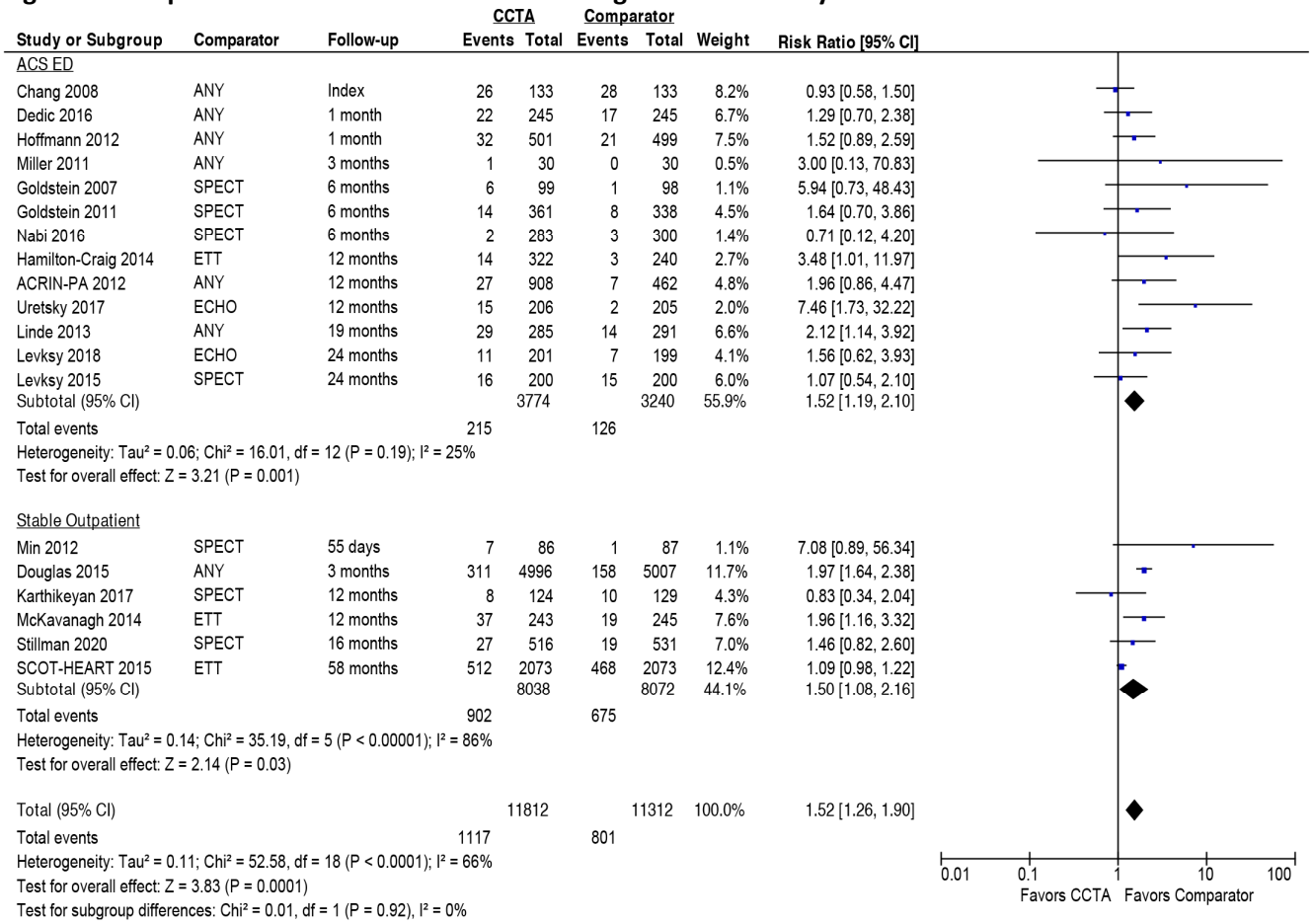
Referral for additional stress imaging specifically in general and stress imaging that involved additional radiation was inconsistently described across trials. Across time frames after index testing (< 6 months and ≥ 12 months after index test), there was no difference between CTTA and functional tests in referral for stress imaging (11 RCTs, pooled RR 0.97, 95% CI 0.73 to 1.19, I^2=38%). Similarly, there was no difference between CCTA and functional tests regarding referral for additional noninvasive stress testing involving radiation (10 RCTs, pooled RR 0.68, 95% CI 0.37 to 1.04, I^2=54%), however, these findings should be interpreted cautiously as authors were vague about which specific tests were performed. (APPENDIX P)

6.1.2.3 Treatment

Referral for any revascularization was reported in 19 RCTS (N= 23,124), six were in stable outpatients with suspected CAD[59,126,153,163,215,238] and 13 were in patients with suspected ACS.[37,47,84,85,96,109,111,138,140,143,145,161,192,248] There was no statistical interaction between the patient populations for any outcome.

Across patient populations, CCTA was associated with more frequent revascularization (9.5 per 100) compared with functional testing (7.1 per 100), pooled RR 1.52, 95% CI 1.26 to 1.90 I^2=66%, RD 2.4, 95% CI 1.4 to 3.3 per 100). (Figure 8) Exclusion of the SCOT-HEART resulted in a slight increase the effect estimate but heterogeneity decreased substantially (1.63, 95% CI 1.33 to 1.98, I^2=31%) and exclusion of three poor-quality RCTs[85,161,163] resulted in a slight diminution of the effect size but did not impact heterogeneity (RR 1.48, 95% CI 1.22 to 1.83, I^2=68%). (Table 29)

Figure 8. Comparison of CCTA and functional testing: Referral for any revascularization



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

In stable outpatients with suspected CAD the association between CCTA and more frequent revascularization versus functional testing (11.2 vs. 8.4 per 100) was seen across RCTs (6 RCTs, N=16,115, pooled RR 1.5, 95% CI 1.08 to 2.16, I^2=86%, RD 2.8, 95% CI 1.4 to 4.2) but there was substantial heterogeneity. Exclusion of one poor-quality trial,[163] which also an outlier, had little impact on the effect size or heterogeneity (5 RCTs, pooled RR 1.46, 95% CI 1.02 to 2.04, I^2=88%). Exclusion on of the SCOT-HEART[215] resulted in a larger effect size and substantially reduced heterogeneity but did not alter overall conclusions (5 RCTs, pooled RR 1.8, 95 %CI 1.37 to 2.24, I^2=31%, RD 2.2, 95% CI 0.9 to 3.4 per 100 patients).

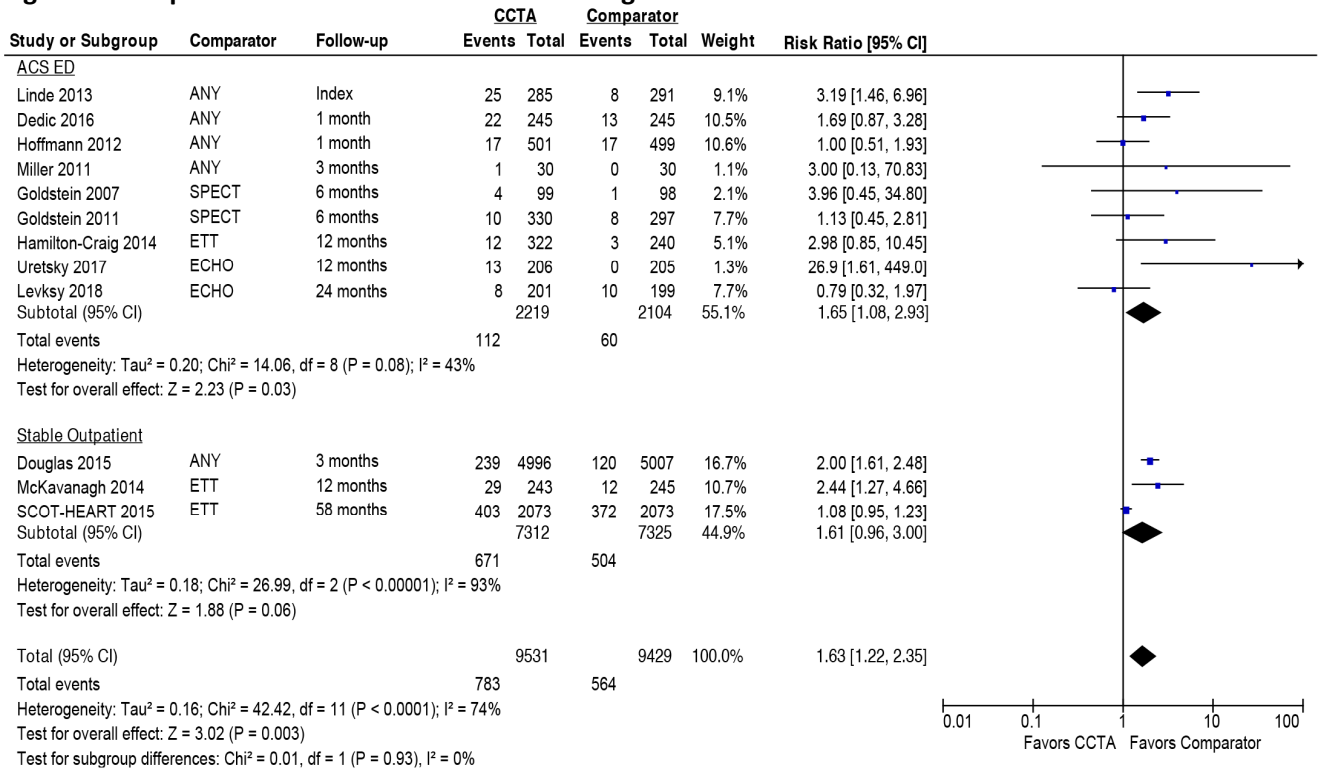
Similarly, *in* ***patients with suspected ACS***, CCTA was associated with more frequent revascularization compared with functional testing (13 RCTS, 5.7 vs 3.9 per 100, pooled RR 1.52, 95% CI 1.19 to 2.10, I^2=25%, RD 2.4, 95% CI 0.7 to 4.2 per 100 patients). Exclusion of two poor-quality trials[85,161] slightly decrease effect size (11 RCTs, pooled RR 1.48, 95% CI 1.16 to 2.02, I^2=29%).

Type of revascularization

PCI was more commonly performed (8 per 100 patients) than CABG as a revascularization procedure in both stable outpatients with suspected CAD and in those with suspected ACS presenting to an emergent setting. Surprisingly it was more common in stable outpatients versus those presenting with suspected ACS (8.0 vs 4.0 per 100 patients)

Across patient populations, CCTA was associated with higher frequency **of PCI** as a revascularization procedure compared with functional testing across (12 RCTs, 8.2 vs. 6.0 per 100, pooled RR 1.63, 95% CI 1.22 to 2.35, I^2=74%, RD 2.4, 95% CI 1.3 to 3.6 per 100),[47,59,84,85,96,109,138,143,153,161,215,248] (Figure 9). Exclusion of two poor-quality RCTs[85,161] or exclusion of one outlier trial,[248] had little impact on effect estimates or heterogeneity. Exclusion of SCOT-HEART,[215] however, increased effect size and reduced heterogeneity by 49% (11 RCTs, pooled RR 1.89, 95% CI 1.3 to 4.0, I^2=36%). The impact of CCTA combined with ETT in this trial on the need for revascularization is unclear (Table 29).

Figure 9. Comparison of CCTA and functional testing: Referral for PCI



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; PCI = percutaneous coronary intervention; SPECT = single photon emission computed tomography.

In stable outpatients with suspected CAD, the overall frequency of **PCI** was 8 per 100 patients. PCI was more commonly performed following CCTA (8.4 per 100 patients) compared with functional testing (6.9 per 100 patients) and the association approached statistical significance, but substantial heterogeneity was noted (3 RCTS, pooled RR 1.61, 95% CI 0.96 to 3.00, I^2=93%; Figure 9).[59,153,215] Exclusion of the SCOT-HEART[215] substantially increased the effect size and reduced heterogeneity to 0% and resulted in a stronger association between CCTA and PCI, (2 RCTS, pooled RR 2.04, 95% CI 1.57 to 2.87, I^2=0%). The impact of CCTA combined with ETT in this trial on the need for revascularization is unclear.

In contrast, **CABG** was performed in 1.7 per 100 patients across testing arms and was more common following CCTA versus functional testing (2.0 vs. 1.5 per 100) but there was no association with CCTA compared with functional testing based on the pooled estimate (3 RCTs, pooled RR 1.39, 95% CI 0.85 to 2.23, I^2=53%). The largest trial[59] did however show an association (RR 1.90, 95% CI 1.28 to 2.81) comparing CCTA with any functional testing but the other two trials comparing CCTA with ETT did not[153,215]; in the largest of these trials,[215] however 85% of patients in the CCTA arm received ETT. The pretest risk across these trials appears to primarily be low to intermediate, which may partially explain less frequent use of CABG. See Appendix P for figure.

In patients with suspected ACS presenting to an emergency setting, **PCI** frequency overall was 4 per 100 patients, with greater cumulative frequency following CCTA compared with functional testing (9 RCTs, 5.0 vs. 2.8 per 100, pooled RR 1.65, 95% CI 1.08 to 2.93, I^2=43%; Figure 9).[47,84,85,96,109,138,144,161,248] With regard to timing, at index testing, CCTA was associated with more frequent PCI use compared with functional testing (4 RCTs, 5.0 vs. 2.6 per 100 patients, pooled RR 1.89, 95% CI 1.02 to 3.48, I^2= 19%).[84,85,109,144] There was, however, no differences between testing arms at 1 to 6.5 months (5 RCTs, pooled RR 1.65, 95% CI 0.83 to 3.31, I^2= 0%)[47,84,85,109,161] or ≥12 months after index testing (4 RCTs, pooled RR, 1.43, 95% CI 0.54 to 7.83, I^2= 71%).[96,138,140,248] Exclusion of one outlying trial[248] for this later time frame reduced the effect estimate and heterogeneity but did not impact conclusions (3 RCTS, pooled RR 1.04, 95% CI 0.45 to 3.12, I^2=51%).[96,138,140]

CABG was less commonly performed than PCI in patients with suspected ACS. There was no association between CCTA and CABG related to timing of the index test (4 RCTs, pooled RR I^2=). At >1 month following index testing, four of the nine RCTs reported that no patients received CABG and pooled estimates across the remaining trials, showed no difference between testing arms (5 RCTs, pooled RR 1.27, 95% CI 0.26 to 6.20, I^2=51%).[47,96,138,140,248] Less frequent use of CABG may in part be due to the low to intermediate pre-test risk of CAD in patients across these trials. See Appendix P for figure.

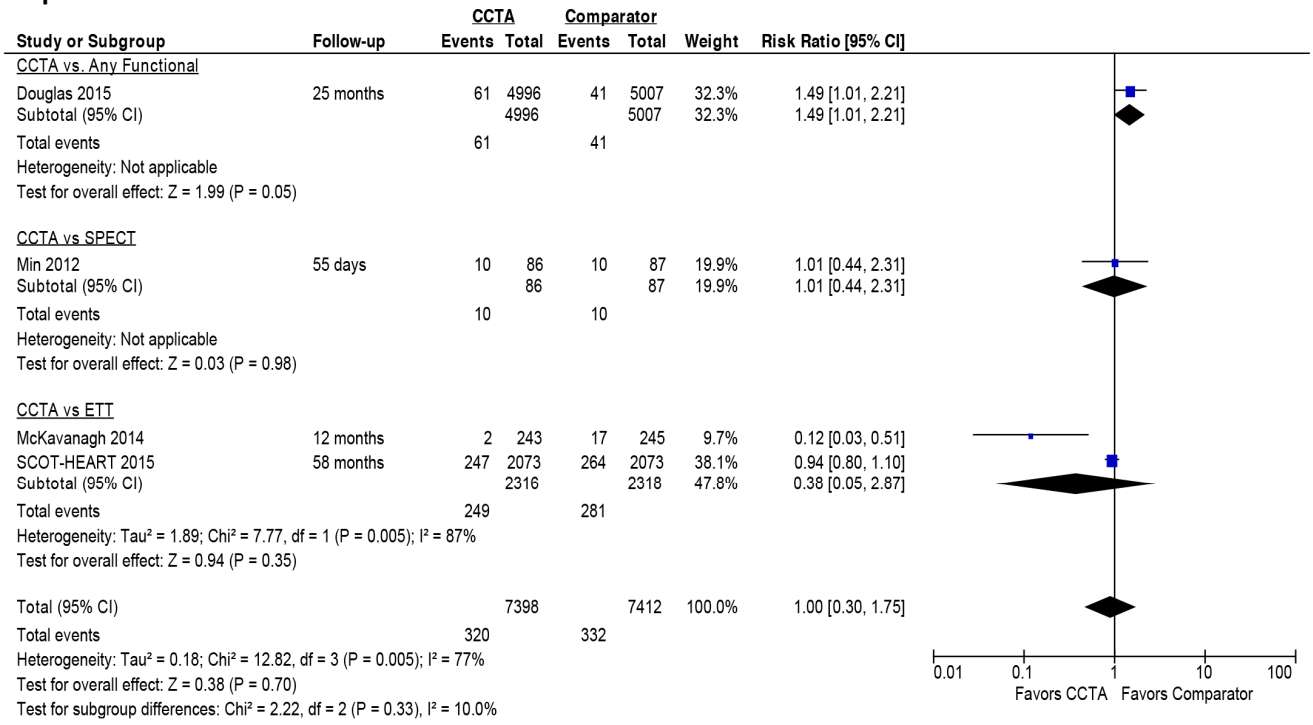
6.1.2.4 Hospitalization

Four RCTs in stable outpatients with suspected CAD[59,153,163,215] and 14 RCTs in patients with suspected ACS[37,47,84,85,96,109,111,138,140,143,145,161,171,192,248] reported on hospitalization. In theory the need for and timing of hospitalization may be different in these populations, thus, we did not pool data for this outcome across them.

Across populations, in general across time frames, there were no differences in hospitalization between CCTA and functional testing. However, there was heterogeneity within populations, so each will be addressed separately.

In stable outpatients with suspected CAD, across four RCTs, there was no difference in hospitalization between CCTA and functional testing (4.3 vs. 4.5 per 100 patients, pooled RR 1.00, 95% CI 0.29 to 1.75, I^2=77%). Heterogeneity is likely related to one RCT[153] which reported that CCTA was associated with lower risk of hospitalization compared with ETT (RR 0.12, 95% CI 0.03 to 0.51) (Figure 10).

Figure 10. Comparison of CCTA and functional testing: Hospitalization in stable outpatients with suspected CAD

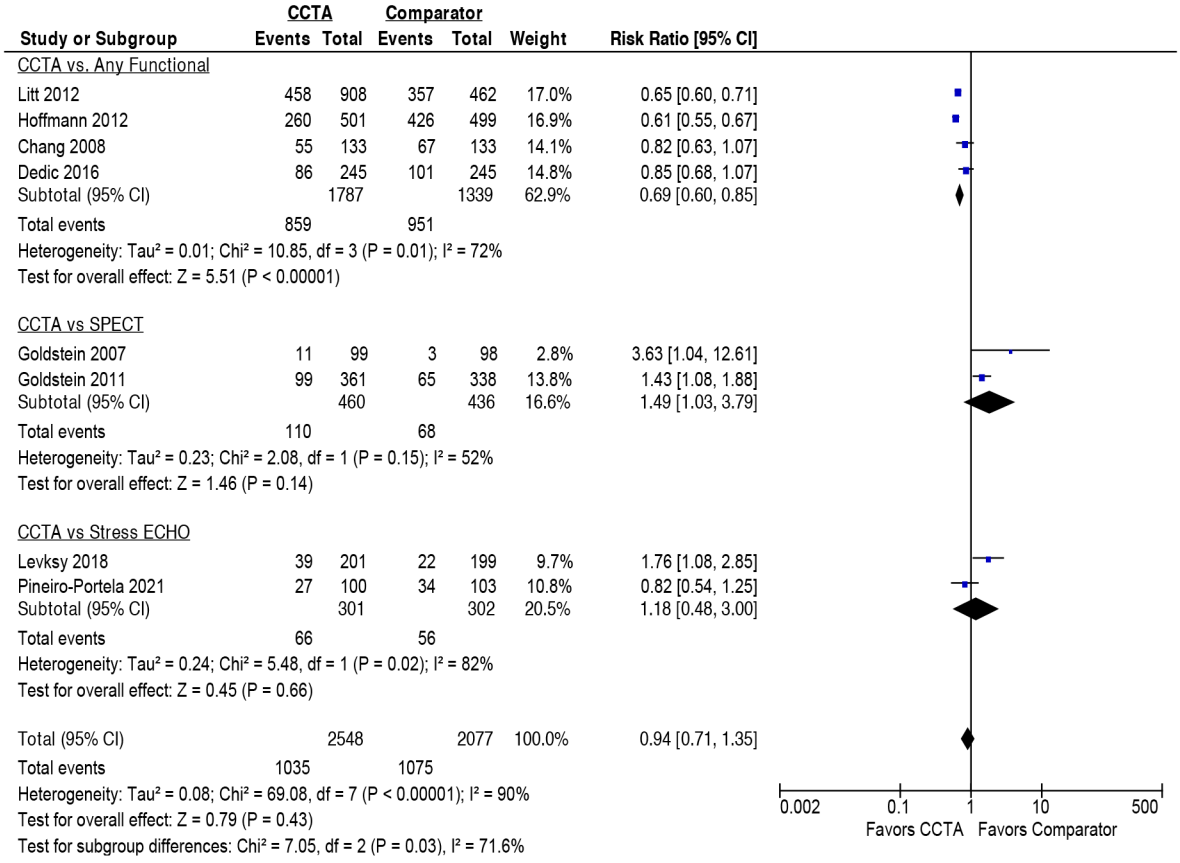


CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

In patients with suspected ACS *presenting to an emergency setting*, at the time of index testing, CCTA was not associated with hospitalization across all functional testing comparators, but substantial heterogeneity was noted (8 RCTs, pooled RR 0.94, 95% CI 0.70 to 1.35, I^2=90%) and the test for interaction suggests that there may be differences based on comparators. (Figure 11) Across four fair-quality RCTs comparing CCTA with any (unspecified) functional testing, CCTA was associated with lower risk of hospitalization (4 RCTS 48 vs. 71 per 100 patients, pooled RR 0.69, 95% CI 0.60 to 0.85, I^2= 93.2, RD –19.6 per 100, 95% CI –31.7 to –7.5 per 100) with the two largest RCTs reaching statistical significance.

In contrast, two RCTs[84,85] individually found an association between CCTA and increased risk of hospitalization compared with use of SPECT, although the pooled estimate was not statistically significant (pooled RR 1.49, 95% CI 1.03 to 3.79). In the larger good-quality RCT (N= 699) in low pre-test risk patients,[84] 27 per 100 patients in the CCTA group were hospitalized versus 19 per 100 patients who received SPECT (RR 1.43, 95% CI 1.08 to 1.88). Across two fair-quality RCTs comparing CCTA with stress echo, hospitalization was overall more common in patients who received CCTA (21.9 vs. 18.5 per 100 persons).[138,192] However, again the pooled estimate showed no association (pooled RR 1.18, 95% CI 0.48 to 3.00). The largest RCT (N=400) found an association between increased in hospitalization and CCTA (RR 1.76, 95% CI 1.08 to 2.85) compared with stress echo.[138] In some trials, patients were only randomized to index testing after ruling out ACS, after normal ECG and normal serum biomarkers, were obtained and/or the tests were performed after the time of the index visits. In addition, not all patients received functional testing.

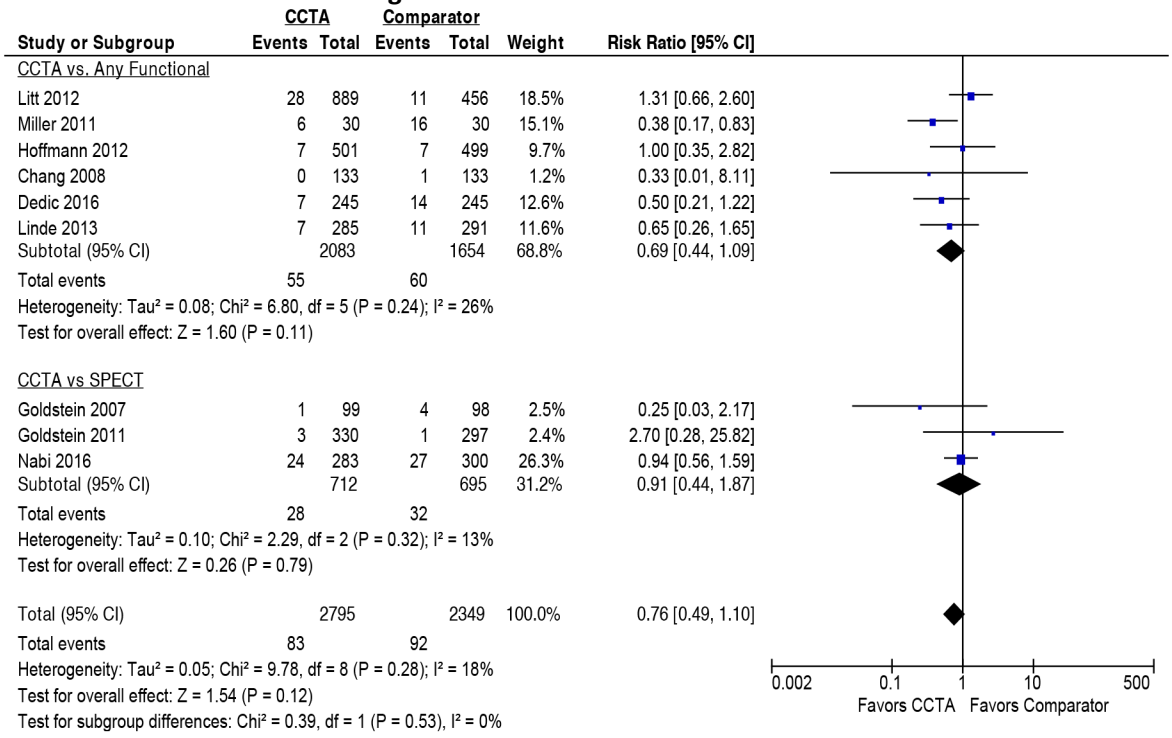
Figure 11. Comparison of CCTA and functional testing: Hospitalization in patients with suspected ACS at time of index ED visit



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = echocardiography; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

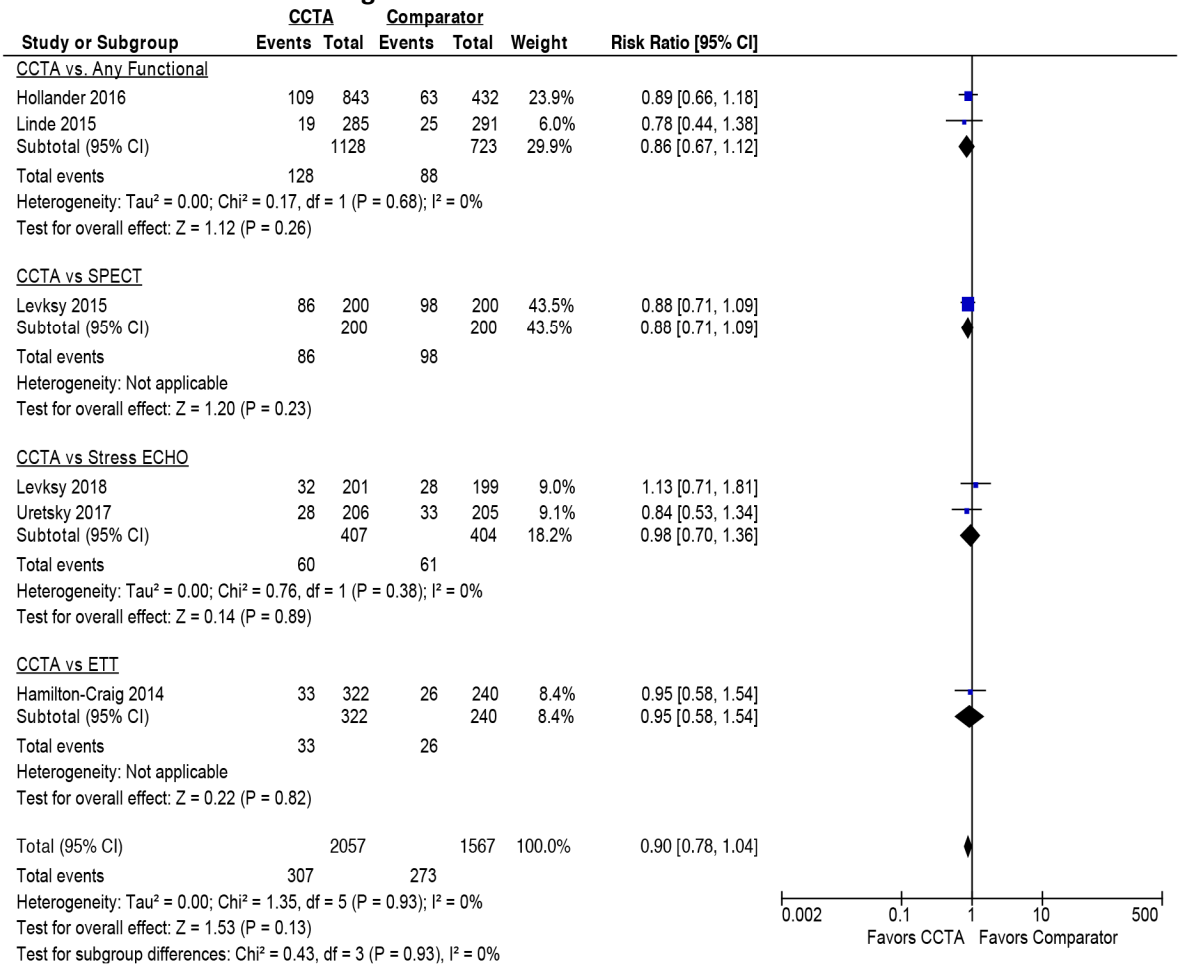
In patients with suspected ACS, there was no difference in hospitalization between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months after index testing (9 RCTs, 3.0 vs. 3.9 per 100 patients, pooled RR 0.76, 95% CI 0.49 to 1.1, I^2=18%).[37,47,84,85,109,143,145,161,171] Similarly, there was no difference between testing arms at ≥12 months (6 RCTs 14.9 vs. 17.4 per 100 patients, pooled RR 0.90, 95% CI 0.77 to 1.03, I^2=0%),[96,111,138,140,143,248] (Figure 12 and Figure 13).

Figure 12. Comparison of CCTA and functional testing: Hospitalization in patients with suspected ACS 1 to 6.5 months after index testing



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

Figure 13. Comparison of CCTA and functional testing: Hospitalization in patients with suspected ACS ≥12 months after index testing

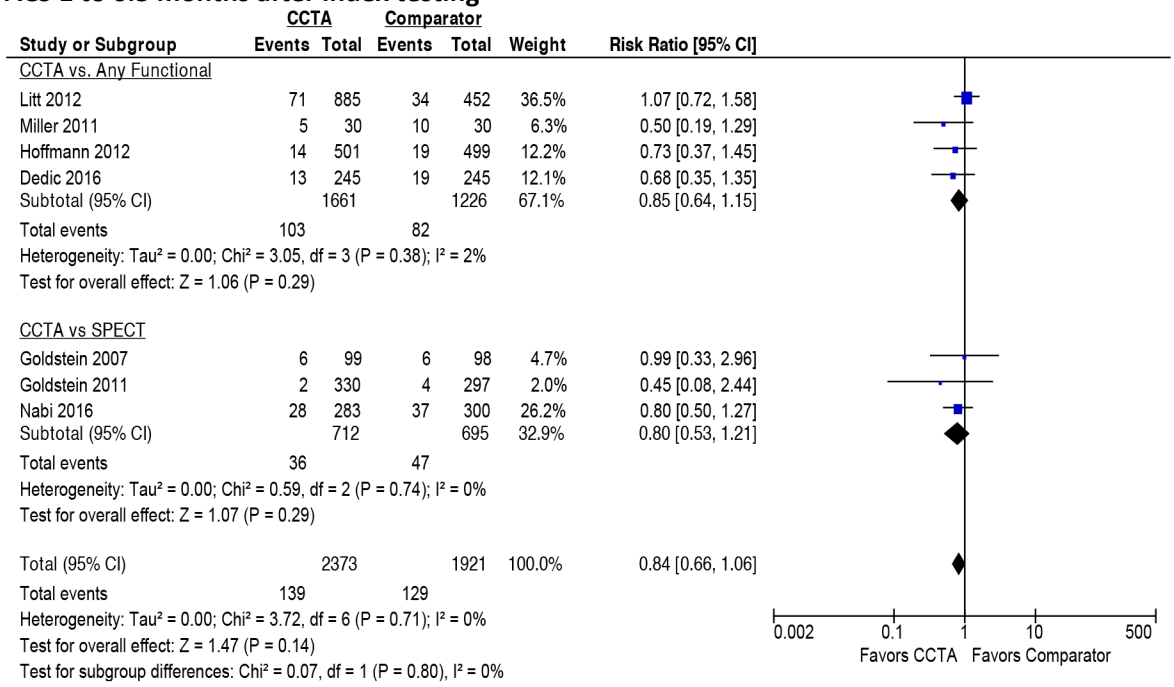


ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = echocardiography; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

6.1.2.5 Subsequent emergency department visits in patients with suspected ACS

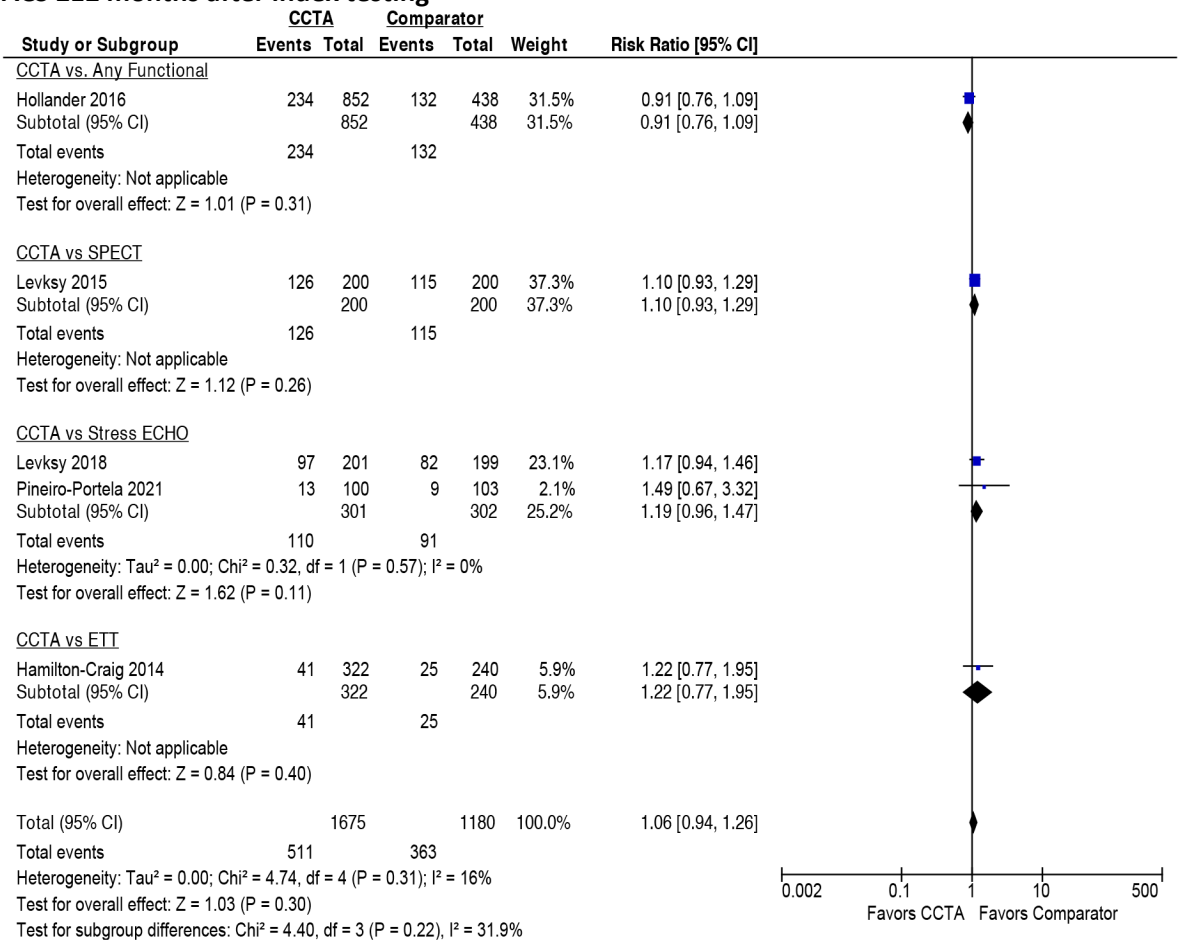
In patients with suspected ACS, there was no difference in emergency department visits after index testing between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months after index testing (7 RCTs, 5.9 vs.6.7 per 100 patients, pooled RR 0.84, 95% CI 0.66 to 1.06, I^2=0%).[47,84,85,109,145,161,171] Exclusion of two poor RCTs[85,161] had little impact on the effect estimates (5 RCT, pooled RR 0.86, 95% CI 0.62 to 1.11). Similarly, at there was no difference between testing arms ≥12 months (5 RCTs, 30.5 per 30.8 per 100 patients, pooled RR 1.06, 95% CI 0.93 to 1.56, I^2=16%),[96,111,138,140,192] (Figure 14 and Figure 15).

Figure 14. Comparison of CCTA and functional testing: Subsequent ED visits in patients with suspected ACS 1 to 6.5 months after index testing



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

Figure 15. Comparison of CCTA and functional testing: Subsequent ED visits in patients with suspected ACS ≥12 months after index testing



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

6.1.2.6 Medication changes (Appendix O, Table O27 and O28)

Across populations and within populations, CCTA was not consistently associated with initiation of, discontinuation of or changes to medications. Results across trials for mediations were mixed. Evidence is insufficient to draw firm conclusions about the impact of testing on medication decisions.

In stable outpatients, initiation, discontinuation or change in medication use are briefly outlined below

- **Aspirin, statin, and beta-blocker use**: One large, good-quality RCT[135] reported that CCTA was associated with changes in use of these medications compared with functional testing with a higher proportion of CCTA recipients initiating them by 60 days. There

didn't appear to be differences in discontinuation. Another small, poor-quality RCT found no differences.[163]

- **ACE inhibitors, ARBs, non-statins**: There were no differences between CCTA and functional tests for the following medications: ACE inhibitors, (Angiotensin converting enzyme inhibitor) or ARBs (Angiotensin receptor blockers) in two RCTs,[135,163] calcium channel blockers or non-statin lipid-lowering mediations.[163]
- **Other medical management**: Two RCTs reported that CCTA was associated with more patients initiating medical management (unspecified) compared with ETT.[115,153,215] The largest of the two RCTs reported that CCTA was associated with both initiation and discontinuation of medications (unspecified) and antianginal medications at 6 weeks and through a median of 4.8 years follow-up.[115,215] (Confidence intervals for discontinuation were large indicating substantial variation.)
- **Lifestyle changes:** The same large good-quality RCT reported no differences between testing groups related to smoking cessation, exercise or changes in overweight/obese status based on changes in BMI.[135]

In patients with suspected ACS, results for initiation, continuation or change in medications are briefly outlined below.

- **Aspirin:** across five RCTs were mixed. Three RCTS found no differences use between CCTA and functional tests[111,138,140,145] while two reported that CCTA was associated with initiation of aspirin (after index visit)[144] or change in use (at median of 48 hours after index).[248]
- **Statins or lipid prescription**: Three trials reported no differences between CCTA and functional tests.[140,143,248] CCTA was associated with higher continued use of statins at 12 months compared with functional testing in the fourth trial[111,145] and with new or increased dose of a lipid prescription in a fifth trial.[138]
- **Antiplatelet drugs**: Only one trial found that CCTA was associated with initiation of antiplatelet therapy following the index visit[143,144] compared with functional testing however a second larger trial found no difference between testing groups for initiation or continuation of such medications at any time frame (up to 12 months following index).[111,145] Two other RCTs comparing CCTA with stress echo also found no differences between testing groups for initiation of or change in these medications.[138,248]
- **Beta-blockers:** Two RCTs reported no difference in initiation or change in use of beta blockers between testing arms.[143,144,248] In contrast, one trial reported that CCTA was associated with initiation of beta blockers compared with stress echo at a median of 2 years follow-up.[138,139]
- **Nitrate**s: Initiation of nitrates was more common following index testing with CCTA versus functional testing in one RCT,[143,144] but there was no difference between testing arms in another trial evaluating change in use.[248]
- **Anti-hypertensive drugs:** CTTA was associated with fewer changes in use in one RCT within 49 hours of index testing compared with stress echo (10% vs. 18%).[248]
- **Diuretics:** These were initiated more frequently following CCTA and the time of index test compared with functional tests in one trial.[143,144]
- **Diabetes medications**: There were no differences between CCTA and stress echo in the percent changes in either insulin or oral hypoglycemics in one trial.[248]

6.1.3 Key Question 3: Safety

6.1.3.1 Test-related Adverse Events

Fourteen trials (across 18 publications; N=21,446)[36,37,47,52,59,83,85,109,111,126,138,140,145,149,153,215,238,257] assessing CCTA provided information on adverse events related to index testing (Table 29). Trials have been previously described and detailed information about each trial can be found in Appendix Q. Briefly, patients had suspected CAD in 7 trials[36,52,59,126,149,153,215,238,257] (N=17,311) and suspected ACS in 7 trials[37,47,83,85,109,111,138,140,145] (N=4,135). Comparator tests included any functional testing in 5 trials [37,47,59,109,111,145,149], SPECT in 4 trials[83,85,126,140,238], exercise ECG in 2 trials[52,215,257], ICA in 2 trials[36,52], and stress echocardiography in 1 trial [138]. In addition, data from one case series was included.[23]

See Appendix F, Table F3 for detailed abstraction of safety-related outcomes by trial.

6.1.3.1.1 Summary of results for test-related adverse events

- Major or serious test-related adverse events/harms are rare for all modalities. Complications reported across studies were minor. For stress testing most reported symptoms are expected responses to the pharmacologic agents used.
- No major complications were observed across three RCTS at time of index test or within 24 hours (SOE Low). The largest RCT in stable outpatients also reported no test-related hospitalization in the CCTA arm and 0.1% (5/4837) in the functional testing arm (SOE Low).
- Minor complications at time of index test or within 24 hours was <4% across treatment arms across five RCTs in stable outpatients and five RCTs in patients with suspected ACS. Two other trials in patients with suspected ACS reported on a broader range of minor complications, one finding that 24% of patients in each testing arm experienced them and the other that 14% of CCTA patients and 6.4% experienced minor complications (1 RCT, RR 2.16, 95% CI 1.12 to 4.14) (SOE Low).
    - Contrast-related events related to CCTA occurred in ≤3% of patients at time of index testing as reported in six RCTs and one case series. Transient creatinine elevation not requiring dialysis were reported in two trials as 0.2% and 1% (SOE Low) and a third RCT reported that no contrast-induced nephropathy occurred (SOE Insufficient). Mild contrast reaction occurred in 0.5% to 2.1% of patients across six RCTs (SOE Low).
    - CCTA was associated with lower risk of chest pain, shortness of breath, or palpitations at the time of index testing compared with stress SPECT (1 RCT, 0.5% vs. 16% RR 0.03, 95% CI 0.004 to 0.24, p<0.001) and stress echo (1 RCT, 0% vs. 3%, p=0.03) in patients with suspected ACS (SOE Low). The symptoms are likely consistent with inducing cardiac stress with pharmacologic agents. One large RCT in stable outpatients reported much lower risk of symptoms related to nuclear stress testing (0.1%) and events related to dipyridamole or adenosine (0.2%) (SOE Low).
    - Arrythmias occurred in ≤ 0.2% in all testing arm across testing arms (SOE Insufficient).

Detailed Results

6.1.3.1.2 Any major or minor test-related complications **(**Table 30**)**

No major test-related complications were observed in one RCT[59,149] in stable outpatients (N=9470) with suspected CAD or in two RCTs (N= 800) in patients with suspected ACS[83,138,140] that compared CCTA with functional testing at time of index testing or within 24 hours of index testing. The RCT[59,149] in stable outpatients defined major complications as death, renal failure requiring dialysis, or anaphylaxis requiring emergency respiratory and/or circulatory support within 24 hours of index test. Hospitalization related to testing complications was rare (<1%), occurring in none of patients receiving CCTA and total of 4 patients receiving stress imaging. In supplemental material, authors of this trial report that within 72 hours of index testing, the following occurred in CCTA vs. functional testing groups: stroke 0.02% (1/4996) vs. 0.04% (2/5007), major bleeding in 0.06% (3/4996) vs. 0.06% (3/5007) and no anaphylaxis or renal failure requiring dialysis in either group. It is unclear if these later events were directly related to testing or subsequent treatment. Stroke and cardiac arrest were considered major adverse events as part of MACE in the other two RCTs.[83,138,140]

Test-related complications considered to be minor by trial authors were described in five RCTs[59,126,149,153,215,238,257] in stable outpatients and seven RCTs[37,47,83,85,109,111,138,140,145] in patients with suspected ACS that compared CCTA with functional testing. Examples of complications considered minor included transient elevation of creatinine levels, contrast extravasation, minor contrast reactions (e.g., hives, rash), dizziness, vasovagal reaction, headache, nausea, shortness of breath, and others. Arrhythmias including tachycardia, bradycardia and atrial fibrillation were reported in some trials and occurred in < 0.5% of patients. Description of specific events varied across trials. Complications are listed by trial in Appendix F, Table F3. Commonly described individual minor complications are summarized below and in Table 30. Some of the minor complications reported are specific to the testing modality. For example, those related to iodinated contrast material are specific the CCTA, those related to pharmacologic stress agents are specific to stress echo or stress SPECT. Patients may have experienced more than one minor event. Given these factors, no direct comparisons between testing arms can be made. This, combined with the heterogeneity of outcomes reported precluded pooling across trials.

Risk of any minor test-related complication at time of index test or within 24 hours was <4% across treatment arms across five RCTs[59,126,149,153,215,238,257] in stable outpatients and five RCTs[37,47,85,109,111,145] in patients with suspected ACS. In the largest trial in stable outpatients, CCTA was associated with having a minor complication compared with functional testing but the absolute risks for both testing arms were low (0.8% vs. 0.5%, RR 1.76, 95% CI 1.04 to 2.87). [59,149] Two trials in patients with suspected ACS, however, reported much higher risk of any minor complication and appear to have included a broader range of potential events. One trial[83,140] comparing CCTA with SPECT reported that 24% of patients in each testing arm experienced one or more minor complication, most commonly headache, nausea, dizziness or feeling of warmth. The other trial from the same author group[138], reported that 14% of CCTA patients and 6.4% of stress echo patients had complaints or adverse reactions to imaging (RR 2.16, 95% CI 1.12 to 4.14). They report 17 CCTA (9%) and 6 stress echo (3%) recipients complained about

examination length or positional discomfort and that none of the CCTA group but 3% of the stress echo group complained about shortness of breath or chest pain during imaging.

*6.1.3.1.3 Individual test-related adverse events (*Table 30*)*

Contrast-related adverse events occurring with CCTA occurred in ≤3% of patients at time of index testing as reported in six RCTs[37,47,59,109,149,215,257] and one case series[23]. Transient creatinine elevation not requiring dialysis were reported in two trials as 0.2%[109] and 1%[47] and a third RCT reported that no contrast-induced nephropathy occurred.[37] Extravasation of contrast occurred in 2%[47] to 3%[59,149] of patients in another. Mild contrast reaction occurred in 0.5% to 2.1% of patients across three trials[59,126,149,215,257] in stable outpatient and in 1% to 1.5% of patients across three trials in patients suspected ACS (skin rash, pruritus). [37,47,83,140] Contrast-related allergic reactions were reported in 1.7% of patients in the case series[23] (N=232).

CCTA was associated with lower risk of **chest pain, shortness of breath, or palpitations** at the time of index testing compared with stress SPECT (1RCT, 0.5% (1/186) vs. 16% (30/188), RR 0.03, 95% CI 0.004 to 0.24, p<0.001)[83,140] and stress echo (1 RCT, 0% vs. 3% (5/188). p=0.03)[138] in patients with suspected ACS. Similarly, in one RCT[59,149] in stable outpatients, **dipyridamole or adenosine-related events** were seen in patients receiving nuclear stress testing as were unspecified stress-induced symptoms, however the risks were small (0.2%, [5/3263] and 0.1% [5/3263] respectively). These responses are expected effects of the stressors and not likely minor adverse events. **Arrythmias, hypotension and hemodynamic instability** were rare across testing arms (≤0.2%). (Table 30)

Table 30. Summary table of test-related adverse events reported by CCTA trials

Outcome	Author, year/Trial name	Intervention vs. comparator	F/U	CCTA % (n/N)	Comparator % (n/N)	Effect size or p-value
Suspected CAD						
Any major complication	PROMISE trial (as tested population)*†	CCTA vs. any functional test	24 hours	0% (0/4633)	0% (0/4837)	NR
Any minor complication	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0.8% (37/4633)	Any functional test: 0.5% (22/4837) - Nuclear Stress: 0.6% (20/3263) - Stress Echo: 0.2% (2/1083) - Exercise ECG: 0% (0/491)	Any functional test: RR 1.76, 95% CI 1.04 to 2.87
	SCOT-HEART trial	CCTA vs. Exercise ECG	Index test	1.7% (31/1778)	NR	NR
	CAPP trial	CCTA vs. Exercise ECG	Index test	0% (0/250)	0% (0/250)	NR
	IAEA-SPECT/CTA trial	CCTA vs. SPECT	Index test	2.1% (3/146)	0% (0/143)	NR
	RESCUE trial	CCTA vs. SPECT	Index test	0.8% (4/473)§§	0% (0/468)	NR
Hypotension	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	- Nuclear Stress: 0.2% (6/3263) - Stress Echo: 0.2% (2/1083) - Exercise ECG: 0% (0/491)	NR
Mild contrast reaction	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0.5% (22/4633)	Any functional test: 0% (0/4837)	NR
	SCOT-HEART trial	CCTA vs. Exercise ECG	Index test	0.7% (13/1778)	NR	NR
	IAEA-SPECT/CTA trial	CCTA vs. SPECT	Index test	2.1% (3/146)	0% (0/143)	NR
Extravasation of contrast	PROMISE trial as	CCTA vs. any	24	0.3%	Any functional test: 0%	NR

Outcome	Author, year/Trial name	Intervention vs. comparator	F/U	CCTA % (n/N)	Comparator % (n/N)	Effect size or p-value
	tested population)*	functional test	hours	(12/4633)	(0/4837)	
	SCOT-HEART trial	CCTA vs. Exercise ECG	Index test	0.4% (7/1778)	NR	NR
Hemodynamic instability	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0.1% (3/4633)	Any functional test: 0% (0/4837)	NR
Acute bronchospasm	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	Any functional test: 0% (0/4837)	NR
Vasovagal reactions	SCOT-HEART trial	CCTA vs. Exercise ECG	Index test	0.2% (4/1778)	NR	NR
Headache	SCOT-HEART trial	CCTA vs. Exercise ECG	Index test	0.2% (4/1778)	NR	NR
Other (not otherwise specified)	SCOT-HEART trial	CCTA vs. Exercise ECG	Index test	0.2% (4/1778)	NR	NR
Ventricular tachycardia	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	- Nuclear Stress: 0.2% (5/3263) - Stress Echo: 0% (0/1083) - Exercise ECG: 0% (0/491)	NR
Rapid atrial fibrillation	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	- Nuclear Stress: 0% (0/3263) - Stress Echo: 0% (0/1083) - Exercise ECG: 0% (0/491)	NR
Stress induced symptoms (not otherwise specified)	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	- Nuclear Stress: 0.1% (4/3263) - Stress Echo: 0% (0/1083) - Exercise ECG: 0% (0/491)	NR
Dipyridamole/adenosine-related events	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	- Nuclear Stress: 0.2% (5/3263) - Stress Echo: 0% (0/1083) - Exercise ECG: 0% (0/491)	NR
Hospital admission related to a test complication	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	Any functional test: 0.1% (5/4837) - Nuclear Stress: 0.1%	NR

Outcome	Author, year/Trial name	Intervention vs. comparator	F/U	CCTA % (n/N)	Comparator % (n/N)	Effect size or p-value
					(3/3263) - Stress Echo: 0% (0/4633) - Exercise electrocardiography: 0.2% (1/491)	
Suspected ACS						
Any major complication**	PROSPECT trial	CCTA vs. SPECT	Index test	0% (0/200)	0% (0/200)	p=1.0
	Levsky, 2018	CCTA vs. Stress Echocardiography	Index test	0% (0/201)	0% (0/199)	p=1.0
Any minor complication	Chang, 2008	CCTA vs. any functional test	Index test	1.5% (2/133)	0% (0/133)	NR
	ROMICAT-II trial	CCTA vs. any functional test	Index test	0.2% (1/501)	0% (0/499)	NR
	ACRIN-PA trial	CCTA vs. any functional test	Index test	0.1% (1/908)	0.2% (1/462)	NR
	BEACON trial	CCTA vs. any functional test	Index test	3.6% (9/250)	0.4% (1/250)	NR
	Goldstein, 2007	CCTA vs. SPECT	Index test	0% (0/99)	0% (0/98)	NR
	PROSPECT trial††	CCTA vs. SPECT	Index test	24% (45/186)	24% (46/188)	NR
	Levsky, 2018	CCTA vs. Stress Echo	Index test	14% (26/189)	6.4% (12/188)	RR 2.16, 95% CI 1.12 to 4.14 p=0.03
Skin rash/reaction; pruritus	Chang, 2008	CCTA vs. any functional test	Index test	1.5% (2/133)	0% (0/133)	NR
	BEACON trial	CCTA vs. any functional test	Index test	1% (2/250)	0% (0/250	NR
	PROSPECT trial	CCTA vs. SPECT	Index test	1.5% (3/186)	0% (0/186)	p=0.25
Contrast-induced nephropathy	Chang, 2008	CCTA vs. any	Index	0% (0/133)	0% (0/133)	NR

Outcome	Author, year/Trial name	Intervention vs. comparator	F/U	CCTA % (n/N)	Comparator % (n/N)	Effect size or p-value
		functional test	test			
Transient increase in the creatinine level without the need for dialysis	ROMICAT-II trial	CCTA vs. any functional test	Index test	0.2% (1/501)	0% (0/499)	NR
	BEACON trial	CCTA vs. any functional test	Index test	1% (3/250)	0.4% (1/250)	NR
Extravasation of contrast	BEACON trial	CCTA vs. any functional test	Index test	2% (4/250)	0% (0/250)	NR
Chest pain, shortness of breath, or palpitations	PROSPECT trial	CCTA vs. SPECT	Index test	0.5% (1/186)	16% (30/188)	RR 0.03, 95% CI 0.004 to 0.24 p<0.001
	Levsky, 2018	CCTA vs. Stress Echo	Index test	0% (0/189)	3% (5/188)	p=0.03
Bradyarrhythmia	ACRIN-PA trial	CCTA vs. any functional test	Index test	0.1% (1/908)	0.2% (1/462)	NR

ACS = acute coronary syndrome, CAD = coronary artery disease, CCTA = coronary computed tomography angiography, ECG = electrical echocardiogram, ICA = invasive coronary angiography, NR = not reported, SPECT = single photon emission computed tomography

* 404 patients had no testing and 29 had ICA as a first test; these patients are not included in the as tested population.

† In the PROMISE trial, for both CCTA and functional testing, major complications were defined as death, renal failure requiring dialysis, or anaphylaxis requiring emergency respiratory and/or circulatory support.

‡ In the CONSERVE trial, only major bleeding was reported as an adverse event. Of the four major bleeds in the ICA group of this trial, one also required major transfusion.

§ Of the minor procedural complications in the CCTA group, four occurred after coronary angiography and two after CCTA. The p-value for the difference between groups for all complications, including those from procedures, was 0.014. Only those related to CCTA are reported in the table above.

** Neither the PROSPECT trial nor Levsky 2018, defined major complications. Both trials simply stated that no patients had serious complications from imaging.

†† Of patients in each testing arm experienced one or more minor complication, most commonly headache, nausea, dizziness or feeling of warmth.

‡‡Authors report this as complaints or adverse reactions to imaging; 17 CCTA and 6 stress echo patients complained about examination length or positional discomfort; None of the CCTA group but 3% of the stress echo group complained about shortness of breath or chest pain during imaging

§§ 3 events were rated as possibly due to testing, 1 rated as unlikely to be due to testing

6.1.3.2 Radiation exposure

Sixteen trials[36,37,47,52,59,83,84,96,109,126,138,140,143,144,149,153,163,171,215,257] (across 20 publications; N=21,627) assessing CCTA provided information on radiation exposure. Trials have been previously described and detailed information about each trial can be found in Appendix Q. Thirteen trials[36,37,59,83,84,96,126,138,140,143,144,149,153,163,171,215,257] (N=19,787) provided information on effective radiation dose for the index test only (**Table 31**). Of these 13 trials, 6 trials[36,59,126,149,153,163,215,257] were in patients with suspected CAD (N=16,210) and 7 trials[37,83,84,96,138,140,143,144,171] were in patients with suspected ACS (N=3,577). Ten trials[47,52,59,83,109,126,138,140,143,144,149,163,171] (N=14,324) reported on the cumulative radiation dose from all tests (**Table 32**). Of these 10 trials, 4 trials[52,59,126,149,163] were in patients with suspected CAD (N=10,826) and 6 trials[47,83,109,138,140,143,144,171] were in patients with suspected ACS (N=3,498).

6.1.3.2.1 Summary of results for radiation exposure

Data reported in **Table 31** for the PROMISE trial[59,149] are among the subgroup intended for nuclear stress testing before randomization (n=3146 vs. 3203 as tested); this was the only group with radiation data available for index test only. Additionally, one trial[52], comparing CCTA with ICA reported on radiation from follow-up procedures (ICAs and revascularizations), in addition to testing.

- **Radiation from index tests**: Across six RCTs comparing CCTA specifically with SPECT radiation exposure at index tended to be lower with CCTA (SOE Low). Five RCTs reported that CCTA was associated with a lower effective radiation dose for the index test; a sixth trial reported that CCTA was associated with slightly higher radiation (estimated difference 1.8 mSv). Rough estimates of difference between tests ranged from approximately 1.30 mSv to 11.9 mSv. Stress echocardiography and ETT do not involve ionizing radiation (SOE Low).
- **Cumulative radiation**: Across nine RCTs, results are somewhat mixed, but suggest that cumulative radiation may be higher when CCTA is the initial test (SOE Low). Good- or fair-quality RCTs found that CCTA was associated with higher cumulative radiation compared with functional testing with rough estimates of differences ranging from 1.9 mSv to 9.0 mSv in these trials. It is unclear from included RCTs what tests (e.g., SPECT, ICA) or procedures (e.g., PCI) were included in the estimates. Stress echocardiography does not involve ionizing radiation. It is unclear if some of the differences between arms would impact clinical decision making. CCTA was associated with lower cumulative radiation versus SPECT in two RCTs (estimated range 6 mSv to 15 mSv) and no statistical difference between CCTA and SPECT was reported in a third smaller poor-quality RCT.

Detailed results

6.1.3.2.2 Index test radiation

Three RCTs[59,126,149,163] in stable outpatients and three RCTs[83,84,140,171] in patients with suspected ACS compared index test effective radiation dose for CCTA with SPECT or any nuclear stress testing. Radiation doses in the CCTA arms of these trials ranged varied substantially across trials (means range 10.4 mSv to 12.7 mSv, median ranges 5.0 mSv to 11.5 mSv) (Table 31). Radiation doses in the SPECT/nuclear stress testing arms also varied (means range 10.9 mSv to 14.1 mSv, median ranges 9.3 mSv to 27 mSv). Across five RCTS, CCTA was associated with a lower effective radiation dose than SPECT (or other nuclear stress test) at index test. One large good-quality RCT (N=6,348) in stable outpatients reported a mean difference (MD –3.7 ,95% CI –3.9 to –3.5).[59,149] In contrast index CCTA was associated with higher effective radiation dose in one smaller fair-quality RCT[171] (N=598) in patients with suspected ACS (MD 1.8, 95% CI 0.89 to 2.7) (Table 31). It is unclear whether some of the differences would impact clinical decision making.

The other RCTs either did not report radiation dose for functional tests[37,143,144] or compared CCTA with tests that do not involve ionizing radiation (i.e., ETT or stress echo).[96,138,153,215,257] Across this group of RCTs, the means ranged from 5.1 mSv to 12.5 mSv and medians ranged from 3.8 mSv to 6.4 mSv (Table 31).

Table 31. Summary table of effective radiation dose for index test only reported by CCTA trials

Author Year	N	Intervention test (n)	Comparator test (n)	Intervention group; radiation from index test only	Comparator group; radiation from index test only	MD (95% CI), p-value [calculated] Author provided p-value for Medians
Suspected CAD						
PROMISE trial	6,349*	CCTA* (n=3,146 as tested)	Nuclear stress testing* (n=3203 as tested)	Mean (SD): 10.4 (6.6) mSv Median (IQR): 8.8 (5.3 to 14.6) mSv	Mean (SD): 14.1 (5.6) mSv Median (IQR): 12.6 (11.3 to 14.6) mSv	MD –3.7 (95% CI –3.9 to –3.5), p=0.0001
IAEA-SPECT/CTA trial Karthikeyan 2017	303	CCTA (n=152 as randomized)	SPECT (n= 151 as randomized)	Median (IQR): 5.0 (3.8 to 10) mSv	Median (IQR): 9.3 (8.5 to 9.7) mSv	p<0.001
Min, 2012	180	CCTA (n=91 as randomized)	SPECT (n= 89 as randomized)	Median (IQR): 6.5 (5.1 to 13.3) mSv	Median (IQR): 13.3 (13.1 to 38.0) mSv	p<0.0001
Compared with ECG or Echo						
SCOT-HEART trial	4146	CCTA (n=2073 as randomized)	Exercise ECG (n=2073 as randomized)	Median (IQR): 4.1 (3.0 to 5.6) mSv	NR	N/A
CAPP trial McKavanagh 2015	500	CCTA (n=243 as randomized)	Exercise ECG (n=245 as randomized)	Mean (SD NR): 5.31 mSv	Mean (SD NR): 0.00 mSv	NR
Suspected ACS						

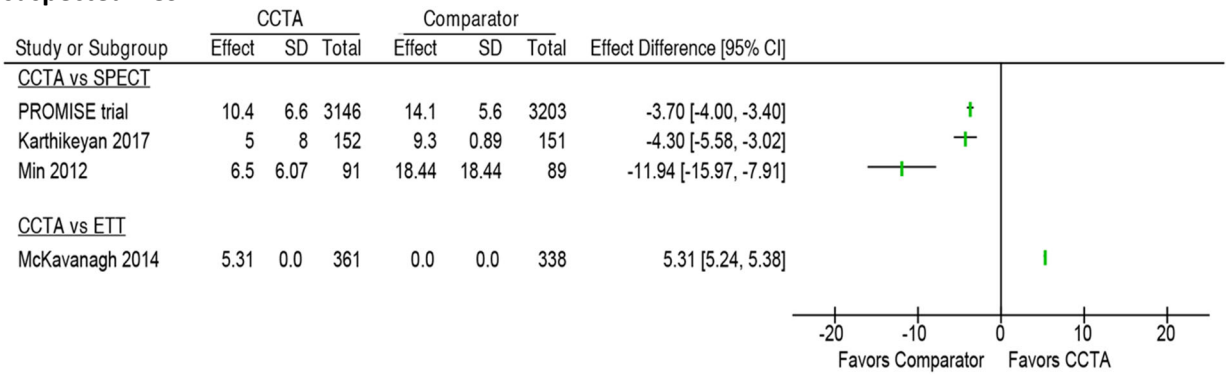
Author Year	N	Intervention test (n)	Comparator test (n)	Intervention group; radiation from index test only	Comparator group; radiation from index test only	MD (95% CI), p-value [calculated] Author provided p-value for Medians
CT-STAT trial Goldstein 2011	749	CCTA (n=361 as randomized)	SPECT (n=338 as randomized)	Median (IQR): 11.5 (6.8 to 16.8) mSv	Median (IQR): 12.8 (11.6 to 13.9) mSv	p=0.02
PROSPECT trial Levsky 2015	400	CCTA (n=200 as randomized)	SPECT (n=200 as randomized)	Median (IQR): 9.6 (6.2 to 23) mSv (n=184)	Median (IQR): 27 (19 to 27) mSv (n=189)	p<0.001
Nabi, 2016	598	CCTA (n=288 as randomized)	SPECT (n=310 as randomized)	Mean (SD): 12.7 (4.9) mSv	Mean (SD): 10.9 (4.4) mSv	MD 1.8 (95% CI 0.89 to 2.7), p=0.0001
Data for comparator NR or compared with ECG or Echo						
Chang 2008	268	CCTA (n=133 as randomized)	Any functional test (n=133 as randomized)	Mean (SD): 12.5 (2.0) mSv	NR	N/A
CATCH trial Linde 2013	600	CCTA (n=299 as randomized)	Any functional test (n=301 as randomized)	Median (IQR): 4.7 (3.8 to 6.0) mSv	NR	N/A
CT-COMPARE trial Hamilton-Craig 2014	562	CCTA (n=322 as randomized)	Exercise ECG (n=240 as randomized)	Median (IQR): 3.8 (3.5 to 4.1) mSv	NR	N/A

Author Year	N	Intervention test (n)	Comparator test (n)	Intervention group; radiation from index test only	Comparator group; radiation from index test only	MD (95% CI), p-value [calculated] Author provided p-value for Medians
Levsky 2018	400	CCTA (n=201 as randomized)	Stress Echo (n=199 as randomized)	Median (IQR): 6.4 (5.3 to 7.8) mSv	Median (IQR): 0 (0 to 0) mSv	p<0.001

ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ED = emergency department; ETT = exercise treadmill test; IQR = interquartile range; MD = mean difference; mSv = millisievert; NR = not reported; SPECT = single photon emission computed tomography; Stress Echo = stress echocardiography.

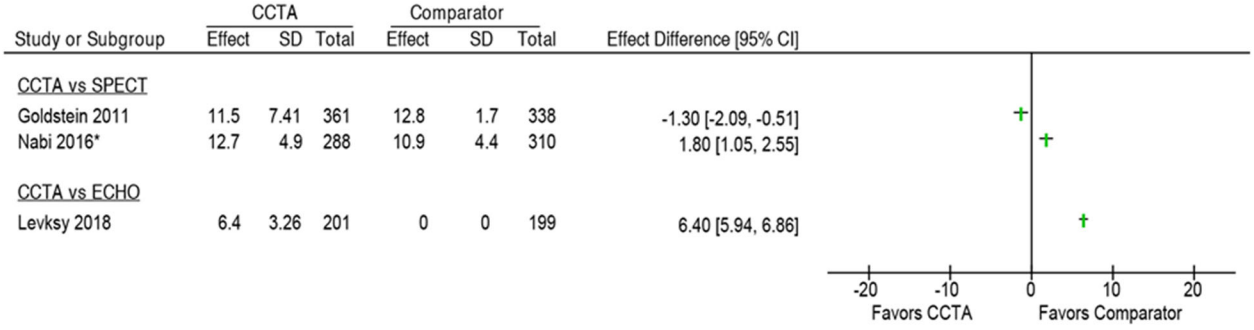
Differences between trials regarding how exposure was reported (means or medians) combined with the substantial heterogeneity across studies precluded pooling of data, however, Figure 16 and Figure 17 provides rough estimates of differences between testing arms and provides a visual representation of the data for studies that reported comparative data. Two of the studies compared CCTA functional tests that do not use ionizing radiations, one with ETT[153] the other with stress echocardiography.[138]

Figure 16. Visual overview of index test radiation exposure in stable outpatients and in patients with suspected ACS



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ETT = exercise treadmill test; SD = standard deviation; SPECT = single photon emission computed tomography.

Figure 17. Visual overview of index test radiation exposure in patients with suspected ACS



CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; SD = standard deviation; SPECT = single photon emission computed tomography**.**

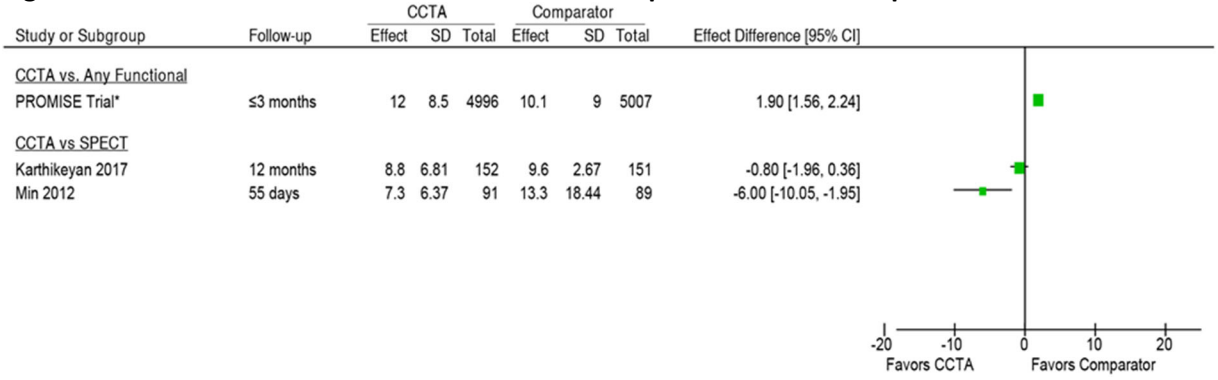
6.1.3.2.3 Cumulative Radiation

Three RCTs[59,126,149,163] in stable outpatients and 6 trials[47,83,109,138,140,143,144,171] in patients with suspected ACS compared cumulative radiation dose by CCTA versus functional testing as initial testing strategies. It is assumed that the cumulative does includes additional downstream testing. Six RCTs[47,59,109,138,143,144,149,171] found that CCTA was associated with higher cumulative radiation compared with functional testing. CCTA was associated with lower cumulative radiation versus SPECT in two

RCTs[83,126,140] and no statistical difference between CCTA and SPECT was reported in a third smaller poor-quality RCT,[163] (Table 32).

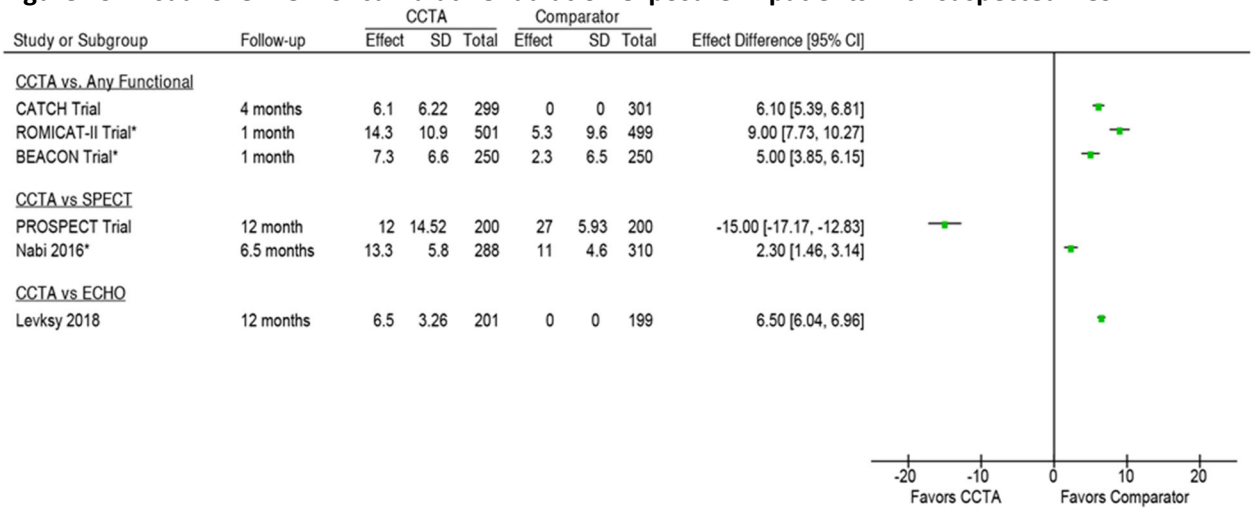
Differences between trials regarding how exposure was reported (means or medians) combined with the substantial heterogeneity across studies precluded pooling of data. Figure 18 and Figure 19 provide rough estimates of differences between arms for a visual overview of differences between testing arms. It is unclear if some differences may impact clinical decision making.

Figure 18. Visual overview of cumulative radiation exposure in stable outpatients



CCTA = coronary computed tomography angiography; CI = confidence interval; SD = standard deviation; SPECT = single photon emission computed tomography.

Figure 19. Visual overview of cumulative radiation exposure in patients with suspected ACS



CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; SD = standard deviation; SPECT = single photon emission computed tomography**.**

In stable outpatients, the largest, good-quality RCT (N=10,003 as randomized, 9470 as tested) CCTA was associated with slightly higher cumulative radiation exposure compared with any functional testing within 3 months of testing (MD 1.90 mSv (95% CI 1.6 to 2.2 mSv).[59,149] In contrast, one smaller (N=303) good-quality RCT[126] reported that CCTA was associated with slightly lower cumulative radiation compared with SPECT at 12 months and one small (N=180) poor-quality RCT found no statistically significant difference between CCTA and SPECT (medians 7.3 mSv vs. 13.3 mSv) at a mean of 55 days. [163] (Table 32)

In patients with suspected ACS, in five[47,109,138,143,144,171] of the six RCTs, CCTA was associated with higher cumulative radiation compared with functional testing in general. The largest, fair-quality RCT (N=1000) reported a mean difference of 9mSv (95% CI 7.7 to 10.3 mSv) at 1 month, one good-quality trial[47] (N=500) reported a mean difference of 4.7 mSv (95% CI 3.5 to 5.9) at 1 month and the mean difference in a third fair-quality trial[171] (N=598) was 2.30mSv (95% CI 1.5 to 3.1mSv) at approximately 6.5 months. Median ranges for cumulative radiation reported in the remaining two fair-quality RCTs[138,143,144] were 6.1 to 6.5mSv for CCTA and 0 for functional testing (IQR 0 to 5.7). One of these RCTs compared CCTA with stress echocardiography.[138]

In contrast, in one fair-quality RCT (N=400), CCTA was associated with substantially lower cumulative radiation compared with SPECT at 12 months (median 12mSv vs. 27 mSv) and at a median of approximately 40 months (median 13mSv vs. 27mSv)[83,140] (Table 32).

Table 32. Summary table of cumulative radiation from all tests reported by CCTA trials

Author Year	N	Intervention test (n)	Comparator test (n)	Follow-up time	Intervention group; cumulative radiation from all tests	Comparator group; cumulative radiation from all tests	MD (95% CI), p-value Author provided p-value for Medians
Suspected CAD							
PROMISE trial*	10,003	CCTA (n=4,996 as randomized)	Any functional test (n=5,007 as randomized)	≤3 months	Mean (SD): 12.0 (8.5) mSv Median (IQR): 10.0 (5.6 to 17.2) mSv	Mean (SD): 10.1 (9.0) mSv Median (IQR): 11.3 (0.0 to 13.5) mSv	MD 1.90 (1.6 to 2.2), p=0.0001
	9,470	CCTA (n=4,633 as tested)	Any functional test (n=4,837 as tested)	≤3 months	Mean (SD): 12.5 (8.4) mSv Median (IQR): 10.3 (6.1 to 17.4) mSv	Mean (SD): 10.6 (8.9) mSv Median (IQR): 11.5 (0.0 to 13.8) mSv	MD 1.90 (95% CI 1.6 to 2.3), p=0.0001
IAEA-SPECT/CTA trial Karthikeyan 2017	303	CCTA (n=152 as randomized)	SPECT (n= 151 as randomized)	12 months	Median (IQR): 8.8 (I4.0 to 13.2)	Median (IQR): 9.6 (8.9 to 12.5)	p=0.04
Min, 2012	180	CCTA (n=91 as randomized)	SPECT (n= 89 as randomized)	Mean: 55 days	Median (IQR): 7.3 (5.1 to 13.7) mSv	Median (IQR): 13.3 (13.1 to 38.0) mSv	p=0.31
Suspected ACS							
CATCH trial Linde 2013	600	CCTA (n=299 as	Any functional test	4 months	Median (IQR): 6.1 (4.2 to 12.6)	Median (IQR): 0.0 (0.0 to 5.7)	p<0.0001

Author Year	N	Intervention test (n)	Comparator test (n)	Follow-up time	Intervention group; cumulative radiation from all tests	Comparator group; cumulative radiation from all tests	MD (95% CI), p-value Author provided p-value for Medians
		randomized)	(n=301 as randomized)				
ROMICAT-II trial Hoffmann	1000	CCTA (n=501 as randomized)	Any functional test (n=499 as randomized)	1 month	Mean (SD): 14.3 (10.9) mSv	Mean (SD): 5.3 (9.6) mSv	MD 9.0 (95% CI 7.7 to 10.3), p=0.0001
BEACON trial Dedic 2016	500	CCTA (n=250 as randomized)	Any functional test (n=250 as randomized)	1 month	Mean (SD): 7.3 (6.6) mSv	Mean (SD): 2.6 (6.5) mSv	MD 4.7 (95% CI 3.5 to 5.9), p= 0.0001
PROSPECT trial Levsky 2015	400	CCTA (n=200 as randomized)	SPECT (n=200 as randomized)	12 months	Median (IQR): 12 (6.4 to 26) mSv	Median (IQR): 27 (19 to 27) mSv	p<0.001
				Median: 41.7 (CCTA) and 39.0 (SPECT) months	Median (IQR): 13 (6.9 to 27) mSv	Median (IQR): 27 (19 to 27) mSv	p<0.001
Nabi, 2016	598	CCTA (n=288 as randomized)	SPECT (n=310 as randomized)	Median: 6.5 (CCTA) and 6.4 (SPECT) months	Mean (SD): 13.3 (5.8) mSv	Mean (SD): 11.0 (4.6) mSv	MD 2.30, 95% CI 1.5 to 3.1 p<0.0001
Levsky 2018	400	CCTA (n=201 as randomized)	Stress Echo (n=199 as randomized)	12 months	Median (IQR): 6.5 (5.3 to 9.7) mSv	Median (IQR): 0 (0 to 0)	p<0.001
				Median: 24 months	Median (IQR): 6.5 (5.5 to 10.0) mSv	Median (IQR): 0 (0 to 0)	p<0.001

ACS = acute coronary syndrome, CAD = coronary artery disease, CCTA = coronary computed tomography angiography, CI = confidence interval; ECG = electrical echocardiogram, ICA = invasive coronary angiography, IQR = interquartile range, MD = mean difference, mSv = millisievert, N/A = not applicable, NR = not reported, SD = standard deviation, SPECT = single photon emission computed tomography.

* All PROMISE subjects who had functional testing or CCTA as their first test were included in the as tested population. Patients who had no test or who had invasive coronary angiography (ICA) as their first test were excluded. Computed tomography (CT) protocols commonly include a non-contrast CT for assessment of coronary artery calcium score before contrast-enhanced CCTA to assess coronary artery stenosis. Some sites chose not to proceed with CCTA in patients with a high calcium score; these participants were excluded as the radiation dose from calcium score CT alone is substantially lower than for CCTA.
† Includes radiation from ICAs and revascularizations, in addition to testing.

6.1.3.3 Incidental findings

Four trials[59,83,140,149,215,238,257] (across 7 publications; N=12,671) assessing CCTA reported on incidental and/or extra cardiac findings found on index test (Table 33). Trials have been previously described and detailed information about each trial can be found in Appendix Q. Three trials[59,149,215,238,257] (N=12,295) were in patients with suspected CAD and 1 trial[83,140] was in patients with suspected ACS (N=376). Comparators consisted of SPECT MPI in 2 trials [83,140,238], exercise ECG in 1 trial[215,257], and any functional testing in 1 trial[59,149].

In addition to the four CCTA trials reporting on incidental findings, 2 systematic reviews[72,125] and 4 retrospective single arm studies[24,66,124,200] provided additional information on extracardiac findings found on CCTA (Table 34). One systematic review included 11,703 patients with suspected CAD (unclear if symptomatic or asymptomatic) across 13 studies. The other systematic review included 15,877 mostly with suspected CAD across 19 studies. Karius 2014 included 9 studies that were not included in the Flor 2013 systematic review, and Flor 2013 included 3 studies that were not included in Karius 2014. Across the 4 additional single arm studies, which all included patients with suspected CAD, sample sizes ranged from 1,383 to 3,898 (Total N=9,090). Focus was on total extracardiac findings, clinically significant or major extracardiac findings, malignant extracardiac findings, and the top 5 most commonly reported extracardiac findings in each study.

6.1.3.3.1 Summary of results

- Incidental findings are common with CCTA (28% to 44%) across included RCTs, systematic reviews and nonrandomized studies with pulmonary findings being most common. The proportion that were considered “potentially significant”, “clinically significant” or “required follow-up” ranged from 4.9% to 16% (SOE Low).

Detailed Results

Incidental and/or extra cardiac findings at index testing were commonly seen and variably defined across four CCTA trials[59,83,140,149,215,238,257] that reported on this. Pulmonary-related findings (nodules, masses, granuloma, emphysema or other parenchymal changes) were most commonly reported across trials. (Table 33) In stable outpatients, “potentially significant” incidental findings occurred in 11.6% of patients in the CCTA group versus 0.7% of those receiving stress nuclear testing or 1.9% of patients receiving stress echocardiography ($p<0.001$ for CCTA vs. any functional test) in the largest trial. [59,149] Two other trials in stable outpatients reported frequencies of any incidental findings of 38.1%[215,257] and 32.8%[238], however additional imaging was required in fewer patients, 7.5% and 11.4% respectively. In one trial in patients with suspected ACS incidental findings occurred in 83.4% of patients; 156 of 187 patients had a total of 386 incidental findings.[83,140] The most common were pulmonary (63%), non-coronary cardiac (37%), gastrointestinal (26%) and hepatobiliary (22%) findings. Findings the authors considered potentially serious or life threatening were pericardial effusion (6.4%), aortic dilatation (3.2%), pulmonary embolism (2.1%), pneumonia (1.6%) and congestive heart failure (1.6%).

Across two systematic reviews[72,125], one retrospective database study[124] and three large retrospective case series[24,66,200], the overall frequency of extracardiac findings (ECFs) ranged from 28.4% to 44%. (Table 34) Again, pulmonary findings were most common. The two systematic reviews[72,125] report a pooled prevalence of 16% (95% CI range 9% to 24%) for clinically significant or major ECFs. The frequency of ECFs major and/or requiring follow-up ranged from 2.4% to 6.8% in three retrospective studies[24,66,124] with the fourth study[200] reporting that 4.9% of ECFs were considered significant. The pooled prevalence of acute life-threatening ECFs was 2.2% in one systematic review[125] and the prevalence of ECFs requiring urgent attention was 0.4%in the retrospective database study[124] by the same author group. The prevalence of malignant ECFs ranged from 0.1% to 0.7% across two systematic reviews[72,125], the database study[124] and two case series[24,200].

Resources required to follow-up incidental findings and use of additional testing involving radiation were not described in these studies. The impact of incidental findings and their follow-up on patients (anxiety, cost, time from work, etc.) was not described.

Table 33. Summary table of incidental findings on index test reported by CCTA trials

Outcome	Author, year (trial name)	Intervention vs. comparator	CCTA; % (n/n)	Comparator test; % (n/N)	Effect Size or p-value
Suspected CAD					
Any incidental finding*	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	11.6% (539/4633)	Any functional test: 0.7% (34/4837)† RR 16.6, 95% CI 11.7 to 23.3 - Nuclear Stress: 0.4% (13/3263) - Stress Echo: 1.9% (21/1083) - Exercise electrocardiography: NR	Any functional test: RR 16.6, 95% CI 11.7 to 23.3 p<0.001 - Nuclear Stress: NR - Stress Echo: NR - Exercise electrocardiography: NR
	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	38.1% (677/1778)‡	NR	NR
	Stillman, 2020 (RESCUE trial)	CCTA vs. SPECT MPI	32.8% (169/516)	1.7% (9/531)	RR 19.32, 95% CI 10.0 to 37.37 NR
Incidental findings requiring additional follow-up imaging	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	7.6% (136/1778)	NR	NR
	Stillman, 2020 (RESCUE trial)	CCTA vs. SPECT MPI	11.4% (59/516)	0.4% (2/531)	RR 03.36, 95% CI 7.45 to 123.6 NR
Coronary anomaly	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	1.5% (71/4633)	NR	NR
Pulmonary nodule, mass, granuloma	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	9.4% (437/4633)	NR	NR
	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	11.2% (200/1778)	NR	NR
Pulmonary embolism	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	0.1% (4/4633)	NR	NR
	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.2% (4/1778)	NR	NR
Pneumonia	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	0.2% (9/4633)	NR	NR
	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.8% (15/1778)	NR	NR

Outcome	Author, year (trial name)	Intervention vs. comparator	CCTA; % (n/n)	Comparator test; % (n/N)	Effect Size or p-value
Aortic aneurysm	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	0.2% (9/4633)	NR	NR
Aortic dissection	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	0.2% (8/4633)	NR	NR
Hiatal hernia	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	7.7% (358/4633)	NR	NR
	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	6.8% (121/1778)	NR	NR
Emphysema or other parenchymal changes	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	11.4% (202/1778)	NR	NR
Lung atelectasis/scarring	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	3.5% (63/1778)	NR	NR
Pleural plaque	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.6% (29/1778)	NR	NR
Bronchiectasis	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.2% (22/1778)	NR	NR
Fibrosis	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.0% (17/1778)	NR	NR
Pleural effusion	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.2% (3/1778)	NR	NR
Lymphadenopathy	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.7% (30/1778)	NR	NR
Calcified lymph nodes	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.0% (16/1778)	NR	NR
Aorta atheroma	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.5% (26/1778)	NR	NR
Aorta dilation	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.0% (17/1778)	NR	NR
Breast nodule	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.3% (5/1778)	NR	NR
Liver cysts	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	2.0% (36/1778)	NR	NR
Liver hemangioma	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.1% (2/1778)	NR	NR
Fatty infiltration	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.1% (2/1778)	NR	NR
Esophagus thickening	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.2% (3/1778)	NR	NR
Other§	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	NR	NR	NR
Suspected ACS					
Any incidental finding	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	83.4% (156/187) [386 incidental findings in 156 patients were	0% (0/189)	

Outcome	Author, year (trial name)	Intervention vs. comparator	CCTA; % (n/n)	Comparator test; % (n/N)	Effect Size or p-value
			found among 187 CCTA studies]		
Pulmonary findings	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	63% (118/187)	0% (0/189)	NR
Noncoronary cardiac findings	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	37% (69/187)	0% (0/189)	NR
Gastrointestinal findings	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	26% (49/187)	0% (0/189)	NR
Hepatobiliary findings	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	22% (42/187)	0% (0/189)	NR
Renal findings	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	9% (17/187)	0% (0/189)	NR
Pneumonia**	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	1.6% (3/187)	0% (0/189)	NR
Congestive heart failure**	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	0.5% (1/187)	0% (0/189)	NR
Pericardial effusion**	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	6.4% (12/187)	0% (0/189)	NR
Aortic dilatation**	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	3.2% (6/187)	0% (0/189)	NR
Pulmonary embolism**	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	2.1 %(4/187)	0% (0/189)	NR

ACS = acute coronary syndrome, CAD = coronary artery disease, CCTA = coronary computed tomography angiography, ECG = electrical echocardiogram, ICA = invasive coronary angiography, NR = not reported, SPECT = single photon emission computed tomography.

* Across the trials, incidental findings were defined as "potentially significant incidental findings" (PROMISE trial), "non-cardiac findings" (SCOT-HEART trial), "non-cardiac findings" (RESCUE trial), and "incidental findings" (PROSPECT trial).

† In the functional testing arm, abnormal breast uptake of radiotracer (0.3%, 11/3263) on nuclear stress testing, and mitral regurgitation (1.0%, 11/1083) on stress echocardiography were the most common incidental findings.

‡ In addition, there were 28.2% (501/1778) other cardiac findings identified.

§ To include: anterior mediastinal mass, arteriovenous malformation, Bochdalek hernia, broncocele, duplication cyst, elevated left hemidiaphragm, gallstones, hamartoma, pericardial cyst, sclerotic vertebrae, syndesmophytes, subclavian vein stenosis, splenomegaly, splenic artery aneurysm, vertebral wedge fractures.

** Considered to be potentially serious or life threatening.

Table 34. Summary of extracardiac findings (ECF) identified by CCTA

Author Year	Study design	N	Population	Incidental findings
Karius 2014	SR	11,703 (across 13 studies)*	Suspected CAD (unclear if symptomatic or asymptomatic)	• Pooled prevalence of overall ECFs: 41% (95% CI 27% to 56%), p<0.0001 [Overall ECF were identified in 3794 of 11,186 participants] • Pooled prevalence of clinically significant ECFs: 16.0% (95% CI 9% to 24%, p<0.0001) [Clinically significant ECF were detected in 1989 of 11,703 patients] • Pooled prevalence of acutely life-threatening ECFs in relation to the study cohort: 2.2% (95% CI 1.9% to 2.5%), p<0.0001 • Pooled prevalence of malignant ECFs in relation to the study cohort: 0.3% (95% CI 0.2% to 0.4%), p<0.0001 • Top 5 most commonly reported ECFs in relation to the total number of clinically significant ECFs: - Suspicious pulmonary nodules: 26.6% (575/2160) - Hiatal hernia: 20.8% (450/2160) - Aortic abnormalities: 10.8% (233/2160) - Emphysema: 8.6% (186/2160) - Pulmonary infiltration: 5.5% (11/2160)
Flor 2013	SR	15,877 (across 19 studies)*	Mixed (suspected CAD, healthy subjects, AFIB)	• Pooled prevalence of overall ECFs: 44% (95% CI 35% to 54%), p=0.275 • Pooled prevalence of major ECFs: 16% (95% CI 14% to 20%), p<0.001 • Pooled prevalence of malignant ECFs: 0.7% (95% CI 0.5% to 1.0%), p=NR *Individual event types were not reported by this study.*
Karius 2019	Retrospective database	3,898 (with 4,209 CCTAs performed)	CCTA examinations performed with an indication to rule out CAD. Patients without significant CAD (coronary stenosis < 50%) on CCTA were included.	• Proportion of patients with an ECF: 30.2% (1117/3898) • Proportion of patients with an ECF with a recommended for follow-up: 2.4% (95% CI 2.0% to 2.9%) (94 patients) • Proportion of patients with an urgent ECF: 0.4% (95% CI 0.3% to 0.7%) (16 patients) • Proportion of patients with a malignant ECF: 0.1% (95% CI 0.0% to 0.2%) (3 patients) • Top 5 most commonly reported ECFs in relation to the total number of patients included in the study: - Chronic changes of lung parenchyma and bronchial system: 12.9% (501/3898) - Extensive atherosclerosis: 5.4% (209/3898) - Pulmonary nodule/consolidation: 4.3% (167/3898) - Extensive spinal degradation: 4.1% (159/3898) - Aortic dilation: 2.9% (112/3898)

Author Year	Study design	N	Population	Incidental findings
Bendix 2011	Retrospective case series	1,383	Suspected CAD	• Proportion of patients with an ECF: 28.4% (393/1383) (with 482 ECFs total) • Proportion of patients with a major ECF requiring follow-up: 6.7% (94/1383) (with 1030 ECFs total) • Proportion of patients with a malignant ECF: 0.3% (4/1383) (with 4 ECFs total) • Top 5 most commonly reported ECFs in relation to the total number of ECFs identified: - Adenopathy: 18.0% (87/482) - Hepatic cyst: 12.2% (59/482) - Atelectasis: 8.5% (41/482) - Emphysema: 8.3% (40/482) - Pleural plaque: 5.4% (26/482)
Ramanathan 2019	Retrospective case series	1,713	Suspected CAD†	• Proportion of patients with an ECF: 35.0% (600/1713) (with 812 ECFs total) • Proportion of ECFs that were considered significant: 4.9% (39/812) • Proportion of patients with a malignant ECF: 0.2% (4/812) • Top 5 most commonly located ECFs in relation to the total number of patients included in the study (actual ECF types are NR): - Lungs: 13% (222/1713) - Liver: 11% (189/1713) - Mediastinum: 5% (85/1713) - Bone: 4% (68/1713) - Great vessels: 3% (51/1713)
Erol 2014	Retrospective case series	2,096	Suspected CAD‡	• Proportion of patients with an ECF: 8.1% (170/2096) (with 174 ECFs total) • Proportion of patients with an ECF requiring further follow-up: 6.8% (142/2096) • Top 5 most commonly reported ECFs in relation to the total number of patients included in the study: - Fusiform dilatation of the ascending aorta: 3.2% (67/2096) - Left atrial diverticula: 1.2% (25/2096) - Massive mitral valve annulus calcification: 0.9% (19/2096) - Bicuspid aortic valve: 0.57% (12/2096) - Acute pulmonary embolism: 0.29% (6/2096) - Secundum-type atrial septal defect: 0.29% (6/2096)

AFIB = atrial fibrillation, CAD = coronary artery disease, CAD = coronary artery disease, CCTA = coronary computed tomography, CI = confidence interval, ECF= extra cardiac finding, SR = systematic review.

* Karius 2014 includes 9 studies that are not included in the Flor 2013 SR, and Flor 2013 includes 3 studies that are not included in Karius 2014

† Indications for CCTA included: Acute and chronic chest pain (44%), Dyspnea (8%), Hypertension (15%), Diabetes mellitus (12%), Abnormal or equivocal stress test (8%), Abnormal ECG (3%), Palpitations (2%), Congestive heart failure (30%), Pre operative: assessment (4%)

‡ Indications for CCTA were atypical chest pain, angina pectoris, coronary artery anomalies, and determination of the patency of bypass grafts or stents.

6.1.4 Key Question 4: Differential Efficacy or Safety

6.1.4.1 Summary of results

Three large RCTs comparing CCTA with functional testing reported tests for interaction between subgroups on efficacy and/or safety outcomes. Two RCTs were in stable outpatients (N = 10,003[59] and 4146[215] respectively) and one RCT was in patients with suspected ACS (N=1000)[109]. These trials are described in previous sections. Only one of these pre-specified subgroup analyses and consider this in sample size determinations. All performed multiple analyses for multiple outcomes, including multiple composite outcomes. None of the RCTs specified all outcomes evaluated. None specified hypotheses to be tested or expected direction.

- **Clinical outcomes**: Only one RCT reported on the primary clinical outcomes of interest for this HTA. At a median of 3.2 years, the effect of CCTA did not appear to vary based on anginal classification (non-anginal chest pain, possible anginal chest pain) for MI (SOE Low), all-cause mortality (SOE Insufficient) or death due to CAD (SOE Insufficient). As many of these outcomes appear to be rare, it is possible that this trial was not sufficiently powered to effectively evaluate interaction. The factors, outcomes and hypothesized direction do not appear to have been specified a priori.
- **Downstream testing:** One RCT in patients with suspected ACS found no significant variation in use of downstream testing with CCTA based on sex or race at either the index visit, or 28 day follow up. Downstream testing did vary by diabetes status; more downstream testing occurred with CCTA in patients with diabetes at index visit and by 28-day follow-up (interaction p-values 0.001 and 0.002 respectively). The factors, outcomes and hypothesized direction do not appear to have been specified a priori in this fair-quality trial (SOE Low).
- **ICA referral:** Across two RCTs, one in stable outpatients and the other in patients with suspected ACS the effect of CCTA versus functional testing on ICA referral did not vary by diabetes status (SOE Low). Similarly, there was no effect modification in the trial in patients with suspected ACS by sex or race at index visit or by 28-day follow-up (SOE Low).
- **Revascularization**: Across two RCTs, one in stable outpatients and the other in patients with suspected ACS the effect of CCTA versus functional testing on revascularization did not vary by diabetes status (SOE Low). The effect of CCTA versus functional testing on revascularization was not modified by either sex (1 RCT) or angina classification (1 RCT) (SOE Insufficient).
- **Radiation exposure:** In stable outpatients, CTTA cumulative radiation may vary based on baseline heart rate. Patients with ≥75 beats-per-minute may have higher cumulative radiation with CCTA compared with functional testing. Tests for interaction by age, sex and BMI were not significant (SOE Insufficient). In patients with suspected ACS, there was insufficient evidence to confidently make conclusions about how radiation dose may vary by sex, diabetes status or race for CCTA versus functional testing index testing or within 28 days (SOE insufficient).

Detailed results

Three large RCTs comparing CCTA with functional testing reported tests for interaction between subgroups on efficacy and/or safety outcomes.[5,146,148,175,186,187,204,217,218,245,246] All three reported on multiple patient characteristics or factor for multiple outcomes (Table 35). This section will focus on the primary outcomes of interest to this HTA (MI, all-cause death, cardiac death, stroke, ICA and revascularization referral, safety-related); we will briefly describe analyses on other outcomes, including the various definitions of MACE. Summary tables detail results for factors and outcomes evaluated in these studies are found in greater detail in Appendix O, Tables O7 through O22. Only select tables will be included here.

In stable outpatients, the largest, RCT described pre-specified subgroup analyses and took this into account for sample size determination and during the randomization process[58] based on their protocol. Authors created three cohorts based on specific functional tests (e.g., SPECT, stress echo, ETT) for the pre-specified analyses; in each, half was randomized to the pre-specified functional test and half to CCTA to form paired CCTA-functional test subgroups. The goal was to evaluate subgroups where anatomic testing might be particularly advantageous, or where the question of a benefit from CTA is particularly relevant. While the subgroups/factors were prespecified, the use of multiple composite outcomes for the analyses do not appear to have been. For the other RCT in stable outpatients (N=4146), neither the protocol[176] nor the primary publication[215] specify subgroup analysis in terms of factors or outcomes. Subgroup analyses were reported in a later publication.[5] Multiple composite outcomes were evaluated. Similarly, the fair-quality trial **in patients with suspected ACS** (N=1000) does not specify subgroup analysis in the protocol or primary publication.[109] Their primary trial endpoint was length of stay.

Table 35. Overview of RCTs evaluating differential efficacy and safety

Trial, (N) Quality (ROB)	Factors specified *a priori or not*	Hypothesis direction	Outcome(s)
Stable Outpatients			
PROMISE (Douglas 2015) N=10,003 Good quality	**Specified a priori:** Age, sex, race, comorbidity, cardiovascular risk factors, pre-randomization choice of functional test, and characteristics precipitating symptoms	NR	• Composite (cardiovascular death, MI) • Composite (cardiovascular death, myocardial infarction, and unstable angina hospitalization) • Composite (death from any cause, nonfatal myocardial infarction, hospitalization for unstable angina, or major procedural complication • Composite of the above plus ICA without obstructive CAD • ICA referral • Any revascularization PCI referral • Medication use • test positive rate (≥70% stenosis in at least one epicardial artery or ≥50% stenosis in the left main
SCOT-HEART (2018) N=4146	**Not specified a priori;** Age, sex, 10 year risk,	NR	• MI (fatal, non-fatal, separately, and together) • Composite (MI, stroke)

Trial, (N) Quality (ROB)	Factors specified *a priori or not*	Hypothesis direction	Outcome(s)
Good quality	previous CAD, Diabetes, NICE classification (angina, nonanginal chest pain)		• Composite (Death from CAD or nonfatal MI) at 5 years • All-cause mortality • Cardiac death (CAD) • CABG
Suspected ACS			
ROMICAT-II (Hoffman) N=1000 Fair quality	**Not specified a priori:** Sex, diabetes, race	NR	• MACE (not defined) • Downstream testing • Repeat ED visit or hospitalization for chest pain • ICA • Revascularization, PCI • Index radiation dose • Mean cumulative radiation does • Administrative/Utilization (direct ED discharge, LOS (hours), hospital admission)

CABG = coronary artery bypass graft; CAD = coronary artery disease; ED = emergency department; ICA = invasive coronary angiography; LOS = length of stay; MACE = major adverse cardiac events; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; PCI = percutaneous coronary intervention; RCT = randomized controlled trial.

6.1.4.2 Primary clinical outcomes

Only one, fair-quality RCT[5] in stable outpatients with suspected CAD reported sub analyses with tests for interaction for the primary clinical outcomes of interest for this HTA. At a median of 3.2 years there was no evidence of differential test effectiveness based on NICE classification of chest pain as non-anginal or possibly anginal for MI, non-fatal stroke, all-cause mortality or death due to CAD. As many of these outcomes appear to be rare, it is possible that this trial was not sufficiently powered to effectively evaluate interaction. The factors, outcomes and hypothesized direction do not appear to have been specified a priori (Table 36).

Table 36. Analyses for impact of NICE classification of chest pain on primary outcomes

Trial name	Follow-up	Subgroup (N)	CCTA, % (n/N))	Exercise ECG, % (n/N)	Author reported HR (95% CI)	Author reported interaction p-value
MI (fatal and nonfatal)						
SCOT-HEART, 2018	Median 3.2 years	NICE classification of non-anginal chest pain*	1.0% (7/712)	1.5% (11/735)	0.65 (0.25 to 1.69)	0.836
		NICE classification of possible anginal chest pain*	1.9% (22/1174)	3.2% (37/1149)	0.58 (0.34 to 0.99)	
Non-fatal stroke						
SCOT-HEART, 2018	Median 3.2 years	NICE classification of non-anginal chest pain*	0.1% (2/712)	0.7% (5/735)	0.21 (0.02 to 1.8)	0.200
		NICE classification of possible anginal chest pain*	0.5% (6/1174)	0.5% (6/1149)	1.01 (0.32 to 3.12)	
All-cause mortality						

SCOT-HEART, 2018	Median 3.2 years	NICE classification of non-anginal chest pain*	1.0% (7/712)	0.5% (4/735)	1.81 (0.53 to 6.18)	0.200
		NICE classification of possible anginal chest pain*	1.5% (18/1174)	1.9% (22/1149)	0.82 (0.44 to 1.53)	
Coronary heart disease death						
SCOT-HEART, 2018	Median 3.2 years	NICE classification of non-anginal chest pain*	0% (0/712)	0.3% (2/735)	0 (0 to Infinity)	0.998
		NICE classification of possible anginal chest pain*	0.3% (3/1174)	0.3% (4/1149)	0.78 (0.17 to 3.48)	

CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; HR = hazard ratio; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence.
* Participants with non-anginal chest pain had the lowest event rates. Patients with possible angina had a higher and time-varying event rate with increased early hazards. Additionally, study reports third group of patients with known CAD that were already on established preventative therapies which were not reported in this data.

Two trials in stable outpatients reported sub analyses with tests for interaction for composite outcome of cardiovascular death or MI.[175,217,218] Both evaluated whether the presence of diabetes modified the effect of testing for this outcome. Results from the largest trial suggest that diabetes may modify testing for the composite outcome of MI or cardiovascular death, however the other, smaller trial reported no interaction (Table 37).

Table 37. Analyses for impact of diabetes on the composite outcome of MI and cardiovascular death

Trial name	Timing	Subgroup (N)	CCTA, % (n/N)	Comparator, % (n/N)	Author reported effect estimate	Author reported interaction p-value
PROMISE trial	Median follow-up: 25 months	With diabetes (N=NR)	1.1% (10/936)	Any functional test: 2.6% (25/972)	Adj. HR 0.38, 95% CI 0.18 to 0.79*	0.020
		Without diabetes (N=NR)	1.4% (50/3564)	Any functional test: 1.29% (45/3494)	Adj. HR 1.03, 95% CI 0.69 to 1.54*	
SCOT-HEART, 2018	Median 4.8 year follow-up	Diabetes (N=NR)	2.2% (41/1850)	Exercise ECG: 3.5% (64/1852)	HR 0.63 (95% CI 0.43 to 0.94)	0.40
		No diabetes (N=NR)	3.1% (7/223)	Exercise ECG: 7.7% (17/221)	HR 0.36 (95% CI 0.15 to 0.87)	

CI = confidence interval; ECG = electrocardiography; HR = hazard ratio; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; NR = not reported.

There was no evidence of interaction from additional subanalyses on this composite outcome in the SCOT-HEART trial for any of the following factors (see Appendix O for tables): Age (< 65, ≥65 years), sex, 10-year cardiovascular risk (<15%, ≥15%), previous coronary heart disease, NICE anginal classification (non-anginal, anginal).

Results for other composite outcomes are also found in Appendix O. In general, there was no evidence of differential effectiveness (interaction p-values were not significant) by sex.

6.1.4.3 Downstream testing

In one fair-quality trial[246] in patients with suspected ACS, testing effect appears to be modified by the presence or absence of diabetes. While downstream testing was more common in the CCTA arm for both those with and without diabetes compared with functional testing, those with diabetes had differentially higher rates of downstream testing with CCTA. Neither sex nor race modified the effect of testing (Table 38).

Table 38. Subgroup analyses for any downstream testing in patients with suspected ACS

Trial name	Timing	Subgroup (N)	CCTA, % (n/N)	Functional Testing, % (n/N)	Author reported effect estimate	Author reported interaction p-value
ROMICAT-II trial	Index Visit	Females (N=NR)	16% (37/239)	10% (22/229)	NR	0.08
		Males (N=NR)	30% (79/262)	12% (31/270)	NR	
	28 day follow-up	Females(N=NR)	20% (47/239)	24% (11/229)	NR	0.23
		Males (N=NR)	33% (86/262)	13% (86/270)	NR	
	Index Visit	With diabetes (N=NR)	38% (33/86)	5% (4/87)	NR	0.001
		Without diabetes (N=NR)	20% (83/415)	12% (49/412)	NR	
	28 day follow-up	With diabetes (N=NR)	42% (36/86)	7% (6/87)	NR	0.002
		Without diabetes (N=NR)	23% (97/415)	13% (54/412)	NR	
	Index Visit	White (N=NR)	24% (80/330)	13% (42/329)	NR	0.16
		Black (N=NR)	22% (/141)	6% (9/140)	NR	
	28 day follow-up	White (N=NR)	29% (95/330)	15% (48/329)	NR	0.18
		Black (N=NR)	23% (32/141)	6% (9/140)	NR	

CCTA = coronary computed tomography angiography; NR = not reported.

6.1.4.4 Test positivity rate of index test

Sex and BMI (<35, ≥35) appear to modify the effect of testing on the test positive rate (≥70% stenosis in at least one epicardial artery or ≥50% stenosis) in one trial[186,187] in stable outpatients, based on test for interaction across functional tests. Tests for interaction for age and diabetes status were not significant (Table 39).

Table 39. Subgroup analyses for test positive rate (≥70% stenosis in at least one epicardial artery or ≥50% stenosis in the left main)

Trial name	Timing	Subgroup (N)	CCTA % (n/N)	Comparator % (n/N)	Author reported adjusted OR (95% CI)*	Author reported interaction p-value
PROMISE trial	Index test	Male (N=NR)	16.1% (350/2168)	Any functional test: 14.0% (290/2078)	1.23 (1.04 to 1.47)	CCTA vs. any functional test: <0.001[†]
				Nuclear Stress: 16.9% (230/1362)	1.03 (0.85 to 1.25)	
				Stress Echo: 7.7% (36/465)	2.10 (1.45 to 3.04)	
				Ex ECG: 9.6% (24/251)	1.79 (1.15 to 2.80)	
		Female (N=NR)	7.9% (184/2332)	Any functional test: 11.5% (274/2388)	0.67 (0.55 to 0.82)	
				Nuclear Stress: 12.0% (205/1704)	0.66 (0.53 to 0.82)	
				Stress Echo: 7.7% (39/505)	0.90 (0.63 to 1.30)	
				Ex ECG: 16.8% (30/179)	0.39 (0.25 to 0.61)	
PROMISE trial	Index test	BMI <35 (N=NR)	12.2% (439/3589)	Nuclear Stress: 13.1% (310/2361)	NR	0.003
				Stress Echo: 7.8% (62/795)	NR	
				Ex ECG: 12.8% (47/368)	NR	
		BMI ≥35 (N=NR)	10.3% (90/872)	Nuclear Stress: 18.1% (123/679)	NR	
				Stress Echo: 7.9% (13/165)	NR	
				Ex ECG: 11.7% (7/60)	NR	
PROMISE trial	Index test	Age <65 years (N=NR)	10.1% (328/3249)	Any functional test: 11.2% (350/3129)	1.13 (0.96 to 1.33)	0.20
		Age 65-74 (N=NR)	15.2% (1553/1008)	Any functional test: 15.6% (164/1054)	1.04 (0.82 to 1.33)	
		Age ≥75 (N=NR)	21.8% (53/243)	Any functional test: 17.7% (50/283)	0.74 (0.48 to 1.15)	
PROMISE trial	Index test	With diabetes (N=NR)	14.9% (139/936)	Nuclear Stress: 17.7% (126/711)	NR	0.930
				Stress Echo: 9.2% (17/185)	NR	
				Ex ECG: 9.2% (7/76)	NR	
		Without diabetes (N=NR)	11.1% (395/3564)	Nuclear Stress: 13.1% (309/2355)	NR	
				Stress Echo: 7.4% (58/785)	NR	
				Ex ECG: 13.3% (47/354)	NR	

CCTA = coronary computed tomography angiography; CI = confidence interval; Ex ECG = exercise electrocardiography; NR = not reported; OR = odds ratio; Stress Echo = stress echocardiography.
* Adjusted for age, race, body mass index, coronary artery disease (CAD) equivalent, Framingham risk score, ASCVD score, 2011 Diamond and Forrester score, hypertension, dyslipidemia, diabetes, family history of premature CAD, sedentary lifestyle, smoking, typicality of chest pain, and physician's estimation of likelihood of significant CAD.
† All other tests: p=NR.

6.1.4.5 ICA referral

For ICA referral, there was no evidence of modification/interaction of testing by sex, race or diabetes status across two RCTs, one in stable outpatients[217,218] and the other in patients with suspected ACS[204,245,246] (Table 40).

Table 40. Subgroup analyses for ICA

Trial name	Timing	Subgroup (N)	CCTA, % (n/N)	Functional testing, % (n/N)	Author reported effect estimate	Author reported interaction p-value
PROMISE trial (Stable outpatients)	Within 90 days of index test	With diabetes (N=NR)	15.1% (141/936)	10.2% (99/972)	Adj. OR 2.12 (95% CI 1.50 to 3.00)*	0.596
		Without diabetes (N=NR)	10.9% (388/3564)	7.6% (265/3494)	Adj. OR 1.90 (95% CI 1.56 to 2.33)*	
ROMICAT-II trial (Patients with suspected ACS)	Index Visit	With diabetes (N=NR)	19% (16/86)	6% (5/87)	NR	0.06
		Without diabetes (N=NR)	9% (38/415)	8% (31/412)	NR	
	28 day follow-up	With diabetes (N=NR)	20% (17/86)	7% (6/87)	NR	0.08
		Without diabetes (N=NR)	10% (42/415)	8% (34/412)	NR	
	Index Visit	Females (N=NR)	5% (12/239)	5% (12/229)	NR	0.15
		Males (N=NR)	16% (42/262)	9% (24/270)	NR	
	28 day follow-up	Females (N=NR)	5% (13/239)	5% (12/229)	NR	0.24
		Males (N=NR)	18% (46/262)	10% (28/270)	NR	
	Index Visit	White (N=NR)	13% (44/330)	9% (30/329)	NR	0.83
		Black (N=NR)	5% (7/141)	3% (4/140)	NR	
	28 day follow-up	White (N=NR)	15% (48/330)	10% (34/329)	NR	0.68
		Black (N=NR)	6% (8/141)	3% (4/140)	NR	

ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ICA = invasive coronary angiography; NR = not reported; OR = odds ratio.
* Adjusted model controls for noninvasive testing results (positive vs. negative), sex, and age.

6.1.4.6 Revascularization

Diabetes did not modify the effect of testing on revascularization across two RCTs, one in in stable outpatients[217,218] and the other in patients with suspected ACS[245,246]. NICE classification did not modify the testing effect on revascularization in stable outpatients[5] (Table 41). Similarly there was no modification by sex or diabetes status[245,246] or NICE angina classification for the use of PCI[5] or for NICE angina classification for CABG[5] (see Appendix O).

Table 41. Subgroup analyses for any revascularization

Trial name	Timing	Subgroup (N)	CCTA, % (n/N)	Comparator (n/N)	Author reported effect estimate	Author reported interaction p-value
PROMISE trial (Stable outpatients	Within 30 days of ICA	With diabetes (N=NR)	55.7% (78/140)	Any functional test: 38.0% (38/100)	Adj. OR 1.51 (95% CI 0.65 to 3.49)*	0.372
		Without diabetes (N=NR)	49.2% (191/388)	Any functional test: 38.7% (103/266)	Adj. OR 0.95 (95% CI 0.55 to 1.65)*	
ROMICAT-II trial (Suspected ACS)	28 day follow-up	With diabetes (N=NR)	8% (7/86)	Any functional test: 2% (2/87)	NR	0.26
		Without diabetes (N=NR)	6% (25/415)	Any functional test: 4% (18/412)	NR	
ROMICAT-II trial (Suspected ACS)	28 day follow-up	Females (N=NR)	3% (7/239)	Any functional test: 1% (2/229)	NR	0.33
		Males (N=NR)	10% (25/262)	Any functional test: 7% (18/270)	NR	
SCOT-HEART, 2018 (Stable outpatients)	Median 3.2 year follow-up	NICE classification of non-anginal chest pain	2.2% (16/712)	Exercise ECG: 1.0% (14/735)	RR 1.2 (95% CI 0.59 to 2.46)	0.938
		NICE classification of possible anginal chest pain	18.7% (220/1174)	Exercise ECG: 16.5% (170/1149)	RR 1.16 (95% CI 0.95 to 1.41)	

CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ICA = invasive coronary angiography; NR = not reported; OR = odds ratio; SD = standard deviation.
* Adjusted model controls for noninvasive testing results (positive vs. negative), sex, and age

6.1.4.7 Medication use

The effect of testing on use of aspirin, statins, beta blockers or angiotensin-converting enzyme inhibitor/angiotensin receptor blockers was not modified by the presence of diabetes in one large trial in stable outpatients (Appendix O).

6.1.4.8 Administrative outcomes in patients with suspected ACS

One fair-quality RCT reported subanalyses for sex, diabetes status and race for administrative outcome. The effect of testing on these outcomes was not modified by diabetes status (Appendix O).

While sex did not appear to modify the testing effect on direct discharge from the emergency department at time of index testing or the composite of repeat ED visit or hospitalization within 28 days of index testing, sex may modify the testing effect for length of stay and hospital admission at the index visit. (Table 42). Race did not modify testing effect for any of the outcomes in the table below (see full tables in Appendix O), with the possible exception of repeat ED visit or hospitalization within 28 days of index testing, where the p-value for the interaction test was 0.049.

Table 42. Subgroup analyses for administrative outcomes

Trial name	Timing	Subgroup (N)	CCTA, % (n/N) or Mean (SD)	Any functional test, % (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
Direct ED discharge						
ROMICAT-II trial	Index Visit	Females (N=NR)	55% (132/239)	14% (33/229)	NR	0.22
		Males (N=NR)	41% (107/262)	12% (33/270)	NR	
Hospital length of stay (hours)						
ROMICAT-II trial	Index Visit	Females (N=NR)	17.0 (24.5)	30.7 (24.1)	NR	0.006
		Males (N=NR)	28.8 (44.7)	31.0 (30.9)	NR	
Hospital admission						
ROMICAT-II trial	Index Visit	Females (N=NR)	33% (14/239)	25% (57/229)	NR	0.005
		Males (N=NR)	29% (75/262)	26% (69/270)	NR	
		White (N=NR)	23% (75/330)	25% (82/329)	NR	0.31
		Black (N=NR)	18% (25/141)	26% (36/140)	NR	
Repeat ED visit or hospitalization for chest pain						
ROMICAT-II trial	28 day follow-up	Females (N=NR)	3% (6/239)	1% (2/229)	NR	0.11
		Males (N=NR)	3% (9/262)	6% (17/270)	NR	
		White (N=NR)	2% (8/330)	5% (16/329)	NR	0.049
		Black (N=NR)	4% (6/141)	1% (2/140)	NR	

ED = emergency department; NR = not reported; SD = standard deviation.

6.1.4.9 Safety

Two RCTs comparing CCTA with functional testing reported tests for interaction between subgroups for the outcome of radiation exposures (Table 43).

One large RCT in stable outpatients did not find that the effect of CCTA varied by age (<65 years vs. ≥65 years), sex, or BMI (<30 (<30 kg/m^2 vs. ≥30 kg/m^2), in patients for whom nuclear stress testing was intended at randomization. However, CTTA cumulative radiation may vary based on baseline heart rate. Patients with ≥75 bpm may have higher cumulative radiation with CCTA. In one RCT in patients with suspected ACS, radiation dose at index varied by sex as did mean cumulative radiation dose; doses were higher for men at each time period for CCTA. Mean cumulative radiation dose also varied diabetes status with patients with diabetes receiving higher doses with CCTA. The effect of CCTA on radiation dose did not vary by race.

Table 43. Subgroup analyses for radiation exposure

Trial name	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Functional Test % (n/N) or Mean (SD)	Interaction p-value
PROMISE trial	≤90 days	Cumulative radiation effective dose among those patients intended for nuclear stress testing	<65 years	12.2 (8.1) (N=2178)	15.3 (6.9) (N=2159)	0.072
			≥65 years	12.6 (8.9) (N=968)	15.0 (6.7) (N=1044)	
			Male	13.7 (9.0) (N=1452)	160 (7.4) (N=1694)	0.82
			Female	11.2 (7.5) (N=1694)	14.6 (6.3) (N=1786)	
			Not Obese (<30 kg/m2)	11.1 (8.0) (N=1556)	14.9 (6.9) (N=1537)	0.10
			Obese (≥30 kg/m2)	13.6 (8.5) (N=1570)	15.5 (6.7) (N=1638)	
			Heart rate <75 bpm*	11.9 (8.4)	15.3 (6.9)	0.042
			Heart rate ≥75 bpm*	13.0 (8.3)	15.0 (6.6)	
ROMICATT-II	Index test only	Radiation Dose During the Index Visit	Female	10.8 (8.7)	4.7 (8.1)	0.003
			Male	14.2 (11.2)	4.7 (8.7)	
	28 days	Mean (SD) cumulative radiation dose (mSv)	Female	11.0 (8.9)	6.0 (8.2)	0.002
			Male	14.7 (12.0)	5.6 (10.7)	
			With diabetes	18.4 (14.7)	6.6 (10.4)	0.04
			Without diabetes	13.4 (9.8)	5.1 (9.5)	
			White	Median (IQR) 12.0 (7.9	Median (IQR) 0.0 (0.0 to	0.60

Trial name	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Functional Test % (n/N) or Mean (SD)	Interaction p-value
				to 17.2)	12.4)	
			Black	Median (IQR) 11.7 (8.6 to 16)	Median (IQR) 0.0 (0.0 to 0.0)	

CCTA = coronary computed tomography angiography; IQR = interquartile range; NR = not reported; SD = standard deviation.
* Baseline resting heart rate was recorded at the enrollment physical examination.

6.1.5 Key Question 5: Cost-Effectiveness

Economic studies identified for inclusion primarily compared combinations of testing strategies involving CCTA, stress nuclear imaging (primarily SPECT), stress echocardiography, exercise ECG treadmill testing and invasive coronary angiography, with only few directly comparing one specific test to another. Only full economic studies that compared a test with one or more tests or strategy of no testing and evaluated cost-effectiveness based on hard clinical outcomes and reporting on cost per QALY (ICER) or cost per correct diagnosis or cost per life saved, were included. A total of three systematic reviews[243,249,263] and 11 primary studies were included. Eight of the studies (in nine publications) were in stable outpatients with suspected CAD,[8,26,27,91,116,123,136,147,162] and three were in patients with suspected ACS.[82,196,197] Of these, two studies in stable outpatients[123,162] and three studies in patients with suspected ACS were conducted in the United States.[82,196,197] Industry funding was noted and/or author ties to related industries were described in three studies.[82,123,162] Studies reporting changes in risk as the benefit to testing, those comparing different pharmacologic stressors or older versus newer technology were excluded. No full economic studies specific to stress PET imaging were identified.

Full economic studies of diagnostic testing are complex, challenging to perform and challenging to interpret. A variety of assumptions and estimates from diverse sources (which may vary in quality) provide input into any economic model and impact the results of that model. There are a number of additional factors that need to be considered in modeling of the cost-effectiveness of diagnostic testing.[68,131,179,203] Such factors include: the disease prevalence in the population, the pre-test likelihood of disease and spectrum of disease in patients included in the testing strategy (and model estimates), the diagnostic accuracy of index tests, the role of indeterminate tests and follow-up of false positives, consideration of the role of a given test (e.g., as a triage test, add-on test), whether tests are sequential (in what sequence and what is the impact of this on accuracy), the clinical decision-making leading to additional testing or treatment based on test results, treatment options and their impact on patient outcomes. Diagnostic testing's impact on patient clinical outcomes (e.g., MI) is **indirect.** Such outcomes are impacted by the clinical decisions made about treatment(s) and the effectiveness of the treatments. The estimates of treatment provision, adherence and success may be challenging to model and impact the results of any model.

For the diagnosis of CAD specific factors related to the above should be considered when putting the results of cost-effectiveness studies for non-invasive imaging for CAD into context. First, there are multiple scenarios and options for non-invasive testing including index tests, follow-up testing and the sequence of testing in both clinical practice and as recommended by ACC/AHA clinical guidelines. Thus, modeling of a given sequence or pathway may or may not be generalizable to different settings and accuracy of testing in sequential testing may be different from stand-alone testing. A proportion of all non-invasive imaging tests, particularly in low-risk patient populations will be false positives and a proportion of tests will be indeterminant; both situations may require additional testing. Similarly, some tests, particularly CCTA may reveal incidental findings that may or may not require follow-up. The impact of the above on both cost and effectiveness was generally not modeled. The historic "gold standard" for evaluating accuracy of cardiac diagnostic testing has been ICA, however, as described elsewhere, its accuracy is not 100% as assumed in the models. In addition, CCTA as an anatomic test may show better accuracy than functional tests as ICA alone does not provide functional information. As noted in the background, an observation of vessel obstruction does not always correspond to either symptoms or diminished function. Some tests are operator-dependent and/or require special expertise for performance and/or interpretation. This is difficult to model. Finally, various assumptions regarding the effectiveness of treatment were employed across models.

Summary of results:

Most economic models described in the systematic reviews and the primary studies compared testing strategies (i.e., different scenarios for index test and subsequent sequential tests) not individual tests, making it difficult to draw definitive conclusions for specific tests. The results below attempt to focus on findings for specific tests. Variation across studies in data sources, estimation of model parameters, clinical pathways for test sequencing and decision making leading to additional testing and/or treatment make comparison across studies challenging. Evidence was mixed for demonstrating a definitive cost-effective diagnostic approach.

- Results across studies (including systematic reviews) were somewhat mixed.
- Cost-effectiveness and ICERs varied based on testing sequencing, pre-test likelihood of CAD, assumed accuracy of tests across populations. These key drivers were also identified in the prior HTAs.
- In stable outpatients with suspected CAD
    - The U.S. studies generally found CCTA to be the dominant initial testing strategy against comparators/other strategies, which included ICA and functional tests. FFRct in addition to CCTA was consider cost-effective in one industry-funded study.
    - Stress echocardiography and SPECT were found to be cost-effective compared to ICA.
    - Two systematic reviews suggest that stress echo or nuclear stress testing may be more cost-effective than comparators in some settings depending on patient prior probability of CAD and prevalence of CAD. Stress echo may be more cost-effective than SPECT in patients with low to intermediate probability.
- In patients presenting with suspected ACS in an emergency setting

  - CCTA was compared with standard of care (variably defined), ETT, expert consensus based on ACC/AHA guidelines and "do nothing" strategies. CCTA was the dominant or cost-effective approach in most all comparisons.
  - In one poor-quality review of seven studies in patients with acute chest pain. Stress nuclear testing was cost-effective versus traditional strategies involving ECG. However, authors note that stress nuclear testing in the acute setting may not often used in 'real life', due to logistical challenges.
- Common limitations across studies include
  - The assumption that ICA has 100% sensitivity and specificity.
  - Extrapolation of data to lifetime time horizon particularly when RCT data is only available for approximately 2 years for many of the studies. Results from short-term time horizons may differ from those seen at longer term.
  - Lack of or insufficient modeling of indeterminate tests, false positive and false negative results, accuracy based on sequencing of tests, potential adverse events and incidental findings.
  - Some modeled strategies (e.g., some "do nothing" strategies) may not be consistent with clinical practice. Modeling of appropriate "no test" strategies was not done.
  - Models assume the availability of all tests and competence in performing and interpreting them across clinical settings.
  - Lack of information on the potential impact of radiation exposure for index and downstream testing.

Detailed results

6.1.5.1 Outpatients with Stable Chest Pain

The cost-effectiveness of using coronary CT angiography (CCTA), stress nuclear imaging and stress echocardiography (ECHO) for the diagnosis of CAD was considered. A total of three systematic reviews[243,249,263] and eight primary economic studies (in nine publications) met the inclusion criteria.[8,26,27,91,116,123,136,147,162]

Evidence was mixed for demonstrating a definitive cost-effective diagnostic approach; however, multiple studies report common findings and indications for cost-effective alternatives while also delineating areas for further research. Table 44 provides an overview of primary findings.

Eight studies of patients with stable chest pain that analyzed the cost-effectiveness of CCTA, ECHO and SPECT against various comparators (including ICA, ETT and "no imaging") met the inclusion criteria.[8,26,27,91,116,123,136,147,162] The Quality of Health Economic Studies (QHES) instrument was used to systematically assess the quality of each study. Scores ranged from 50 to 94 out of 100. Data for clinical parameters based on government funded clinical studies in some reports. The funding support from government agencies was reported for some studies or in two cases was not reported.[91,116] Of the

remaining six, three appear to have had at least partial industry funding and/or author ties to industry.[82,123,162]

Generally, six of the seven studies that investigated CCTA reported it to be a cost-effective, if not the dominant strategy, against various comparators including ETT and ICA.[8,26,27,123,136,147,162] Of the four studies that reported results for stress ECHO versus ETT or ICA,[26,27,116,147,162] three studies indicated that stress ECHO was the cost-effective approach.[26,27,147,162] In each case, for both the CTTA and ECHO comparisons, the contradicting results came from the same study and that study notably had the lowest QHES score. In general, when SPECT was compared with ICA it was found to be cost-effective, however, CCTA tended to be the preferred alternative. Beyond the base-case results, the primary drivers of cost-effectiveness were the pretest likelihood of CAD, test accuracy and how post-test care was defined. Increasing the prior probability of CAD or lowering a test's accuracy generally caused less favorable ICER. Administering more aggressive post-test care also tended to decrease a test's cost-effectiveness. Detailed data abstraction is found in Appendix K.

Many of the primary studies reviewed drew attention to the large number of influential variables and the intricacy of modeling the cost-effectiveness of diagnostic testing. Consequently, the optimal strategy remained difficult to define. There were several notable limitations that further complicated a conclusive strategy. A high level of variability within studies, as well as between studies, led to uncertainty, which often failed to be thoroughly analyzed in a comprehensive sensitivity analysis. The majority of studies used a model based on a "payer" perspective rather than a more complete societal perspective. A common assumption made to facilitate the analysis was to grant ICA 100% sensitivity and that all positive diagnostic tests resulted in ICA. Studies generally did not consider modeling the impact of indeterminate tests or follow-up of false positive results. Furthermore, some studies had short time horizons or were underpowered to detect significant results. Given that the majority of the studies reviewed were performed outside the United States, the implementation of testing, care provided and relative costs were prone to variability.

Systematic reviews

Three systematic reviews investigated the cost-effectiveness of diagnostic testing for CAD.[243,249,263] Two of the reviews were very poor quality and were narrative in nature.[243,263] They will be only briefly described. The findings of which were consistent with the majority of individual, primary studies reviewed.

The most comprehensive systematic review by van Waardhuizen et al. 2016 included 70 economic studies published between January 1995 to December 2015 (20 years).[249] Confidence in this review was considered moderate based AMSTAR-2 appraisal. Some studies in this review were published prior to the previous HTAs and assumed to have been considered in them. Thirteen studies from our search were included in this SR and will not be described individually. They are listed in Appendix K with the data abstraction. Authors critically appraise included articles; 54% were considered to be at high or moderate risk of bias. Heterogeneity prevented the authors from completing a quantitative meta-analysis. Overall, in patients with low to intermediate prior probability, the optimal diagnostic imaging strategy from a cost-effectiveness perspective was not definitive. However, collectively the studies

revealed several patterns that led the reviewers to conclude that CCTA may be the best as an initial "gatekeeper" test for patients with stable chest pain and low-to-intermediate likelihood of CAD. van Waardhuizen et al. further went on to suggest that ECHO or SPECT to be cost-effective strategies if functional testing is needed in patients with an intermediate prior probability of CAD. When compared directly, ECHO was considered cost-effective versus SPECT in patients with low to intermediate probability. An in-depth assessment of the sensitivity analyses carried out in the 70 studies reviewed highlighted the primary factors determining the cost-effectiveness of the tests. The most common influencing factor was the prior probability of CAD. Of the 51 sensitivity analyses, 26 of them indicated the prior probability of CAD as the most important influence. Testing sensitivity was the next most frequent factor followed by the cost of the diagnostic test, particularly the cost of CCTA testing. In addition to identifying the drivers of cost-effectiveness, the reviewers also noted that many of the studies exhibited similar limitations, which also appeared in the individual studies reviewed here. The main limitation was the heterogeneity of the studies, the range of assumptions and variability of input parameters of the models. Next, the diversity of the country of origin of the studies often made direct comparisons unfeasible (only 13 of the 70 were performed in the U.S. or Canada). Furthermore, the perspectives (healthcare payer or healthcare provider) of many of the analyses were too limited in scope to make fully informed decisions. Short-term time horizons and not reporting the willingness-to-pay threshold were other common limitations.

Another poor-quality systematic review by Zeb et al 2014 looked at the cost-effectiveness of only CCTA and included 42 articles with the goal of assessing CCTA as a "gatekeeper" to ICA.[263] Although authors report a systematic approach to searching for economic studies, inclusion/exclusion criteria were vague, and neither a full list of included studies nor a list of excluded studies with rationale was provided. The narrative description of selected studies and summary tables do not account for all 42 articles. No critical appraisal of individual studies was done and limited data on cost-effectiveness parameters (e.g. ICERs) were provided. Confidence in this review was considered critically low based on AMSTAR-2 appraisal. It is not clear that all studies were full economic studies. Of the 42 articles, 20 looked at CE of CCTA and subsequent downstream testing in stable chest pain patients, 18 articles in patients with acute chest pain presenting to ED and 4 at the cost-effectiveness of CACS as an initial test. The authors found the optimal strategy was dependent on CAD prevalence. CCTA was cost-effective when CAD prevalence was assumed to be between 10% to 50%. When CAD prevalence exceeded 70% ICA was cost-effective.

A third poor-quality review focused on evaluation cost-effectiveness of nuclear stress testing in both patients with stable chest pain, described below and patients presenting with acute chest pain which are discussed with the primary studies for this population.[243] Although authors report using a systematic approach to searching for economic studies, many components of the systematic review were not described, and critical appraisal of individual studies was not done. It was more narrative in nature. A total of 57 studies were reportedly included, however formal lists of included and exclude studies were not provided. Confidence in this review was considered critically low based on AMSTAR-2 appraisal. This is the only review to focus on cost-effectiveness of nuclear stress testing (MPI with SPECT or PET). The review reports findings for three comparisons with MPS in patients with stable chest pain; ETT, ICA and other noninvasive tests. When comparing MPS versus ETT the review assessed 25 studies and found MPS to be more cost-effective than ETT in patients with intermediate likelihood of CAD. The review

included one study that compared initial MPS with selective ICA and direct ICA. MPS reduced the number of ICA by 30% to 41%. MPS was cheaper and equally effective when compared with strategies not using MPS. Lastly, the authors compared MPS with other noninvasive tests. 16 complete studies were included along with four ongoing studies. The results of the cost-effectiveness of MPS over other non-invasive tests, such as CTCA, stress echocardiography, PET, and CMR were conflicting and inconclusive. In patients with suspected stable CAD, ETT was found to be cost-effective as a first line test in patients with low likelihood. However, at higher pretest likelihoods, non-invasive imaging including MPS is more cost-effective than ETT due it its increased accuracy. Overall, MPS was a cost-effective gatekeeper to ICA.

Individual primary studies published subsequent to prior reports and systematic reviews

The individual, primary cost-effectiveness studies, not already included in the systematic reviews, had comparable findings. Two high-quality studies based in the United States were identified. Because of their more direct relevance to this HTA, they will form the focus of the results below. Additional data from these studies and studies outside of the U.S. are found in Appendix K. A summary of the primary findings for all studies in Table 44.

US-Based Studies

Two high-quality studies based in the United States published subsequent to the van Waardhuizen 2016 review are described below.[123,162]

Karady et al. 2020[123]

Overview and Design:

A high-quality study of low-risk, stable chest pain patients that compared CCTA and CCTA combined with CT-derived FFR (FFRct) with functional tests, primarily SPECT as initial tests for diagnosis of CAD A Markov decision-analytic model was populated based on observed outcomes from the PROMISE trial was used as a primary source to simulate changes in health states over time. PROMISE data were combined with assumptions from clinical guidelines, registry data and other sources regarding referral for ICA and treatment options (e.g., medication, PCI) as well as the progression of obstructive and nonobstructive CAD. Data were collected at 6 months and 2 years and costs for testing and subsequent procedures, including ICA with or without revascularization, were recorded. ICERs were calculated for a lifetime time horizon with costs discounted at a rate of 3% to 2014 USD. A societal perspective was stated, however data on indirect costs and other factors usually considered in such analyses were not described; only cost of care appears to have been delineated. Pre-planned subgroup analyses were done based on age and sex. Sensitivity analyses included a probabilistic sensitivity analysis as well as a number of one-way sensitivity analyses ranging from gender to adherence to statin therapy. Authors considered adherence to medical therapy in their modeling. Authors validated their model by comparing it to outcomes as reported in the PROMISE trial through its 2-year follow-up. This economic study was industry-funded (HeartFlow) and multiple authors report relationships with industries related to this study. The PROMISE trial was government-funded. The study scored 90/100 using the QHES.

Key Assumptions:

A mean 53.3% pretest likelihood of CAD was incorporated into the model with an average patient age of 60-years-old; 52.7% of the patients were female and 77.7% white. Diagnostic sensitivity of ETT, CCTA and SPECT were 45-50%, 95-99% and 63-87% respectively while specificity was 85-90%, 64-83% and 63-87% respectively. 25.3% of the sample population had a CAD risk equivalent and 67.6% of patients had a 10-year risk of events of at least 7.5%. FFRct was reportedly done in 31.4% of patients who had 30% to 69% stenosis on CCTA. Models assumed that CCTA and CCTA with FFRct led to more effective selection of patients for ICA and that higher costs for CCTA with FFRct were offset by lower rates of ICA and revascularization compared with CCTA alone.

Results:

Based on a lifetime time horizon, CCTA was considered cost-effective compared with functional testing as an initial testing strategy with an ICER of $2743/QALY at willingness to pay of $100,000/QALY. Although the CTTA strategy cost was higher ($8636, 95% CI $8652 to 8713) compared with functional testing ($7989, 95% CI $7959 to $8020), QALYs/patient were higher for CCTA (25.16) than those for functional testing (24.68). Modeling of the CCTA plus FFRct strategy resulted in lower costs ($7222, 95% CI $7192 to $7252) than either CCTA alone or functional testing with a QALY/patient similar to CCTA alone (25.14). This strategy dominates functional testing based on the assumption the higher cost for the combination of CCTA and FFR were offset by fewer ICA and revascularizations and higher QALY. The difference in life-years gained between CCTA (or CCTA with FFRct) compared with functional testing was approximately one-half year favoring CCTA

The ICERs ranged from $1900 to $3500/QALY when employing a probabilistic sensitivity analysis and CCTA remained cost-effective across genders and when accounting for declining adherence to statin therapy. Despite anatomic approaches having higher costs at both 2 years and 5 years, and also having higher rates of ICA and revascularization, the author's model suggests that the additional 45 days of good health gained led to the anatomical tests' cost-effectiveness. Modeling over a patient's lifetime a total of 6 months of good health were gained. The models in this cost-utility analysis for CCTA and functional strategies differ in the proportion of patients requiring additional downstream testing. Meta-analyses across RCTs in this HTA suggest that referral for ICA was associated with CCTA and an initial test but that there were no differences in the use of additional non-invasive testing between CCTA and functional testing strategies.

Driving these improved outcomes was the assumed overall better diagnostic accuracy for obstructive and nonobstructive CAD, which led to greater statin use for those in the anatomic group versus the function group 85.4% and 67.0% respectively. CCTA continued to be cost-effective in both women and men as well as in both older and younger patients (ICER range, $1912/QALY for women to $3559/QALY for men). CCTA FFRct combined with CCTA was cost-effective in men (ICER, $192/QALY) and dominant for all other subgroups explored.

Authors also report sensitivity analysis involving a "do nothing" strategy in which only medical therapy is provided based on their risk-factor profile. As one would expect, the "do nothing" strategy had the lowest costs associated with it and also yielded the fewest quality adjusted life years when compared

with the other strategies. All other strategies were considered to be cost-effective with a willingness to pay of $100,000. CCTA, CCTA FFRct, and the functional strategies had ICERs relative to the "do nothing" strategy of $59,436/QALY, $36,968/QALY, and $99,678/QALY respectively.

Limitations:

Assumptions regarding diagnostic accuracy were an essential element to the model results, however, uncertainty surrounding these assumptions was a limitation for this study. Furthermore, the authors note gaps in how major adverse cardiovascular events were accounted for and the extent of the effects of medical therapy. Author's objective was to model the cost-effectiveness of patients at low risk of CAD. The population modeled had a substantial cardiovascular risk factor burden and estimated pre-test likelihood of obstructive CAD of 53.3%; it is unclear if results may apply to patients with lower pre-test risk. Modeling of the CCTA strategy appears to assume that only SPECT is used for additional testing in patients with a moderate abnormality on CTTA. Given that costs for stress echocardiography may be less than for SPECT, the impact of modeling of stress echocardiography (and or ETT) may be important to consider. Currently, FFRct is not routinely performed and requires special analysis methods based on CT data. Its role, accuracy and value do not appear to be widely established yet and high-quality evidence of impact on clinical outcomes is sparse.[100] Another potential bias exists when comparing CCTA plus FFRct as some patients were unable to receive FFRct causing a potential imbalance in baseline characteristics across the two groups. Two years of results from the PROMISE trial were available; the model extrapolates to a lifetime. Lastly, the grouping of various functional tests and presentation of results made it difficult to make direct comparisons between specific tests.

Min et al. 2017[162]

Overview and Design:

A well-conducted, but complex study of stable CP patients that explored twelve testing pathways and reported results assuming multiple levels of CAD prevalence. CCTA, ECHO and stress nuclear testing (MPS) were measured against ETT and ICA (among other comparisons). Primary sources for clinical components were from published literature. For modeling treatment, data based on the COURAGE and SYNTAX RCTs were used. The study partially funded by industry, a cardiac imaging institute and reports on data from government-funded research. The lead author reports receiving support from industry. Sensitivity analyses include varying pretest likelihoods from 20% to 50% and to 80% as well as varying post-test treatment plans. A Markov model was used to estimate the costs and assess each test's impact on patients' quality of life from a payer's perspective. The time horizon of the model was over a patient's lifetime. All costs were discounted at a rate of 3%, however, the costing year was not reported. Incremental cost-effectiveness ratios were the primary cost-effectiveness outcome measure. The study scored a 94/100 using the QHES. Funding for this economic study is somewhat unclear; clinical data appear to come from government funding sources. Other funding listed includes the Dalio Institute of Cardiovascular Imaging and an unrestricted educational grant from GE.

Key Assumptions:

The study population consisted of patients of intermediate risk but no prior CAD. A hypothetical cohort of 55-year-old males was considered in the model. The diagnostic sensitivity of ETT, CCTA and ECHO were modeled as 68.0%, 93.7% and 86.7% respectively and specificity ranged from 77% to 84%. Authors provide thresholds for test positivity and categorization of disease. ETT was assumed to be indeterminate 62% of the time while CCTA and ECHO were assumed to be indeterminate in 7% of the tests and depending on the strategy, were referred for either additional downstream non-invasive testing or ICA. All positive test results from noninvasive tests were referred for ICA.

Results:

While the authors found that overall, in patients without known CAD presenting with stable chest pain, a sequence of imaging tests to be the most cost-effective (ETT, followed by ECHO, followed by ICA), they further found that at 20%, 50% and 80% pretest likelihood of CAD an ICER that favored CCTA, ECHO and MPS over ICA given a WTP of $100,000 per QALY. At higher pretest likelihood ICA yielded a marginally greater number of QALY, however, ICA's higher cost led to exorbitant ICERs ranging from $906,222 up to $3,857,303.

Relative to other studies, the QALYs reported were markedly similar. Of the 12 strategies tested in the primary analysis, the largest change in effectiveness was 0.0238 QALYs (or about 9 days) over the course of a lifetime time horizon while many comparisons had effectiveness results of less than a day of good health separating them over a lifetime. This meant that it was predominantly the difference in cost that drove the cost-effectiveness between strategies. In the primary analysis with 20% pretest likelihood CCTA was found to cost $12,274 yielding 16.1283 QALYs, ECHO $11,356 with 16.1097 QALYs and MPS $11,798 with 16.1073 QALYs. While over a lifetime time horizon ICA costed $14,003 generating 16.1205 QALYs

This study also investigated the role of varying post-test care as part of the cost-effectiveness modeling. Given the long-term time horizon, slight variability in assumptions regarding the type of care showed a significant impact on both costs and effectiveness. Min et al. report that the cost-effectiveness of each test depends largely on patient characteristics and how treatment approaches are tailored to patient care based upon test findings. Therefore, in addition to the base-case analysis, they also report results for "conservative" post-test care (defined as medical therapy alone for patients with 1–2 vessel CAD and PCI for all patients with 3-vessel or left main CAD) and "aggressive" post-test care (using PCI for all patients with 1–2 vessel CAD and coronary artery bypass surgery for all patients with 3-vessel CAD). When comparing CCTA versus ICA, CCTA changes from being the dominant strategy in conservative cases to ICA being cost-effective with an ICER of $17,173 when more aggressive treatments are employed. Varying post-test treatment approach showed cost-effectiveness contingent on follow-up care post-test. The authors discuss how this serves to underscore the complexity of evaluating the cost-effectiveness of diagnostic testing.

Limitations:

A potential limitation of this study was that all positive diagnostic tests resulted in ICA, which was assumed to have perfect sensitivity and specificity. The impact of false-positive tests was not modeled. It

appears that positive tests at any stage were referred to ICA, including false positives. Authors left some ambiguity surrounds how patients transition between health states within the model. Limited data for some sensitivity analyses were described. PET was not considered in any testing strategy. It remains unclear how reliably or appropriately the sources used for the model inputs can be extended over the course of the model's lifetime time horizon. Additionally, the sensitivity analysis was limited in scope and did not fully explore potential biases or discuss in detail its own potential limitations.

Studies based outside of the U.S.

In addition to the two studies conducted in the United States six international studies not included in the van Waardhuizen systematic review were identified. Three of these were based in Europe and the remainder was comprised of a diverse geographic, socio-economic range from South Korea, Brazil and Iran. Given the differences in healthcare systems between the US and other countries, these studies will only be briefly summarized. Additional detail is found in Appendix K.

Agus et al. 2016[8]

A study conducted alongside an RCT in Northern Ireland and it investigated the cost-effectiveness of CCTA vs ETT. (QHES 64) CCTA was found to be the dominant strategy for patients when a pretest likelihood of less than 30% was assumed. As the pretest likelihood increased to 30%-60% and then above 60% the ICER increased to £2820 and £24106 respectively still suggesting CCTA to be a cost-effective approach with a willingness to pay of $50,000.

The interpretation of the final results was made difficult because the baseline characteristics across groups were different. Notably, there was imbalanced CAD prevalence across groups, which has been seen as a driving factor for cost-effectiveness in the other studies. Missing data was also an issue when building the model and determining the input parameters. Beyond that, the outcome assessment was not fully blinded from investigators. Also, the sample population excluded BMI greater than 35% and included a low number of diabetic patients. Therefore, it may not be a representative sample. Lastly, the study had a relatively short follow-up time and may not have allowed for all costs and outcomes to occur.

Gurunathan et al 2018[91]

This study was also conducted along with a RCT. It was a relatively poor-quality study (QHES 50/100) carried out in the UK, evaluated the predictive value and costs of stress ECHO and ETT. Its measure of cost-effectiveness was a simple sum of costs and a comparison of the positive predictive value of each test. Authors found ECHO to have a 20% reduction in cost and less downstream testing, hospital visits. ETT yielded a 64% positive predictive value in determining a flow-limiting disease on angiography. Meanwhile, ECHO achieved 100% positive predictions. The cost of ECHO and ETT were £631 and £796 respectively.

A significant limitation from the outset for this study was that it was underpowered to detect most clinical outcomes. It also used an overly simplistic analytic model in which it did not validate or pursue any subgroup or sensitivity analyses.

Lorenzoni et al. 2019[147]

A moderately well-conducted (QHES 84/100) Italian study evaluated several testing strategies. The primary results showed CCTA to be cost-saving and more effective versus no imaging with a negative ICER of -€796.85/diagnosis. ECHO and SPECT approaches were both found to be a less expensive alternative but yielded fewer correct diagnoses.

Heterogeneity in data relating to sourcing from multiple countries with variation in practices and costs was an issue in this study. It also unrealistically assumed that anyone not receiving ICA was a true negative test result. Adding to that, authors also assumed perfect accuracy of ICA.

Bertoldi et al. 2016/2017[26,27]

A Brazilian study where CCTA appeared to be a cost-effective approach for CAD in this well-conducted study (QHES 94/100). Its measure of cost-effectiveness was both the cost per diagnosis and the ICER. CCTA was found to costs $750/diagnosis and $3100/QALY when compared with ETT. ECHO was found to cost $623/diagnosis. SPECT testing strategies were dominated by the other test options. Additionally, sensitivity analysis showed that procedural costs and test sensitivity were significant factors in determining cost-effectiveness.

Many of the potential comparisons were not reported. Furthermore, the authors assumed ICA to have 100% sensitivity and specificity.

Lee et al. 2015[136]

A moderately well-designed study (QHES 77/100) conducted in South Korea that explored the diagnostic accuracy of CCTA and SPECT followed by a brief cost-utility analysis. Its measure of cost-effectiveness was a cost per correct diagnosis. CCTA was shown to be the more accurate, effective and less expensive alternative in the majority of cases. Therefore, CCTA dominated SPECT. For every 1000 patients, CCTA accurately diagnosed 835 while SPECT accurately diagnosed 779 patients. Subgroup analysis by pretest likelihood showed SPECT to perform slightly better with lower pretest probability but CCTA remained cost-effective with the most accepted willingness to pay thresholds.

The baseline characteristics of groups were different, which causes results difficult to interpret. For instance, the SPECT group had significantly older and had a higher pretest likelihood probability. There were also issues with procedural implementation. The CCTA data derived from 2006 when techniques may not have been as developed in Korea.

Jafari et al. 2020[116]

A relatively poorly conducted study (QHES 62/100) conducted in Iran compared several testing options including CCTA, ECHO and SPECT against ETT and ICA among others. It reported its results against a strategy using a combination of tests (that it had found to be optimal). Results reported here are individual testing strategies with stand-alone ETT and ICA testing. The cost-effectiveness measure reported was the cost per diagnosis. In general, it found ETT and ICA to perform better than CCTA and ECHO. With SPECT being slightly more costly but more effective than ETT yielding a small ICER of

$46.74/diagnosis. CCTA and ECHO were both dominated by ETT while SPECT vs ETT costed $46.74/diagnosis (SPECT was more costly but more effective). ICA was more costly but also more effective than all other strategies. Authors reported when compared with CCTA, ICA costed $13.00/diagnosis and when compared with ECHO, ICA costed $12.07/diagnosis.

The cost data used in this study seems difficult to reconcile to a US setting. Furthermore, there was poor description of patient characteristics with no reporting of demographic information or CAD pretest likelihood. It was also assumed ICA 100% sensitive. Lastly, given the uncertainty involved in the results the sensitivity analysis was very limited.

Table 44. Overview of reported cost-effectiveness (CE) stratified by pretest likelihood, stable CP, assuming a willingness-to-pay WTP of $100,000

Pretest Risk %	Origin	CCTA	ECHO	SPECT
<30%	USA	Min 2017 CCTA dominates ICA	Min 2017 ECHO is CE vs ICA	Min 2017 MPS is CE vs ICA
	Foreign	Lorenzoni 2019 CCTA dominates "no imaging" Bertoldi 2017 CCTA $1420/diagnosis vs ETT Jafari 2020 ETT dominates CCTA Lee 2015 CCTA dominates SPECT	Lorenzoni 2019 ECHO costs €3316/diagnosis vs. "no imaging" Bertoldi 2017 ETT dominates ECHO Jafari 2020 ETT dominates ECHO	Lorenzoni 2019 SPECT costs €2111/diagnosis vs. "no imaging" Bertoldi 2017 CCTA, ECHO dominated SPECT Jafari 2020 SPECT costs $46.74/ diagnosis relative to ETT SPECT costs $11.51/diagnosis relative to ICA
30-60%	USA	Min 2017 CCTA is CE vs ICA Karady 2020 CCTA costs additional $2743/QALY vs. functional tests	Min 2017 ECHO is CE vs. ICA	Min 2017 MPS is CE vs. ICA

Pretest Risk %	Origin	CCTA	ECHO	SPECT
	Foreign	Agus 2016 CCTA dominates ETT Bertoldi 2017 CCTA costs $3100/QALY ($750/diagnosis) vs. ETT	Gurunathan 2018 ECHO dominates ETT Bertoldi 2017 ECHO costs $623/diagnosis vs. ETT	Bertoldi 2017 CCTA, ECHO dominated SPECT Lee 2015 SPECT costs additional $88740/QALY vs. CCTA
>60%	**USA**	Min 2017 CCTA is CE vs. ICA	Min 2017 ECHO is CE vs. ICA	Min 2017 MPS is CE vs. ICA
	Foreign	Bertoldi 2017 CCTA $790/diagnosis vs ETT Lee 2015 CCTA dominates SPECT	Bertoldi 2017 ECHO costs $890/diagnosis vs. ETT	Bertoldi 2017 CCTA, ECHO dominated SPECT

CCTA = coronary computed tomography angiography; CE = cost-effective; ECHO = stress echocardiography; ETT = exercise treadmill test; ICA = invasive coronary angiography; MPS = myocardial perfusions scan; QALY = quality-adjusted life years; SPECT = single photon emission computed tomography.

6.1.5.2 Patients with suspected ACS (Acute Chest Pain)

One poor-quality review[243] and three US-based economic studies[82,196,197] evaluated the cost-effectiveness of various imaging strategies in patients with suspected ACS or acute chest pain presenting to an emergency department or observational unit.

One systematic review focused on evaluating the cost-effectiveness of nuclear stress testing in both stable chest pain, (described above) and patients presenting with acute chest pain which are discussed here.[243] Authors report that MPI was evaluated in 7 studies of patients with acute chest pain. The review found that MPS was cost-effective when compared with traditional strategies involving ECG. However, authors note that MPS in the acute setting is not very often used in 'real life', due to logistical challenges.

Primary studies published subsequent to prior reports and systematic reviews

Three primary economic studies evaluated testing strategies for patients in emergency departments or observatory units were include and are described below.[82,196,197] Their QHES scores ranged from 69 to 90 out of 100. Table 45 provides an overview of primary findings.

Goehler 2020[82]

Overview and Design:

A study using a well-constructed model of short, intermediate and long-term cost-effectiveness carried out in the United States. CCTA performance was analyzed against three strategies: standard of care, expert consensus following AHA/ACD guidelines and expedited ED discharge with further testing done in an outpatient setting. A Markov model was used to model the cost-effectiveness of the interventions over time. The hypothetical cohort was designed drawing primarily from finding of the ROMICAT II trial, which was subsequently validated using the same trial. Utility values for various chest discomfort classifications were derived from published literature. Initial cost data came from a micro-costing assessment at each ROMICAT-II clinical site while outpatient costs were based on Medicare reimbursements. Long-term cost approximations came from RedBook. Authors assessed outcomes at 28 days, 1 year, 3 years, 10 years and overall lifetime of patients. The primary outcome measure was the ICER for each strategy. Though not explicitly stated, the perspective assumed was most consistent with a payer's perspective. Costs were discounted at a rate of 3%, however, the costing year was not clearly stated. The trial data used to for the model's parameters ended in 2012 USD. Funding came from grants provided by National Heart, Lung, and Blood Institute, National Institute of Health and the American Heart Association, however, authors also report ties with related industry (imaging companies). Sensitivity analyses looked at varying medical compliance over time and tested the confidence interval bounds of relative risks across interventions. Testing diagnostic sensitivity and specificity were also varied and ICERs recalculated. The study scored 90/100 using the QHES.

Key Assumptions:

A population of emergency department patients with suspected ACS was considered with a mean age of 54.2 years and 53% male. Patients comprised of low-intermediate risk of ACS having an average of 7.5% prevalence of ACS. Diagnostic sensitivity ranged from 85% to 100% while the specificity varied from 50% to 100%. Baseline characteristics of the hypothetical cohort assumed 50.7% of patients had no CAD, 43.0% of patients had non-obstructive CAD and 6.3 presented obstructed CAD.

Results:

Short-term results found CCTA to be both more costly and required more revascularization procedures than all other comparators. Notably, revascularization rates for CCTA were 5.2% versus 2.6 to 3.7% for other strategies. However, in the long-term model, CCTA became cost-effective. Lower mortality (5.06% for CCTA versus 5.21% to 5.36% for other strategies after 10 years) led CCTA to dominate standard of care and ACC/AHA guidelines and have an ICER of $49,428/QALY when compared with expedited ED discharge. CCTA was the most effective at identifying obstructive CAD (98% accurate), followed by

expert consensus (75%) and standard of care (69%). Expedited discharged was only 46% accurate at identifying obstructive CAD. Initial costs found CCTA was the most expensive at $2,692. Standard of care costed $2,535, expert consensus following AHA/ACD Guidelines costed $2,501 while expedited ED discharge was the least costly at $1,891. Extending the horizon over the patient's lifetime the total costs for CCTA was $4,490, which resulted in 23.09 QALYs. Expedited ED discharge with OP testing was again the least expensive costing $2,513 and generating 0.07 less QALY than CCTA. Standard of Care and expert consensus were in the middle) $4144 with 23.09 QALYs and $4064 with 23.06 QALYs respectively). Therefore, over a lifetime time horizon, CCTA dominated standard of care and expert consensus following AHA/ACD Guidelines. Furthermore, CCTA was cost-effective against expedited ED discharge with OP testing with an ICER of $49,428/QALY.

Letting the relative risk decrease by 0.18 to the lower bound of the confidence interval caused the ICER to increase to $60,000. Decreasing medical compliance increased the ICER of CCTA to $78,500/QALY. Follow-up with a cardiologist was found to be 37% for those that were discharged expeditiously. If a rate of 50% is assumed for cardiologist follow-up the ICER falls to approximately $34,000/QALY. Varying tests' sensitivity and specificity caused the ICER to range from $46,000 to $70,000.

Limitations:

While overall well conducted, there were some limitations. Pretest likelihood of CAD is often a major determining factor to a test's cost-effectiveness. The authors did not incorporate that key aspect. Also not included in the model were repeated visits to the emergency department or the cost of litigation for missed detection of CAD. Additionally, some model input parameters were sourced from older studies which may not reflect current healthcare settings. With regards to presenting the results some useful information was not included such as what scope of the perspective assumed and the costing year that estimates were discounted to.

Powell et al. 2012[196]

Overview and Design:

A moderately well-conducted study comparing CCTA, standard of care and "do nothing" strategies in an observation unit setting. A decision-analytic model was used. The patient population and the strategies' characteristics were derived from data obtained from published literature and from a retrospective cohort review. The time horizon of the model was not made clear. The costing data was reported in 2009 USD and discounted using the Consumer Price Index. The primary outcome measure was the ICER for each strategy. The source study's funding was not reported. The study scored 69/100.

Key Assumptions:

The study considered patients in an observation unit for the evaluation of low-risk chest pain. Patients were found to have either indeterminate or positive-stress test results. The mean age was 50-year-old and 54% were male. The assumed sensitivity of CCTA 98.9% while the specificity for CCTA was 84%. Given an abnormal stress test result, the probability of that the patient has no CAD was assumed to be 69.5%. The probability of an indeterminate CCTA test was 3.8%.

Results:

Authors found CCTA to have similar effectiveness as the standard of care while being approximately 20% less expensive. The "do nothing" approach was the cheapest, however, also the least effective. This led CCTA to have a generally considered cost-effective ICER of $8,135. The marginal cost-effectiveness of standard-of-care as compared with CTCA was $352,651. (CCTA cheaper but marginally less effective).

CTTA was found to cost $8,306 and yielded 23.54QALYs. Meanwhile, standard of care costed $10,273 yielding 23.55QALYs and the "do nothing" strategy costed the least at $1,815 and also yielded the lowest number of QALYs with 22.75 QALYs.

The standard of care strategy becomes preferable only at extremely high willingness to pay thresholds because it has a slight effectiveness advantage. The do-nothing strategy was preferable at only a very low WTP ($8,306).

Limitations:

The "do-nothing strategy" in which all patients were discharged home after positive- or indeterminate-stress tests without further testing analyzed in this study is likely an unrealistic scenario and does not provide a very valuable comparison. Furthermore, like many other studies, the authors here assumed that ICA 100% sensitive, which also may not be a realistic assumption. It is not entirely clear which costs the authors included in the analysis. They do note that the study does not consider startup costs of a CCTA or additional ED revisits. Additionally, the time horizon of the study is not reported, which potentially has significant implications for interpreting the results. Lastly, given the complexity of the model and degree of uncertainty the scope of the sensitivity analysis was limited.

Priest et al. 2011[197]

Overview and Design:

A fairly well-designed cost-effectiveness study that investigated several testing options in and emergency department including a strategy of doing an initial CCTA followed by confirmatory SPECT for indeterminate CCTA results, CCTA alone, stress ECHO, stress SPECT and ETT. A decision model was implemented with a 12-month time horizon. Estimates were discounted using the Consumer Price Index to 2010 USD. Sensitivity analyses were conducted to compare the differences in the type of stress-based test used (specifically in terms of diagnostic accuracy) and also explore the effect that the rate of incidence of adverse events as well as the costs associated with each test. A payer's perspective was assumed for costs. The study was funded by the National Health and Medical Research Council The study scored 75/100 using the QHES.

Key Assumptions:

Several testing strategies were compared in an emergency department setting with patients having a CAD prevalence of 2–30%. Published literature and a meta-analysis were used to build the model. The sensitivity and specificity of CCTA 2were assumed to be 100% and 80% respectively. The sensitivity and specificity of ETT were assumed to be 67% and 72% respectively. For both ECHO and SPECT, the

estimates varied by to the stress was induced. For stress ECHO, the sensitivity ranged from 72% to 83% while its specificity ranged from 84% to 95%. For stress SPECT, the sensitivity ranged from 84% to 91% while its specificity ranged from 69% to 81%. The procedural costs for ETT, SPEC, ECHO and CCTA were $144, $461, $290, and $374 respectively.

Results:

CCTA with "confirmatory SPECT" was considered the most cost-effective strategy at all prevalence thresholds investigated compared with all other strategies explored. The CCTA with SPECT strategy also had the lowest average cost per patient diagnosed based on the evaluation of diagnostic accuracy. Using the results reported it was possible to compare CCTA, ECHO and SPECT against ETT. ETT was consistently dominated by all three alternative tests at varying levels of CAD prevalence. As the prevalence increase, however, the dominance be narrower. The total 12-month costs with a 5% prevalence of CAD for ETT, SPECT, ECHO, CCTA and CCTA the SPECT were $10,430, $10,799, $7,539, $4,862 and $3,464 respectively. Under the same circumstances the QALYs generated for ETT, SPECT, ECHO, CCTA and CCTA the SPECT were 0.8523, 0.8548, 0.8579, 0.8568 and 0.8602.

Limitations:

A major limitation found in this study is the short follow-up time. Goehler et al found the comparison of tests' cost-effectiveness to be reversed from the short-term follow-up to the longer-term follow-up. Beyond the insufficient time horizon, when compared to other studies on the topic the model presented is relatively simple and authors indicate a lack of available data to specify the parameters necessary for a more complex model. Specifically, revisits to the emergency department and other complications were not considered. The model also does not include the likely benefits of revascularization or distinguish between varying levels of stenosis. Lastly, as with many other studies, the potential risks and costs associated with radiation exposure from CCTA and SPECT were not factored into the analysis.

Table 45. Overview of reported cost-effectiveness (CE) stratified by pretest likelihood, Acute/ED patients, assuming a willingness-to-pay WTP of $100,000

Pretest Risk %	CCTA	ECHO	SPECT
Standard of Care	Powell 2012 CCTA vs. Standard of care: $352,652/QALY (CCTA cheaper but marginally less effective) Goehler 2020 CCTA dominated Standard of Care	No studies meeting inclusion criteria found	No studies meeting inclusion criteria found
ETT	Priest 2011 CCTA dominates ETT -$669,300/QALY	Priest 2011 ECHO dominates ETT -$138,006/QALY	Priest 2011 SPECT dominates ETT -$94,500/QALY

Pretest Risk %	CCTA	ECHO	SPECT
Do Nothing	Powell 2012 CCTA vs. "Do nothing": $8,135/QALY (CCTA is more expensive and effective)	No studies meeting inclusion criteria found	No studies meeting inclusion criteria found
Expert Consensus (Based on ACC/AHA guidelines)	Goehler 2020 CCTA dominated Expert Consensus	No studies meeting inclusion criteria found	No studies meeting inclusion criteria found
Expedited ED protocol (w/ OP testing)	Goehler 2020 CCTA was CE against Expedited ED discharge with OP testing with an ICER of $ 49,428/QALY	No studies meeting inclusion criteria found	No studies meeting inclusion criteria found

ACC/AHA = American College of Cardiology/American Heart Association; CCTA = coronary computed tomography angiography; CE = cost-effective; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; ICA = invasive coronary angiography; ICER = incremental cost-effectiveness ratio; MPS = myocardial perfusions scan; OP = outpatient; QALY = quality-adjusted life years; SPECT = single photon emission computed tomography.

6.2 CCTA versus ICA

Two randomized control trials compared CCTA with ICA in patients with suspected CAD (N=1,951). (See Appendix F for details.) One trial was conducted exclusively in the outpatient setting[36] and in the other trial,[52] 43% of patients were treated in the outpatient setting and 57% in the inpatient setting. One trial[36] used a 64-slice CT scanner for CCTA imaging and the other trial[52] did not report on this information. Both trials used iodinated contrast agents. One trial included CACS imaging as part of their CCTA protocol.[52]

In both trials, the mean patient age was 60 years and the proportion of females ranged from 44% to 49%. In the one trial reporting race, 87% of patients identified as non-white. Both trials excluded patients with prior MIs and/or revascularizations. One trial excluded patients with known CAD,[36] and in the other trial,[52] 6% of patients had known CAD. In one trial,[52] 100% of patients had chest pain (specific chest pain sub-types included atypical angina in 44% of patients, non-anginal chest pain in 54% of patients, and other chest discomfort in 2% of patients. In the other trial, 72% of patients presented with chest pain (specific sub-types included atypical angina in 40% of patients, typical angina pain in 31% of patients, and non-anginal chest pain in 2% of patients).[36] Eleven percent of patients in the latter trial

were asymptomatic. Neither of the trials reported on the proportion of patients with unstable angina. Across both trials, the proportion of patients reporting diabetes ranged from 28% to 71%; hypertension ranged from 34% to 53%; and current smoking ranged from 14% to 23%. In one trial, 58% of patients had hypertension and 17% presented with dyspnea.[215] Duration of follow-up ranged from 1 to 3.3 years.

One trial was conducted in Germany[52] and the other trial was conducted across multiple countries in North America, East Asia, Europe, and India.[36] One trial received funding from the government[36] and the other trial received funding from a non-profit agency. [52]

One trial was rated good quality[52] and the other was rated fair quality[36] In the good quality trials, blinding of outcome assessors was unclear. Other methodological shortcomings in the fair-quality trial included unclear allocation concealment methods and higher than acceptable attrition at 12 months.

6.2.1 Summary of results (Key questions 1, 2 and 3)

- There was no difference in the risk of all-cause mortality or MI in CCTA versus ICA group at 12 and a median 40 months across one good- and one fair-quality RCT (SOE Low for both). Cardiac mortality was rare (SOE Insufficient).
- Compared with direct referral to ICA, CCTA was associated with a reduced risk of ICA without obstructive CAD (2 RCTs, N=1,019; 22 versus 65 per 100 patients; pooled RR 0.32, 95% CI 0.18 to 0.51, I^2=0%; pooled RD –48.0%, 95% CI –67.0% to –29.2%, I^2=73%) (SOE Moderate) and any revascularization (2 RCTs, N=1,832; 13 vs. 18 per 100 patients; pooled RR 0.71, 95% CI 0.55 to 0.96, I^2=0%; pooled RD –5.0%, 95% CI –8.0% to –2.0%, I^2=0%) (SOE Moderate) to include PCI but not CABG procedures, but an increased risk of additional downstream noninvasive testing (1 fair-quality RCT, N=1,503; 53 vs. 27 per 100 patients; RR 1.96, 95% CI 1.71 to 2.25; RD 26.0%, 95% CI 21.1% to 30.7%) (SOE Moderate). This latter trial found no difference between tests in the risk of cardiac hospitalization (4 vs. 4 per 100 patients) over 12 months (SOE Moderate).
- No major complications were reported in one good-quality trial and only one major complication was reported in the second fair-quality trial, major bleeding, which occurred in two patients (0.4%) in the ICA group; one patient (0.1%) required transfusion (SOE Low).

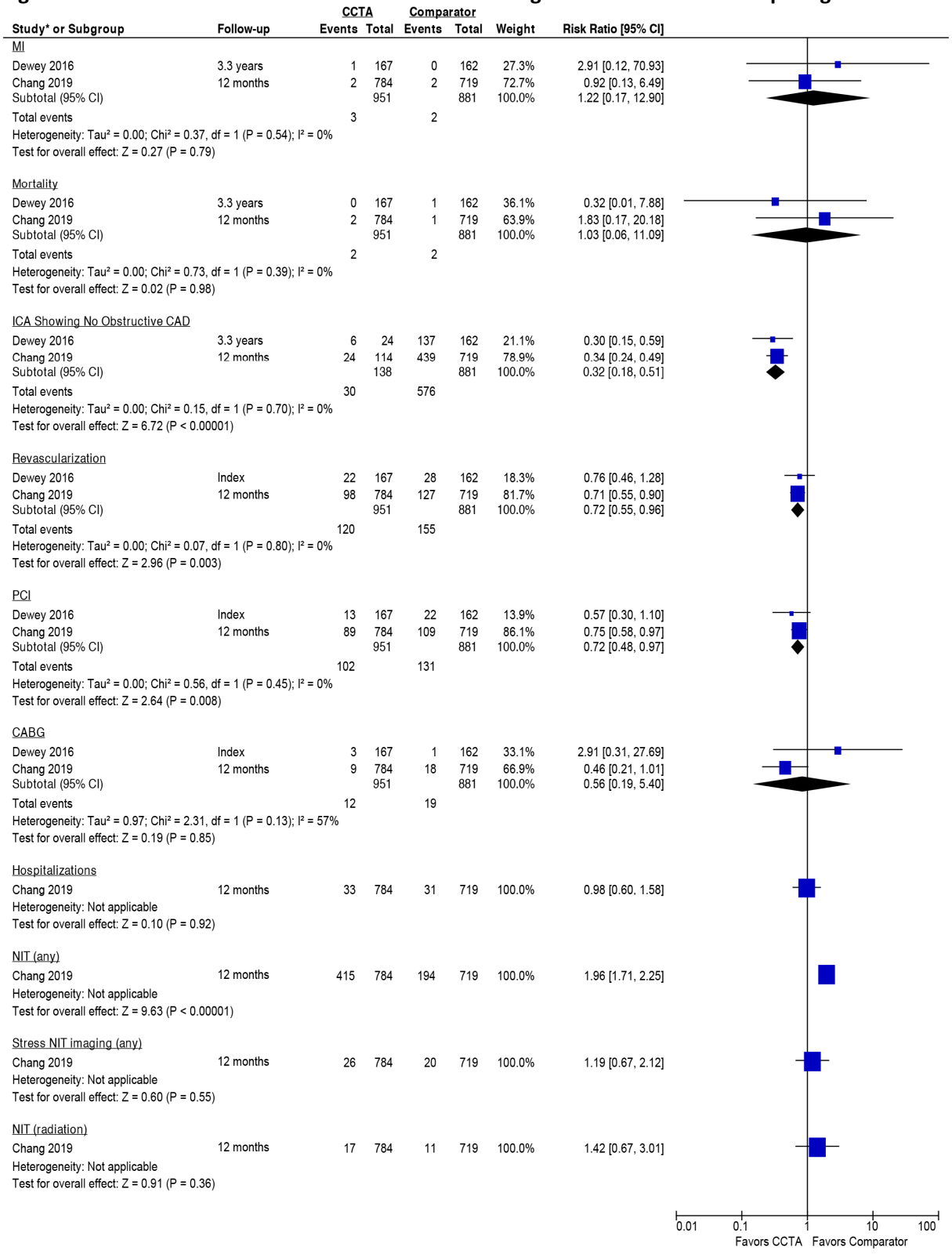
Detailed results

6.2.2 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Myocardial infarction, all-cause mortality and cardiac death

There were no differences between CCTA and ICA in the incidence of MI (0.3 vs. 0.2 per 100 patients; pooled RR 1.26, 95% CI 0.24 to 6.67, I^2=0%) and all-cause mortality (0.2 vs. 0.2 per 100 patients; pooled RR 1.03, 95% CI 0.06 to 11.08, I^2=0%) across 2 RCTs (N=1,832) with follow-up periods of 12 months and a median 40 months (Figure 20).[36,52] One cardiac-related death was reported over a median of 40 months in one trial and it occurred in the ICA group; this death was also counted under all-cause mortality[52].

Figure 20. Clinical outcomes and clinical decision-making outcomes for RCTs comparing CCTA with ICA



Other Outcomes

There were no differences between CCTA and ICA in the incidence of unstable angina, stroke, or MACE across both RCTs (Table 46).

Table 46. Secondary outcomes in trials comparing CCTA vs. ICA in patients with suspected CAD

Outcome	Author, year RCT	Time point	CCTA	ICA	Risk Ratio (95% CI)*
Unstable angina	Dewey, 2016† *CAD-Man*	Median 3.3 years	1.2% (2/167)	0% (0/162)	NC, p=0.16
	Chang, 2019‡ *CONVERSE*	Median 12.3 months	1.1% (9/784)	1.1% (8/719)	1.03 (0.40 to 2.66)
Stroke	Dewey, 2016† *CAD-Man*	Median 3.3 years	0% (0/167)	0.6% (1/162)	NC, p=0.31
	Chang, 2019‡ *CONVERSE*	Median 12.3 months	0.3% (2/784)	0.3% (2/719)	0.92 (0.13 to 6.49)
MACE§	Dewey, 2016† *CAD-Man*	Median 3.3 years	4.2% (7/167)	3.7% (6/162)	1.13 (0.39 to 3.30)
	Chang, 2019‡ *CONVERSE*	Median 12.3 months	4.6% (36/784)	4.6% (33/719)	1.0 (0.63 to 1.59)
Angina-free	Chang, 2019‡ *CONVERSE*	Median 12.3 months	60% (470/784)	62% (446/719)	0.96 (0.89 to 1.05)

adj. = adjusted; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ED = emergency department; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction; NR = not reported; RCT = randomized controlled trial; UA = unstable angina.

*Calculated by AAI.

†Patients with stable or unstable angina treated as inpatients (56%) or outpatients (44%)

‡Patients with stable angina treated on an outpatient basis

§MACE definitions:

Dewey: MI, cardiac death, stroke, UA pectoris, re-revascularization or first revascularization more than 2 months after randomization

Chang: death, acute non-fatal MI, UA, cardiac hospitalization, or stroke

6.2.3 Key Question 2: Clinical decision making

Additional testing

Compared with a diagnostic strategy of direct referral to ICA, only 14 per 100 patients (24/167) patients randomized to CCTA in one good-quality trial[52] and 23 per 100 patients (179/784) in one fair-quality trial[36] underwent subsequent ICA over median follow-ups of 12 and 40 months. One of the trials reported that 30 patients in the ICA group (n=719) underwent a second ICA during follow-up[36] (4 per 100 patients). The proportion of patients without obstructive CAD on ICA was significantly lower in patients randomized to index CCTA compared with those randomized to direct ICA in both trials (total N=1,019)[36,52]: 22 versus 65 per 100 patients; pooled RR 0.32 (95% CI 0.18 to 0.51), I^2=0%; pooled RD –48.0% (95% CI –67.0% to –29.2%), I^2=73% (Figure 20). One trial, in mixed stable and acute patients with

atypical chest pain, reported that ICA led to revascularization of obstructive CAD in more CCTA patients (16/24) than ICA patients (23/162) (67 vs. 14 per 100 patients; RR 4.70, 95% CI 2.93 to 7.53; RD 52.5%, 95% CI 32.9% to 72.1%).[52]

Additional downstream noninvasive testing was twice as common following index CCTA compared with direct referral to ICA in one fair-quality trial evaluating stable patients (53 vs. 27 per 100 patients; RR 1.96, 95% CI 1.71 to 2.25; RD 26.0%, 95% CI 21.1% to 30.7%) but there was no difference between groups in the frequency of these tests that required stress testing with imaging or that required radiation (Figure 20).[36] Additional testing (in order of most to least common) included rest echocardiography, exercise ECG, nuclear perfusion, stress echocardiography and CCTA. More CCTA patients underwent subsequent rest echocardiography compared with ICA patients (36 vs. 13 per 100 patients; RR 2.71, 95% CI 2.20 to 3.34; RD 22.6%, 95% CI 18.5% to 26.8%); the frequency of all other tests was similar between groups.

Treatment

When data were pooled across both trials, CCTA was associated with fewer revascularization procedures compared with ICA over median follow-up periods of 12 and 40 months (2 RCTs, N=1,832; 13 vs. 18 per 100 patients; pooled RR 0.71, 95% CI 0.55 to 0.96, I^2=0%; pooled RD –5.0%, 95% CI –8.0% to –2.0%, I^2=0%), Figure 20. Individually, only the larger fair-quality trial (N=1,503) in stable outpatients reported a statistically significant difference between groups over 12 months: 13 versus 18 per 100 patients, RR 0.71 (95% CI 0.55 to 0.90), RD –5.0% (95% CI –9.0% to –2.0%). Results were similar when the frequency of PCI was considered separately but there were no differences in the frequency of CABG between groups (Figure 20). In the trial evaluating both stable and acute patients with atypical chest pain, most patients underwent revascularization following the index visit with similar proportions (re)revascularized more than 2 months after randomization (6/167 vs. 5/162, 4 vs. 3 per 100 patients; adjusted HR 0.89, 95% CI 0.27 to 2.90).[52]

Hospitalization and ED visits

Hospitalization for cardiac causes occurred with similar frequency between the CCTA and ICA groups over a median follow-up of 12 months in one trial evaluating stable patients treated on an outpatient basis: 4 vs. 4 per 100 patients, RR 0.98 (95% CI 0.60 to 1.58)[36]; Figure 20. The other trial, in a mixed stable and acute population with atypical chest pain, did not report hospitalization rates but did report that for those patients hospitalized, CCTA was associated with a shorter hospital length of stay compared with ICA: median 30 (IQR 3.5 to 77.3) versus 52.9 (IQR 49.5 to 76.4) hours.[52]

6.2.4 Key Question 3: Safety

The good-quality trial evaluating both stable and acute patients with atypical chest pain reported that no major complications occurred, i.e., complications that prolonged hospital stay by 24 hours or more.[52] Minor procedural complications were less frequent following CCTA compared with ICA (4 vs. 11 per 100 patients), primarily driven by the rate of hematoma at the puncture site (1 vs. 9 per 100 patients), Table 47. In one fair-quality trial evaluating stable outpatients, only one major complication was reported,

major bleeding, which occurred in two patients (0.4%) in the ICA group; one patient (0.1%) required transfusion[36] (Table 47).

Table 47. Safety data for RCTs comparing CCTA vs. ICA in patients with suspected CAD

Author, year RCT Timepoint	Adverse event	CCTA	ICA	Estimate (95% CI)*
D**ewey, 2016*** ***CAD-Man*** ≤48 hours after last procedure related to CCTA or ICA	**Any complications prolonging hospital stay by ≥ 24 hours**	0% (0/165)	0% (0/162)	NC, p=NS
	Any minor procedural complication	3.6% (6/165)	10.5% (17/162)	RR 0.35 (0.14 to 0.86) RD –6.9% (–12.4% to –1.3%)
	Hematoma at puncture site	0.6% (1/165)	8.6% (14/162)	RR 0.07 (0.01 to 0.53) RD –8.0% (–12.5% to –3.6%)
	Secondary bleeding at puncture site	0.6% (1/165)	0.6% (1/162)	RR 0.98 (0.06 to 15.56)
	Bradycardia	1.2% (2/165)	0% (0/162)	NC, p=NS
	Angina without infarction	0.6% (1/165)	0% (0/162)	NC, p=NS
	Allergoid reaction to contrast agent	0.6% (1/165)	0% (0/162)	NC, p=NS
	Hypotension requiring treatment	0% (0/165)	0.6% (1/162)	NC, p=NS
	Stent migration	0% (0/165)	0.6% (1/162)	NC, p=NS
Chang, 2019† ***CONSERVE*** Median 12.3 months	**Any major bleeding**	0% (0/784)	0.3% (2/719)	NC, p=NS
	Major bleeding needing transfusion	0% (0/784)	0.1% (1/719)	NC, p=NS

CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; NC = not calculable; NS = not statistically significant; RCT = randomized controlled trial.
*Calculated by AAI.
†Patients with stable or unstable angina treated as inpatients (56%) or outpatients (44%)
‡Patients with stable angina treated on an outpatient basis

6.2.5 Key Question 4: Differential Effectiveness or Safety

No trials reported on differential effectiveness or safety.

6.2.6 Key Question 5: Cost-Effectiveness

Given the complexities in how cost-effectiveness was reported in the included studies, cost-effectiveness related to CCTA versus is covered in section 6.1.5 under the comparison of CCTA versus any functional testing.

6.3 CCTA with Fractional Flow Reserve (FFR)

One prospective comparative cohort (across 2 publications), the PLATFORM study, compared CCTA plus Fractional Flow Reserve (FFR) versus any non-invasive testing (N=204) and versus ICA (N=380) in the outpatient setting in patients with suspected CAD who had an intermediate risk of coronary disease.[57,60] Patients were subdivided into two consecutive cohorts based on the evaluation plan decided upon before enrollment (any non-invasive testing or ICA). (See Appendix J for details.) The decision to send patients for noninvasive or invasive testing prior to enrollment was made by the patients' physicians; it is unclear what criteria were used to make this decision, though it is assumed that those patients who were being sent directly to ICA were higher risk than those being sent for noninvasive testing. Among patients originally planned to receive non-invasive testing, 104 were allocated to CCTA (with 64% also receiving FFR) and 100 were allocated to any non-invasive test. Among patients originally planned to receive ICA, 193 were allocated to CCTA (with 69% also receiving FFR) and 187 were allocated to ICA. FFR analyses were performed centrally using HeartFlow when requested by the site (recommended if the CTA revealed ≥30% stenosis or if the patient was referred to ICA), thus not all patients received FFR as indicated previously. CCTA was complete with a 64 slice or greater CT scanner and contrast was used but the type and dose were not reported. CACS was not performed in any patient. For those allocated to the any non-invasive testing arm, tests included stress echocardiogram, SPECT, CMR, CCTA, and other (not further specified).

Patients in the planned ICA cohort were somewhat older than those in the planned non-invasive cohort (mean 62 vs. 59 years); within the planned ICA cohort, patients allocated to receive CCTA with FFR were younger than those allocated to ICA (61 vs. 63 years), Appendix J. The proportion of females ranged from 38% to 40% across the two cohorts. Less than 2% of all patients identified as a racial or ethnic minority. The study excluded patients with previously diagnosed CAD and did not report information on prior revascularizations, myocardial infarctions, or the proportion of patients with dyspnea. Most patients presented with atypical angina (74%); in the planned noninvasive test cohort, fewer patients who were allocated to CCTA with FFR had at atypical angina compared to those who received noninvasive testing (77% vs. 91%). Across all patients, the proportion with hypertension, diabetes, and hyperlipidemia was 54%, 13%, and 71%, respectively, and 54% smoked in the past or presently. In the planned non-invasive test cohort, more patients who were allocated to CCTA with FFR had hypertension (55% vs. 38%) and were taking aspirin (43% vs. 29%) compared with those who received other noninvasive testing. In the planned ICA cohort, fewer patient allocated to CCTA with FFR were taking aspirin (47% vs. 62%). All patients had intermediate likelihood of CAD; mean pretest risk was 45% in the planned noninvasive test cohort and 50.5% in the planned ICA cohort based on the Diamond-Forrester risk model. Follow-up occurred at 3, 6, and 12 months. The study was conducted at 11 sites in Europe and one site in the United States. Authors received funding from industry (HeartFlow, Inc.).

The study quality was rated as good. There were some differences in key characteristics between arms at baseline; however, the authors performed a sensitivity analysis of their primary outcome using propensity score matching (based on age, sex, diabetes, smoking status, and type of angina) to control for these imbalances and the unrandomized nature of the test allocation.

6.3.1 Summary of Results

CCTA with FFR vs. any NIT (planned NIT cohort)

- There was no difference between groups in any outcome over 12 months (SOE Insufficient for all outcomes).
- One MI occurred in the any noninvasive test group (0 vs. 1 per 100 patients). There were no deaths or hospitalizations with urgent revascularization in either group. Given that these are rare events, the study may not have been sufficiently powered to detect a difference.
- Risk of ICA was 21 vs. 16 per 100 patients; of ICA without obstructive CAD was 13 vs. 6 per 100 patients (at 3 months); and of any revascularization was 10 vs. 7 per 100 patients, respectively.

CCTA with FFR vs. ICA (planned ICA cohort)

- There were no differences between groups over 12 months in the risk of MI (1 vs. 1 per 100 patients), all-cause death (0 vs. 1 per 100 patients) or hospitalization with urgent revascularization (1 vs. 0 per 100 patients). Given that these are rare events, the study may not have been sufficiently powered to detect a difference (SOE Insufficient).
- Compared with direct referral to ICA, patients who underwent CCTA with FFR were referred to ICA significantly less often (51 vs. 100 per 100 patients; RR 0.51, 95% CI 0.45 to 0.59) and importantly, there were no events in the 61% of CCTA with FFR patients in whom ICA was cancelled in the planned ICA cohort. The risk of ICA without obstructive CAD was also significantly reduced following CCTA with FFR (39 vs. 100 per 100 patients; RR 0.39, 95% CI 0.33 to 0.47) (SOE Insufficient).
- There was no difference between groups in the risk of any revascularization (SOE Insufficient).

Key Question 3, Safety

- There was one mild contrast reaction from CCTA testing; no other information was provided (SOE Insufficient).
- Patients who received CCTA with FFR had significantly greater cumulative radiation exposure over 12 months compared to those who received any noninvasive test (planned noninvasive test cohort): 9.6 vs. 6.4 mSv, MD 3.1 (95% CI, 0.6 to 5.7); there was no difference for CCTA with FFR versus direct referral to ICA (planned ICA cohort) (SOE Low).

Detailed Results

6.3.2 Key Question 1: Primary clinical outcomes (MI, all-cause mortality, cardiac death)

For both the planned noninvasive test cohort (CCTA with FFR vs. any noninvasive test) and the planned ICA cohort (CCTA with FFR vs. ICA), there were no differences between testing arms in the risk of nonfatal MI (≤1 per 100 patients across all arms) or all-cause mortality (0 per 100 patients in the noninvasive test cohort and <1 per 100 patients in the ICA cohort, across both arms), as well as in the risk of the composite outcomes of MACE or MACE plus vascular complications across 12 months of follow-up (Table 48).[57,60] Importantly, there were no events in the 61% of CCTA with FFR patients in whom ICA was cancelled in the planned ICA cohort. Cardiac mortality was not reported.

6.3.3 Key Question 2: Clinical Decision-making outcomes

Additional testing

In the planned noninvasive cohort, the risk of ICA, as well as the risk of ICA without obstructive CAD, was similar between patients who received CCTA with FFR versus any noninvasive test over 12 months (Table 48).[57,60] In the planned ICA cohort, allocation to CCTA with FFR was associated with a 50% reduction in the risk of ICA over 12 months compared with direct referral to ICA (51 vs. 100 per 100 patients; RR 0.51, 95% CI 0.45 to 0.59; RD –48.7% 95% CI –41.7% to –55.8%). The risk of ICA without obstructive CAD was also significantly reduced in patients who received CCTA with FFR compared with ICA as measured at 3 months (12 vs. 73 per 100 patients; RR 0.17, 95% CI 0.12 to 0.25; RD –60.8%, 95% CI –53.0% to –68.7%). Results from the propensity score matching analysis (n=148 in each arm) were similar (12 vs. 72 per 100 patients).

Over the 12 months after enrollment, in the planned noninvasive testing cohort, CCTA with FFR was associated with fewer total referrals for stress echocardiography (2 vs. 29 per 100 patients) and stress nuclear scans (8 vs. 17 per 100 patients) but a similar frequency of stress ECG and cardiac MRI compared with any noninvasive testing; 62% of patients allocated to the noninvasive testing arm received CCTA over the study duration (Table 48).[57,60] In the noninvasive testing arm, it was unclear which tests patients received at index visit so we could not calculate the proportion of additional noninvasive tests required post-index testing making it difficult to draw conclusions regarding the risk of additional downstream testing for this cohort. In the planned ICA cohort, there was no difference between patients who received CCTA with FFR versus ICA in additional noninvasive testing to include stress ECG, stress echocardiography, stress nuclear, cardiac MRI and CCTA (Table 48).

Additional treatment and hospitalization

There were no differences between test arms in risk of any revascularization or of hospitalization with urgent revascularization over 12 months for both the planned noninvasive test cohort (CCTA with FFR vs. noninvasive testing) and the planned ICA cohort (CCTA with FFR vs. direct referral to ICA), Table 48.[57,60]

Changes in medication use (i.e., aspirin, statins and $P2Y1_{12}$ inhibitors) over 12 months were similar in the two arms of both cohorts except for $P2Y1_{12}$ inhibitors (i.e., clopidogrel, prasugrel, and ticagrelor) in the planned ICA cohort which were greater in the CCTA with FFR arm compared with the ICA arm.[57,60] It is unclear what medication changes were made (e.g., dose increase or decrease, initiation or discontinuation).

Table 48. CCTA FFR versus any noninvasive functional testing and ICA

			Cohort intended for NIT			Cohort intended for ICA		
Author, year RCT	**Outcome**	**Timepoint, cumulative (months)**	**CCTA FFR**	**NIT***	**Estimate (95% CI)**	**CCTA FFR**	**ICA**	**Estimate (95% CI)**
Douglas 2015, 2016 PLATFORM Prospective comparative cohort study Population: - Suspected CAD‡ - Stable, OP - Intermediate pretest risk	**Nonfatal MI**	3	0% (0/104)	0% (0/100)	NC, p=NS	0.5% (1/193)	0% (0/187)	NC, p=NS
		12	0% (0/104)	1.0% (1/100)	NC, p=NS	0.5% (1/193)	0.5% (1/187)	RR 0.97 (0.06 to 15.38)
	All-cause mortality	3	0% (0/104)	0% (0/100)	NC, p=NS	0% (0/193)	0% (0/187)	NC, p=NS
		12	0% (0/104)	0% (0/100)	NC, p=NS	0% (0/193)	0.5% (1/187)	NC, p=NS
	MACE†	3	0% (0/104)	0% (0/100)	NC, p=NS	1.0% (2/193)	0% (0/187)	NC, p=NS
		12	0% (0/104)	1.0% (1/100)	NC, p=NS	1.0% (2/193)	1.1% (2/187)	RR 0.97 (0.14 to 6.81)
	MACE + vascular complication	3	1.0% (1/104)	0% (0/100)	NC, p=NS	3.6% (7/193)	1.1% (2/187)	RR 3.39 (0.71 to 16.12)
		12	1.0% (1/104)	1.0% (1/100)	RR 0.96 (0.06 to 15.17)	3.6% (7/193)	2.1% (4/187)	RR 1.70 (0.50 to 5.70)
	ICA	3	18.3% (19/104)	12.0% (12/100)	RR 1.52 (0.78 to 2.97)	39.4% (76/193)	100% (187/187)	**RR 0.39 (0.33 to 0.47)**
		12	21.2% (22/104)	16.0% (16/100)	RR 1.32 (0.74 to 2.37)	51.3% (99/193)	100% (187/187)	**RR 0.51 (0.45 to 0.59)**
	ICA without obstructive CAD – core lab quantitative	3	12.5% (13/104)	6.0% (6/100)	RR 2.08 (0.82 to 5.27)	12.4% (24/193)	73.3% (137/187)	**RR 0.17 (0.12 to 0.25)**
	ICA without obstructive CAD – site interpretation	3	7.7% (8/104)	5.0% (5/100)	RR 1.54 (0.52 to 4.54)	9.3% (18/193)	56.7% (106/187)	**RR 0.16 (0.10 to 0.26)**
	Any NIT							
	Stress ECG	unclear	8.7% (9/104)	11.0% (11/100)	RR 0.79 (0.34 to 1.82)	9.8% (19/193)	9.1% (17/187)	RR 1.08 (0.58 to 2.02)
	Stress Echo	unclear	1.9% (2/104)	29.0% (29/100)	RR 0.07 (0.02 to 0.27)	3.1% (6/193)	2.7% (5/187)	RR 1.16 (0.36 to 3.75)
	Stress nuclear	unclear	7.7% (8/104)	17.0% (17/100)	RR 0.45 (0.20 to 1.00)	1.6% (3/193)	3.2% (6/187)	RR 0.48 (0.12 to 1.91)
	Cardiac MRI	unclear	2.9% (3/104)	3.0% (3/100)	RR 0.96 (0.20 to 4.65)	1.6% (3/193)	3.2% (6/187)	RR 0.48 (0.12 to 1.91)
	CCTA	unclear	100% (104/104)	62.0% (62/100)	NA	100% (193/193)	0.5% (1/187)	NA
	FFR CT	unclear	57.7% (60/104)§	0% (0/100)	NA	60.6% (117/193)	0% (0/187)	NA
	Revascularization (any)	3	9.6% (10/104)	5.0% (5/100)	RR 1.92 (0.68 to 5.43)	28.5% (55/193)	31.6% (59/187)	RR 0.90 (0.66 to 1.23)

		12	9.6% (10/104)	7.0% (7/100)	RR 1.37 (0.54 to 3.47)	33.7% (65/193)	35.8% (67/187)	RR 0.94 (0.71 to 1.24)
	PCI	3	8.7% (9/104)	3.0% (3/100)	RR 2.88 (0.80 to 10.35)	23.3% (45/193)	22.5% (42/187)	RR 1.04 (0.72 to 1.50)
		12	8.7% (9/104)	5.0% (5/100)	RR 1.73 (0.60 to 4.99)	28.5% (55/193)	26.2% (49/187)	RR 1.09 (0.78 to 1.51)
	CABG	3	1.0% (1/104)	2.0% (2/100)	RR 0.48 (0.04 to 5.22)	5.2% (10/193)	9.1% (17/187)	RR 0.57 (0.27 to 1.21)
		12	1.0% (1/104)	2.0% (2/100)	RR 0.48 (0.04 to 5.22)	5.2% (10/193)	9.6% (18/187)	RR 0.54 (0.26 to 1.14)
	Hospitalization with urgent revascularization	3	0% (0/104)	0% (0/100)	NS	0.5% (1/193)	0% (0/187)	NC, p=NS
		12	0% (0/104)	0% (0/100)	NS	0.5% (1/193)	0% (0/187)	NC, p=NS

ACP = acute chest pain; ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CI = confidence interval; ICA = invasive coronary angiography; MD = mean difference; MI = myocardial infarction; NA = not applicable; NS = not statistically significant; OP= outpatient; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation.

*It is unclear what patients received at index testing.

†MACE includes all-cause mortality, non-fatal MI, hospitalization with urgent revascularization.

‡Known/history of CAD was an exclusion criterium.

§Requested in 67 but not completed in 7 due to poor image quality or inadequate acquisition.

6.3.4 Key Question 3: Safety

There was one reported adverse event from CCTA testing, a mild contrast reaction. The authors did not provide any other information or report on any other test-related adverse events.[57,60]

In the planned noninvasive test cohort, CCTA with FFR was associated with greater cumulative radiation exposure compared with the any noninvasive testing arm at both 3 months (8.8 vs. 5.8 mSv; mean difference 3.0, 95% CI 0.6 to 5.4) and 12 months (9.6 vs. 6.4 mSv; mean difference 3.1, 95% CI 0.6 to 5.7). In the planned ICA cohort, there was no difference in cumulative radiation exposure between the CCTA with FFR group and the ICA group (9.9 vs. 9.4 mSv at 3 months and 10.7 vs. 10.4 mSv at 12 months, respectively).

6.3.5 Key Question 4: Differential Effectiveness and Safety

Authors performed analyses on predefined subgroups (age, sex, race, diabetes, pretest risk of CAD) and evaluated interaction to explore differential effects of testing on the finding of no obstructive CAD on ICA within 90 days.[57,60] There was no evidence of differential effectiveness (interaction p-values not statistically significant) by any subgroup for the outcome of ICA without obstructive CAD within 90 days in either the cohort originally planned to receive noninvasive testing or the higher CAD risk cohort originally planned to receive ICA with one exception. In the higher risk cohort, there was a statistically significant test for interaction between subgroups based on pre-test probability of CAD (<50% versus ≥50%) (Appendix O). It appears that the analyses were done on raw data from the respective cohorts that were not adjusted for potential confounding or selection bias. Confounding and selection bias are primary factors which threaten the validity of non-randomized observational studies and causal inference is not possible. Thus, there is insufficient information to draw firm conclusion from these analyses.

6.3.6 Key Question 5: Cost-Effectiveness

Given the complexities in how cost-effectiveness was reported in the included studies, cost-effectiveness related to CCTA with FFR is covered in section 6.1.5 under the comparison of CCTA versus any functional testing.

7 Single Photon Emission Computed Tomography (SPECT) Results

Six trials (across 7 publications) evaluated the effectiveness and/or safety of SPECT compared with stress echocardiography (2 RCTs)[220,241], exercise ECG (2 RCTs)[209,223], clinical assessment only (1 RCT)[142], NICE-guideline directed care (1 RCT)[88], and ICA (1 RCT)[220,241]. One trial included both a stress echocardiography and an ICA comparison arm.[220,241]

7.1 SPECT versus Stress Echocardiography and versus Exercise ECG

Given that the results across the four trials comparing SPECT with stress echocardiography and exercise ECG showed similar results in general, they are summarized together in the bullet points below, in the strength of evidence table, and their results are presented together in the same plots/figures. However, each comparison is described in detail separately in the sections that follow. All figures corresponding to the meta-analyses can be found after the section comparing SPECT versus exercise ECG.

7.1.1 Summary of results

- There was no difference in the risk of MI (SOE Insufficient), all-cause mortality (SOE Low) or cardiac mortality (SOE Insufficient) between SPECT and stress echocardiography (2 trials) or exercise ECG (2 trials) across four trials (N=1,908) with varying populations and follow-up periods. The absolute risk was <2 per 100 patients across all testing arms for all outcomes over follow-up periods ranging from 1 to 24 months. Given that these are rare events, trials may not have been sufficiently powered to detect a difference.
- There was no difference in the risk of ICA (4 trials, N=1,908) (SOE Low) or additional noninvasive testing (N=3 trials, N=1,679) (SOE Insufficient) for SPECT versus stress echocardiography or exercise ECG across all four trials over follow-up periods ranging from 1 to 24 months, however, there was substantial heterogeneity. Individually, only the trials comparing SPECT versus exercise ECG reported statistically significant differences which favored SPECT for both ICA (1 trial) and additional noninvasive testing (2 trials); however, for the latter, the estimates across trials were inconsistent and imprecise. Differences in testing protocols, patient populations and/or pretest risk, and follow-up periods may have played a role in these findings.
- There was no difference in the risk of revascularization (4 trials, N=1,908) (SOE Moderate) or hospitalization (3 RCTs, N=1,451) (SOE Low) between SPECT and stress echocardiography or exercise ECG, or ED visits in 1 trial (N=229) of SPECT vs. echocardiography through 24 months of follow-up (SOE Low).

7.1.2 SPECT versus Stress Echocardiography

Two trials (total N=679)[210,220,241] compared Tc-99m sestamibi SPECT imaging with stress echocardiography in a mixed population of patients with suspected or known CAD, one in stable patients and one in acute patients (See Appendix Q). One trial enrolled patients with stable CAD referred for outpatient angiography (mean age 62 years, 30% female, 27% with prior MI/known CAD). Referral to angiography was based on the results of an exercise ECG complete within 1 month of enrollment, the

results of which were not available to the trial personnel. Patients were considered high risk (69%) or low risk (31%) according to the Pryor risk assessment. Baseline cardiac risk factors included prior cerebrovascular accident (6%), peripheral vascular disease (9%), diabetes (12%), family history of CAD (25%), hypertension (58%), hyperlipidemia (78%), and smoking (43%). Patients were on a variety of cardiovascular related medications at baseline including antiplatelets, statins, and beta-blockers primarily as well as ACE inhibitors, calcium channel blockers, nicorandil, nitrates, diuretics, and angiotensin-II receptor antagonists. The second trial enrolled patients with acute chest pain presenting to the ED[210] and subsequently hospitalized (mean age 57 years, 54% female, 24% known CAD). Baseline cardiac risk factors included prior MI (15%), cerebrovascular disease (8%), diabetes (39%), hypertension (76%), hyperlipidemia (48%), and COPD (10%). Patients were on a variety of cardiovascular related medications at baseline including antihypertensives (beta blockers and other), aspirin, and lipid-lowering medication primarily, as well as diabetes medication, warfarin and clopidogrel. SPECT was performed using adenosine as the stress agent in one trial (the stable outpatient population) and dipyridamole (73%) or treadmill exercise (27%) as the stressor in the other (acute ED population). Stress echocardiography was performed using dobutamine in the stable population and either dobutamine (58%) or exercise (42%) stress in the acute ED population; both trials used contrast to enhance the images. Follow-up was 30 days in the acute ED trial and up to 72 months in the stable outpatient trial. One trial was conducted in the United States and was funded by industry (GE Healthcare)[210] and the other was conducted in the United Kingdom and funded by the National Institute for Health Research.

One trial was considered good quality[220,241] and the other fair quality[210]. The only methodological shortcoming in the good-quality trial was unclear blinding of outcome assessors; in the fair-quality trial, limitations included unclear allocation concealment methods and between-group differences at baseline on a CAD risk factor. See Appendix D for details regarding study quality determination.

Detailed results

7.1.2.1 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Myocardial infarction

Across both trials, the frequency of MI following SPECT versus stress echocardiography was 0.6 versus 1.8 per 100 patients. No events occurred within 30 days in the fair-quality trial evaluating patients hospitalized with acute chest pain.[210] In the good-quality trial evaluating stable outpatients at higher pretest risk, two patients who received SPECT were admitted for acute MI with 18 months of randomization compared with six patients who received dobutamine stress echocardiography; the difference was not statistically significant: 0.9 versus 2.7 per 100 patients; RR 0.34 (95% CI 0.07 to 1.65)[220], Figure 21.

All-cause mortality and cardiac mortality

There was no difference in all-cause mortality between SPECT and stress echocardiography across the two trials, both individually and when pooled (2 RCTs, N=679, 2.4 vs. 3.2 per 100 patients; RR 0.71, 95% CI 0.22 to 4.58, I^2=0%), Figure 22. The good-quality trial in stable outpatients at higher pretest risk

reported a total of seven and 11 deaths, respectively, over 72 months of follow-up (3.1 vs. 4.9 per 100 patients)[241]. The fair-quality trial in acute ED patients reported one death in the SPECT arm over 30 days (0.9 vs. 0 per 100 patients).[210] Cardiac mortality was reported in five SPECT patients and one echocardiography patient at 18 months in the trial evaluating stable outpatients (2.2 vs. 0.4 per 100 patients; RR 5.04, 95% CI 0.59 to 42.84)[220], Figure 23.

Other Outcomes

There was no difference between SPECT and Echo for the composite outcomes of any nonfatal event (admission for chest pain, admission for acute MI, unplanned PCI, unplanned CABG, or other) (10.7 vs. 13.7 per 100 patients; RR 0.78, 95% CI 0.47 to 1.29) and any fatal plus nonfatal event (12.9 vs. 16.4 per 100 patients; RR 0.79, 95% CI 0.50 to 1.24) over 18 months in the good-quality trial evaluating stable outpatients referred for ICA.[220] In this same trial here was no difference in the proportion of patients achieving a clinically significant improvement in CCS angina class at 18 months (42 vs. 34 per 100 patients). Similarly, there were no differences between groups for mean scores on all subscales of the Seattle Angina Questionnaire at 6 and 18 months (See Appendix O for all secondary outcomes).

7.1.2.2 Key Question 2: Clinical decision making

Additional testing

There was no difference in the frequency of ICA between SPECT and stress echocardiography across the two trials, both individually and when pooled (2 RCTs, N=679, 52.1 vs. 51.3 per 100 patients; RR 1.04, 95% CI 0.77 to 1.24, I^2=33%), Figure 24. The good-quality trial in stable outpatients at higher pretest risk reported that 175 and 169 patients, respectively, were referred for ICA over 18 months of follow-up (78 vs. 75 per 100 patients; RR 1.04, 95% CI 0.94 to 1.16)[220] while the fair-quality trial in acute ED patients reported that two and five patients received subsequent ICA within 30 days (1.7 vs. 4.4 per 100 patients; RR 0.39, 95% CI 0.08 to 1.97).[210] In the good-quality trial, one patient in the SPECT arm received additional noninvasive testing (repeat SPECT) compared with no patient in the echocardiography arm (0.4 vs. 0 per 100 patients; RR 3.03, 95% CI 0.12 to 73.90)[220]; the timing of additional noninvasive testing was unclear (Figure 25).

Treatment

There was no difference in the risk of any revascularization for SPECT compared with stress echocardiography across both trials (2 RCTs, N=679, 29 vs. 36 per 100 patients; RR 0.82, 95% CI 0.53 to 1.16, I^2=0%), Figure 26. Individually, the larger, good-quality trial evaluating stable outpatients at higher pretest risk showed an association favoring SPECT (lower risk) over 36 months of follow-up: 43.8 versus 53.5 per 100 patients, RR 0.82 (95% CI 0.67 to 0.99)[241], RD –9.8% (95% CI –19.0% to –0.6%); however, the estimate was just barely statistically significant. The fair-quality trial in acute ED patients reported no difference between diagnostic strategies over 30 days, with only one patient in the stress echocardiography arm undergoing revascularization (PCI) (0 vs. 0.9 per 100 patients).[210] Differences in populations and the length of follow-up periods may have played a role in these findings. When

considered separately, there were no difference between test groups in the risk of PCI (Figure 27) or CABG (Figure 28), though both trials tended to favor SPECT with regarding to PCI (lower risk).

Hospitalization and ED visits

There was no difference in the frequency of hospitalizations due to cardiac causes between SPECT and stress echocardiography across the two trials, both individually and when pooled (2 RCTs, N=679, 7.1 vs. 9.1 per 100 patients; RR 0.76, 95% CI 0.39 to 3.19, I^2=32%), Figure 29. Except for eight acute MIs requiring hospitalization (2 in the SPECT and 6 in echocardiography arm) in the good-quality trial evaluating stable outpatients at higher pretest risk[220], all hospitalizations were due to chest pain. The rate of cardiac hospitalization in the good-quality trial was 9.4 versus 13.3 per 100 patients (RR 0.71, 95% CI 0.42 to 1.20)[220], respectively, over 18 months and in the fair-quality trial evaluating acute ED patients was 2.6 versus 0.9 per 100 patients (RR 2.92, 95% CI 0.31 to 27.68)[210] over 30 days. In the latter trial, three patients (3 per 100) in each group returned to the ED within 30 days. There was no difference between groups in the length of hospital stay in this same trial (Appendix O).

7.1.3 SPECT versus Exercise ECG

Two trials (total N=1,281) compared Tc-99m sestamibi SPECT imaging with exercise ECG in stable patients with suspected CAD (known CAD was an exclusion criteria) treated on an outpatient basis[209,223] (See Appendix Q). Mean patient age was 60 to 63 years. One trial[223] enrolled only women (78% postmenopausal) who were 87% Caucasian while the second trial included 44% women and the population was 52% Caucasian and 40% Indian-subcontinent origin. Most patients across both trials were at intermediate to high pretest risk (100% in the trial enrolling women only[223] and 84% in the other trial[209]); the remaining 16% in the one trial were considered low risk. Regarding cardiac risk factors, there was a similar proportion of patients with hypertension (50% and 53%), diabetes (13% and 17%) and family history of CAD (43% and 47%) in both trials but a greater proportion of patients with smoking history (45% and 14%) in the trial enrolling women only. In the latter trial, presenting symptoms included typical angina (60%), atypical angina (9%), nonspecific angina (28%) and dyspnea (51%). In addition, medications at baseline in this trial included aspirin (35%), statins (32%), gastrointestinal drugs (27%) (39% had coexisting esophageal reflux) primarily as well as beta-blockers, antidepressants, ACE inhibitors, NSAIDs, angiotensin receptor blockers and others. The other trial did not report presenting symptoms (other than chest pain, 100%) or baseline medication use. In the trial enrolling only women, patients in both diagnostic testing arms received exercise stress testing according to Bruce protocol. In the other trial, 62% of patients in the SPECT arm underwent exercise treadmill testing and 38% had pharmacological stressors (dipyridamole or dobutamine) while all patients in the ECG arm underwent exercise using the symptom-limited modified Bruce protocol. Follow-up periods were similar, 24 months and a mean 20 months. One trial was conducted in the United States and the other in the United Kingdom. Both were funded by industry; the United Kingdom trial also received research grants.

Both trials were considered fair quality. The primary methodological shortcoming in both trials included unclear allocation concealment methods and in one, unclear blinding of outcome assessors. See Appendix D for details regarding study quality determination.

Detailed results

7.1.3.1 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Myocardial infarction

Across both trials there were a total of four MIs. One trial reported no difference between SPECT and exercise ECG in the frequency of MI over 24 months (N=457, 0 vs. 0.5 per 100 patients, RR 0.28, 95% CI 0.01 to 6.74)[209]; this was a fatal MI (Figure 21). The other trial reported that there were three nonfatal MIs (0.4 per 100 patients) over a mean of 20 months but did not specify the group to which the patients were randomized.[223]

All-cause mortality and cardiac mortality

There was no difference in all-cause mortality between SPECT and exercise ECG across the two fair-quality trials, both individually and when pooled (2 RCTs, N=1,229, 0.9 vs. 0.7 per 100 patients; RR 1.38, 95% CI 0.27 to 6.44, I^2=0%), Figure 22. There was a total of two cardiac deaths across both RCTs: one fatal MI in the exercise ECG group in one trial (0 vs. 0.5 per 100 patients; RR 0.28, 95% CI 0.01 to 6.74) Figure 23) and one sudden cardiac death (0.1 per 100 patients) in the second trial that enrolled only women, however the authors did not report to which group the patient was randomized.[223]

Other Outcomes

In the trial enrolling women only, the frequency of MACE (composite of cardiac death, nonfatal MI, or hospital admission for an ACS or heart failure) was similar between the SPECT and exercise ECG over 24 months (N=772, 2.3 vs. 1.7 per 100 patients; RR 1.14, 95% CI 0.44 to 2.92).[223] No difference in the frequency of MACE was seen for SPECT versus ECG when women with normal test results and those with abnormal test results were considered separately. Heart failure was reported in one woman (0.1 per 100 patients) and acute coronary syndrome in 12 (1.6 per 100 patients) all of which required hospitalization, but they did not report to which arms the patients were randomized (this data is repeated below in Key Question 2 under Hospitalization). The proportion of women who were angina-free (65 vs. 60 per 100 patients at 24 months) and the median scores across all subscales of the Seattle Angina Questionnaire (data not provided) were also similar between groups during follow-up. The second trial did not report on any secondary outcomes.

7.1.3.2 Key Question 2: Clinical decision making

Additional testing

In one trial, SPECT was associated with an almost 3-fold reduction in referral for ICA compared with exercise ECG over a mean follow-up of 20 months: 16.4 versus 47.3 per 100 patients; RR 0.35 (95% CI 0.25 to 0.47[209]; RD –30.9%, 95% CI –39.2% to –22.7%). The other trial which enrolled only women reported no difference in ICA rates between diagnostic strategies over 24 months (5.5 vs. 6.7 per 100 patients, respectively; RR 0.82, 95% CI 0.47 to 1.43).[223] When the two trials were pooled the difference was not statistically significant and there was substantial heterogeneity (2 RCTs, N=1,229, 9.8 vs. 20.8

per 100 patients; RR 0.50, 95% CI 0.19 to 1.47, I^2=86%), Figure 24. Difference in populations, testing protocols, and treatment algorithms may partially explain the heterogeneity.

In both trials, SPECT was associated with significantly fewer downstream noninvasive tests compared with exercise ECG. In the trial enrolling only women, the risk of subsequent noninvasive testing was 9.4 versus 18.6 per 100 patients, respectively, over 24 months (RR 0.51, 95% CI 0.35 to 0.73), almost all of which were SPECT (9.1 vs. 17.8 per 100 patients); only one SPECT patient and two exercise ECG patients had additional exercise ECG (0.3 vs. 0.5 per 100 patients). In the second trial, no patients randomized to SPECT underwent additional noninvasive testing while 23.2% of patients in the exercise ECG arm received subsequent stress (pharmacological) echocardiography (0 vs. 23.2 per 100 patients; RR 0.01, 95% CI 0.00 to 0.14)[209] over a mean of 20 months. However, when results were pooled across the two trials there was no difference between the two test groups (5.7 vs. 20.0 per 100 patients; RR 0.11, 95% CI 0.00 to 8.87, I^2=93%), likely due to the substantial heterogeneity across the trials (Figure 25).

Treatment

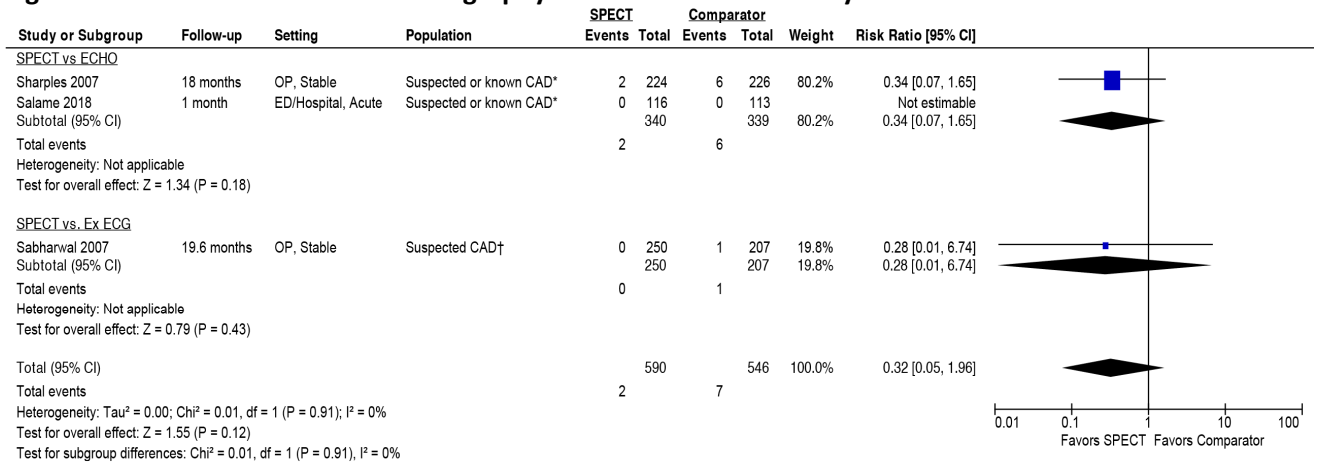
In one trial, SPECT was associated with fewer revascularization procedures compared with exercise ECG over a mean follow-up of 20 months: 10.8 vs. 17.9 per 100 patients, RR 0.60 (95% CI 0.38 to 0.96)[209], RD –7.1% (95% CI –13.6% to –0.6%); however, the difference was only marginally significant. The other trial which enrolled only women reported no difference in revascularization rates between diagnostic strategies over 24 months (2.1 vs. 1.1 per 100 patients, respectively; RR 2.02, 95% CI 0.61 to 6.66).[223] When the two trials were pooled the difference was not statistically significant, however heterogeneity was high (2 RCTs, N=1,229, 5.5 vs. 6.9 per 100 patients; RR 0.71, 95% CI 0.29 to 3.78, I^2=71%), Figure 26. Difference in populations, testing protocols, and treatment algorithms may partially explain the heterogeneity.

More patients randomized to SPECT versus exercise ECG started aggressive medical therapy (not defined) as a result of the test (83.6 vs. 30.4 per 100 patients; RR 2.75, 95% CI 2.22 to 3.40) in one trial.[209] The other trial enrolling only women reported similar rates of new use or discontinuation of nitrates, beta-blockers, statins and antidepressants between groups (no data provided, p=0.20).[223]

Hospitalization and ED visits

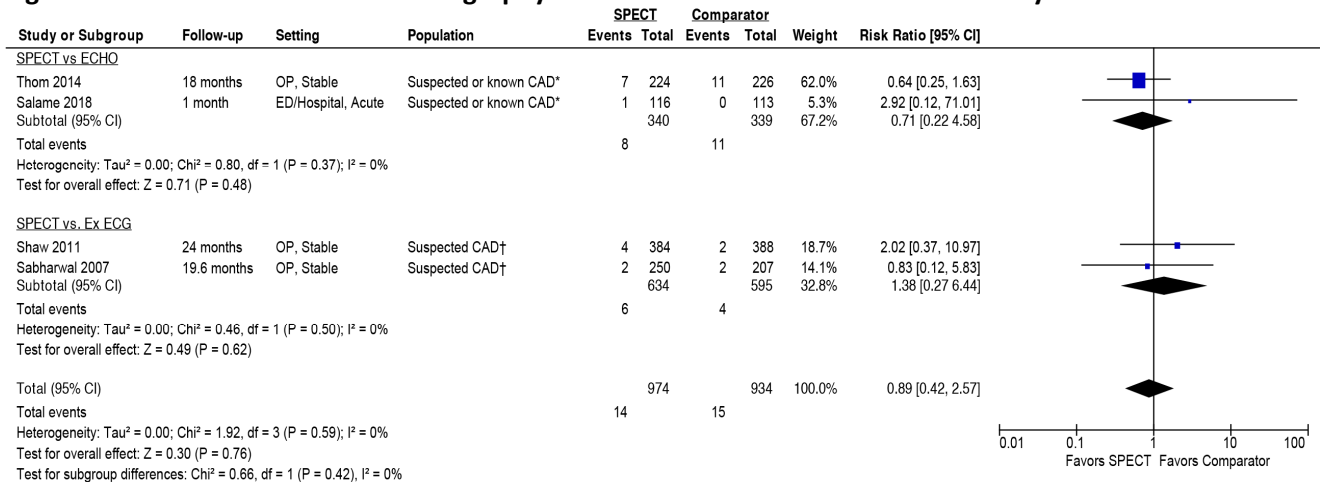
There was no difference between SPECT versus exercise ECG in the frequency of hospitalization for chest pain symptoms over 24 months in the trial enrolling only women (N=772, 3.9 vs. 3.1 per 100 patients; RR 1.26, 95% CI 0.60 to 2.66)[223], Figure 29. This same trial also reported one hospitalization for heart failure (0.1 per 100 patients) and 12 hospitalizations for acute coronary syndrome (1.6 per 100 patients) but they did not report to which arms the patients were randomized (this data is repeated above for Key Question 1 under Other Outcomes).

Figure 21. SPECT vs. stress echocardiography and vs. exercise ECG: Myocardial infarction



*Sharples: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED. †Known/history of CAD was an exclusion criterium.

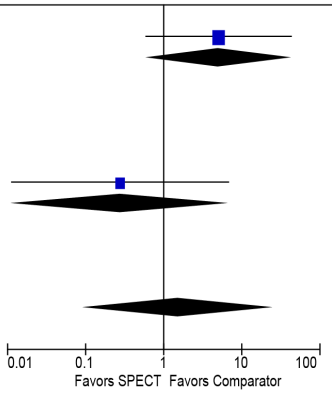
Figure 22. SPECT vs. stress echocardiography and vs. exercise ECG: All-cause mortality



*Thom: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED. †Known/history of CAD was an exclusion criterium. Shaw included women only.

Figure 23. SPECT vs. stress echocardiography and vs. exercise ECG: Cardiac mortality

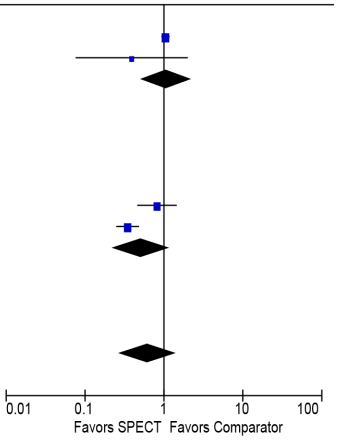
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Sharples 2007	18 months	OP, Stable	Suspected or known CAD*	5	224	1	226	58.7%	5.04 [0.59, 42.84]
Subtotal (95% CI)					224		226	58.7%	5.04 [0.59, 42.84]
Total events				5		1			
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.48 (P = 0.14)									
SPECT vs. Ex ECG									
Sabharwal 2007	19.6 months	OP, Stable	Suspected CAD†	0	250	1	207	41.3%	0.28 [0.01, 6.74]
Subtotal (95% CI)					250		207	41.3%	0.28 [0.01, 6.74]
Total events				0		1			
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.79 (P = 0.43)									
Total (95% CI)					474		433	100.0%	2.21 [0.05, 35.30]
Total events				5		2			
Heterogeneity: Tau² = 2.29; Chi² = 2.19, df = 1 (P = 0.14); I² = 54%									
Test for overall effect: Z = 0.29 (P = 0.77)									
Test for subgroup differences: Chi² = 2.19, df = 1 (P = 0.14), I² = 54.4%									



*27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography.
†Known/history of CAD was an exclusion criterium.

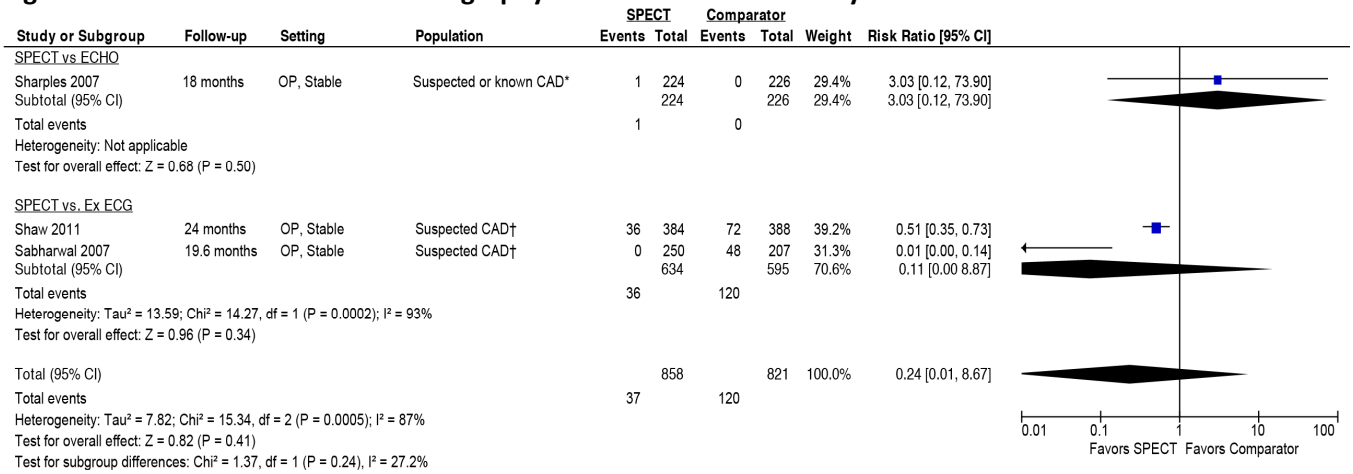
Figure 24. SPECT vs. stress echocardiography and vs. exercise ECG: ICA

Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Sharples 2007	18 months	OP, Stable	Suspected or known CAD*	175	224	169	226	30.2%	1.04 [0.94, 1.16]
Salame 2018	1 month	ED/Hospital, Acute	Suspected or known CAD*	2	116	5	113	14.1%	0.39 [0.08, 1.97]
Subtotal (95% CI)					340		339	44.3%	1.04 [0.77, 1.24]
Total events				177		174			
Heterogeneity: Tau² = 0.17; Chi² = 1.50, df = 1 (P = 0.22); I² = 33%									
Test for overall effect: Z = 0.32 (P = 0.75)									
SPECT vs. Ex ECG									
Shaw 2011	24 months	OP, Stable	Suspected CAD†	21	384	26	388	26.7%	0.82 [0.47, 1.43]
Sabharwal 2007	19.6 months	OP, Stable	Suspected CAD†	41	250	98	207	29.0%	0.35 [0.25, 0.47]
Subtotal (95% CI)					634		595	55.7%	0.50 [0.19 1.47]
Total events				62		124			
Heterogeneity: Tau² = 0.32; Chi² = 6.92, df = 1 (P = 0.009); I² = 86%									
Test for overall effect: Z = 1.55 (P = 0.12)									
Total (95% CI)					974		934	100.0%	0.64 [0.31, 1.22]
Total events				239		298			
Heterogeneity: Tau² = 0.60; Chi² = 59.39, df = 3 (P < 0.00001); I² = 95%									
Test for overall effect: Z = 1.13 (P = 0.26)									
Test for subgroup differences: Chi² = 0.89, df = 1 (P = 0.34), I² = 0%									



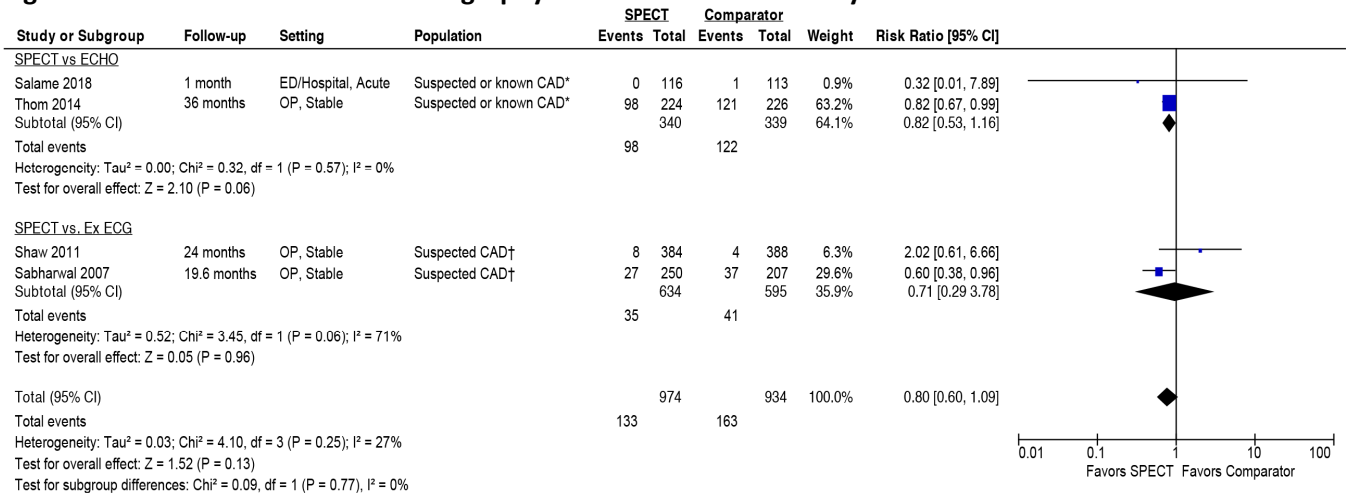
*Sharples: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED.
†Known/history of CAD was an exclusion criterium. Shaw included women only.

Figure 25. SPECT vs. stress echocardiography and vs. exercise ECG: Any additional NIT



*27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. †Known/history of CAD was an exclusion criterium. Shaw included women only.

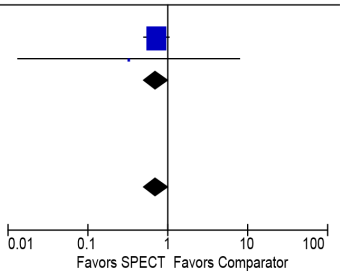
Figure 26. SPECT vs. stress echocardiography and vs. exercise ECG: Any revascularization



*Thom: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED. †Known/history of CAD was an exclusion criterium. Shaw included women only.

Figure 27. SPECT vs. stress echocardiography and vs. exercise ECG: PCI

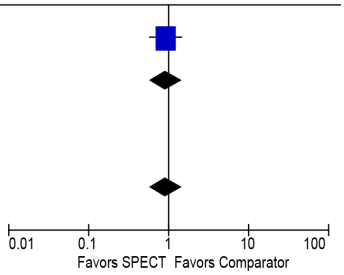
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Sharples 2007	18 months	OP, Stable	Suspected or known CAD*	40	224	56	226	98.7%	0.72 [0.50, 1.03]
Salame 2018	1 month	ED/Hospital, Acute	Suspected or known CAD*	0	116	1	113	1.3%	0.32 [0.01, 7.89]
Subtotal (95% CI)					340		339	100.0%	0.71 [0.33, 1.31]
Total events				40		57			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%									
Test for overall effect: Z = 1.84 (P = 0.07)									
Total (95% CI)					340		339	100.0%	0.71 [0.33, 1.31]
Total events				40		57			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%									
Test for overall effect: Z = 1.84 (P = 0.07)									
Test for subgroup differences: Not applicable									



*Sharples: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED.

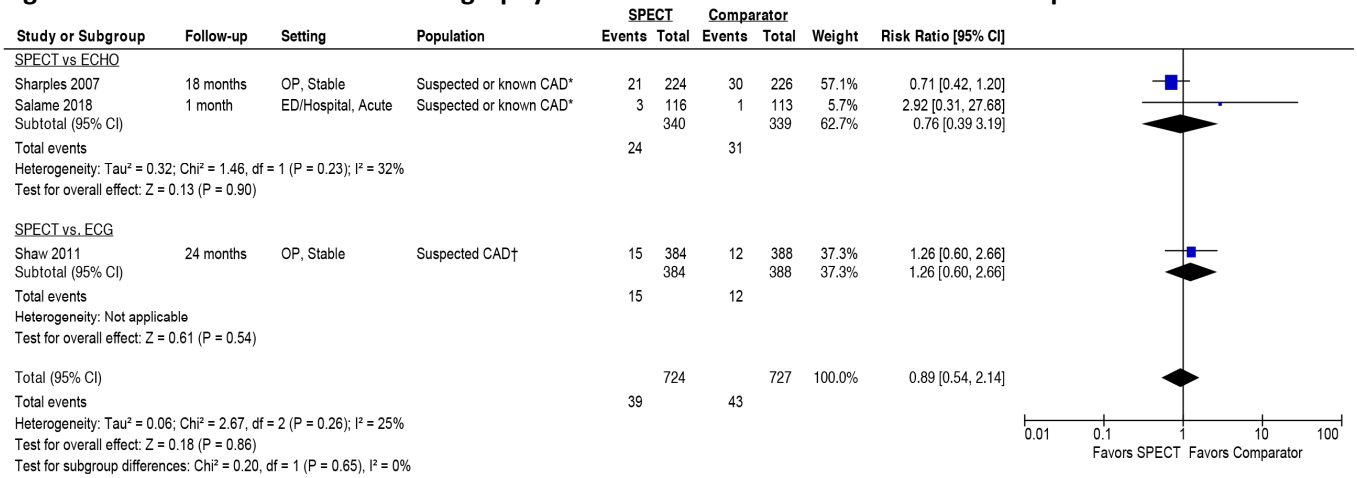
Figure 28. SPECT vs. stress echocardiography and vs. exercise ECG: CABG

Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Sharples 2007	18 months	OP, Stable	Suspected or known CAD*	30	224	33	226	100.0%	0.92 [0.58, 1.45]
Salame 2018	1 month	ED/Hospital, Acute	Suspected or known CAD*	0	116	0	113		Not estimable
Subtotal (95% CI)					340		339	100.0%	0.92 [0.58, 1.45]
Total events				30		33			
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.37 (P = 0.71)									
Total (95% CI)					340		339	100.0%	0.92 [0.58, 1.45]
Total events				30		33			
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.37 (P = 0.71)									
Test for subgroup differences: Not applicable									



*Sharples: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED.

Figure 29. SPECT vs. stress echocardiography and vs. exercise ECG: Cardiac-related hospitalization



*Sharples: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED.
†Known/history of CAD was an exclusion criterium. This trial included women only.

7.2 SPECT versus Clinical Assessment Alone and versus NICE Guideline-Directed Care

Given that the results across the two trials comparing SPECT with clinical assessment alone and with NICE guideline-directed care showed similar results in general, they are summarized together in the bullet points below, in the strength of evidence table, and their results are presented together in the same plots/figures. However, each comparison is described in detail separately in the sections that follow. All figures corresponding to the meta-analyses can be found after the section comparing SPECT versus NICE guideline-directed care.

7.2.1 Summary of results

- There was insufficient evidence to draw conclusions regarding the risk of MI and all-cause mortality in one RCT in stable outpatients (SPECT vs. NICE guideline-directed care) with a median follow-up of 16 months and cardiac death across both RCTs, one in stable and one in acute patients (follow-up range, 1 to median 16 months). The absolute risk was ≤1.3 per 100 patients across both test arms in both trials for all outcomes. Given that these are rare events, the trials may not have been sufficiently powered to detect a difference (SOE Insufficient).
- SPECT was associated with a decreased risk of ICA across both trials (10.2 vs. 21.1 per 100, pooled RR 0.49, 95% CI 0.26 to 0.95, I^2=85%; pooled RD –11.1%, 95% CI –14.4% to –7.8%) (SOE Low); the association was stronger in the trial comparing SPECT versus NICE guideline-directed care, likely due the direct referral to ICA of patients with high pretest risk per the NICE guideline algorithm, and could account for much of the heterogeneity in the pooled estimate. SPECT was also associated with a decreased risk of ICA showing no obstructive CAD (1 RCT, SPECT vs. clinical assessment alone: 21.9 vs. 39.3 per 100 patients; RR 0.56, 95% CI 0.32 to 0.96; RD –17.4%, 95% CI –33.3% to –1.4%) and unnecessary ICA (1 RCT, SPECT vs. NICE guideline-directed care: 7.1 vs. 28.8 per 100 patients; RR 0.25, 95% CI 0.17 to 0.36; RD –21.7%, 95% CI –27.9% to –15.5%) (SOE: Low for both).
- There was no difference between SPECT and clinical assessment alone or NICE guideline-directed care in the risk of any revascularization (2 RCTs, 5.9 vs. 7.0 per 100 patients; RR 0.85, 95% CI 0.57 to 1.28, I^2=0%) (SOE Low).
- SPECT was associated with decreased risk of additional downstream NIT over 12 months (12.1 vs. 68.3 per 100 patients; RR 0.18, 95% CI 0.15 to 0.21; RD –56.2%, 95% CI –60.7% to –51.7%) and hospitalization at the index visit (10.2 vs. 18.5 per 100 patients; RR 0.55, 95% CI 0.42 to 0.71; RD –8.3%, 95% CI –12.2% to –4.4%) compared with clinical assessment alone in one trial (SOE Low for both).

7.2.2 SPECT versus Clinical Assessment Alone

One trial (N=1,508)[142] compared Tc-99m tetrofosmin SPECT imaging (n=1,004) with clinical assessment only (n=504) in acute patients with suspected ACS presenting to the ED (See Appendix Q). All patients first underwent standard observation (continuous 12-lead ECG monitoring and cardiac biomarkers) over

a 6-hour period; only those who had a negative 6-hour observation received their randomly assigned protocol. Mean patient age was 52 years, 41% were female, and 69% were Chinese. A small number of patients had known CAD (4%) or had suffered a prior MI (1%). Patients had the following cardiac risk factors: hypertension (42%), smoker (32%) and diabetes (18%). Stress SPECT was performed using exercise (preferred) or dipyridamole or dobutamine if pharmacological stressors were required. Patients in the clinical assessment group were assessed for the likelihood of ACS by the emergency medicine physician based on patients' characteristics and cardiac risk factors and ECG results; 82% were considered intermediate or high risk and 18% were considered low risk. Patients considered to be at intermediate or high risk per physician assessment were admitted to the hospital. Pretest risk was not reported for those randomized to SPECT. The follow-up period was 12 months. This trial was conducted in Singapore and received government grants.

This trial was considered fair quality; it was unclear if outcome assessors were blinded and attrition at 12 months was unclear. See Appendix D for details regarding study quality determination.

Detailed results

7.2.2.1 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Cardiac mortality

Over 12 months of follow-up, three cardiac deaths were reported, and all occurred in the SPECT arm after 30 days (0.3 vs. 0 per 100 patients), Figure 30. The trial did not report the outcomes of MI and all-cause mortality.

Other outcomes

The incidence of cardiac events (composite outcome defined as cardiac-related death, ventricular fibrillation, MI, cardiogenic shock, or acute pulmonary oedema requiring endotracheal intubation) was similar between SPECT and clinical assessment alone at the end of follow-up (0.7 vs. 1 per 100 patients; RR 0.70, 95% CI 0.22 to 2.20); most events occurred within 30 days (0.4 vs. 0.8 per 100 patients; RR 0.5, 95% CI 0.13 to 2.0).

7.2.2.2 Key Question 2: Clinical decision making

Additional testing

SPECT was associated with fewer referrals for ICA compared with clinical assessment over 12 months: 7.3 versus 11.1 per 100 patients, RR 0.65 (95% CI 0.47 to 0.91), RD –3.8% (95% CI –7.0% to –0.7%), Figure 31. For those who underwent ICA, fewer patients in the SPECT group did not show significant CAD compared to the clinical assessment group: 21.9 versus 39.3 per 100 patients; RR 0.56 (95% CI 0.32 to 0.96), RD –17.4% (95% CI –33.3% to –1.4%). SPECT was also associated with less additional noninvasive testing of any type over 12 months (12.1 vs. 68.3 per 100 patients; RR 0.18, 95% CI 0.15 to 0.21; RD –56.2%, 95% CI –60.7% to –51.7%) as well as noninvasive stress testing requiring imaging (2.6 vs. 32.3 per 100 patients; RR 0.08, 95% CI 0.05 to 0.12; RD –29.8%, 95% CI –34.0% to –25.6%) and requiring radiation

(1.6 vs. 23.8 per 100 patients; RR 0.07, 95% CI 0.04 to 0.11; RD –22.2%, 95% CI –26.0% to –18.4%). The majority of additional testing was resting echocardiography in the SPECT group and equal proportions of SPECT and exercise ECG in the clinical assessment group.

Treatment

There was no difference between the SPECT and clinical assessment groups in the rate of any revascularization procedure over 12 months (4.8 vs. 6.2 per 100 patients; RR 0.78, 95% CI 0.50 to 1.21), Figure 32.

Hospitalization

SPECT was associated with an almost 50% reduction in hospitalization at index testing compared with clinical assessment (10.2 vs. 18.5 per 100 patients; RR 0.55, 95% CI 0.42 to 0.71; RD –8.3%, 95% CI –12.2% to –4.4%). In the clinical assessment arm, 94% of patients admitted to the hospital were considered intermediate or high risk for ACS according to the attending physician. The frequency of subsequent hospitalization following the index visit was not reported.

7.2.3 SPECT versus NICE guideline-directed care

One good-quality trial (N=721)[88] compared Tc-99m tetrofosmin or sestamibi SPECT (n=481) imaging versus NICE guideline-directed care (n=240) in stable patients with suspected CAD treated on an outpatient basis (See Appendix Q). A history of prior MI and prior revascularization were exclusion criteria. Mean patient age was 56 years, 47% of patients were female, and 92% were Caucasian. Patients presented with atypical (67%) and typical angina (33%) and had the following cardiac risk factors: former or current smoker (58%), family history of CAD (55%), dyslipidemia (41%), hypertension (39%), diabetes (13%), cerebrovascular disease (3%) and peripheral vascular disease (3%). Group allocation was stratified by the pretest likelihood of CAD (as well as age, sex, and center) which was determined according to NICE guidelines CG95; the pretest risk was 10% to 29% in 26%, 30% to 60% in 38%, and 61% to 90% in 36% of the population. Patients randomized to the NICE guideline group received specific diagnostic tests based on their pretest risk: those at a pretest risk of 10% to 29% received cardiac CT; 30% to 60% received SPECT; and 61% to 90% proceeded directly to ICA. In the SPECT group, stress imaging was performed using treadmill exercise as the default, with adenosine stress for those who could not exercise. Follow-up was a median 16 months (12 months minimum). This trial was conducted in the United Kingdom and received professional research grants.

See Appendix D for details regarding study quality determination.

Detailed results

7.2.3.1 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Myocardial infarction, all-cause mortality and cardiac mortality

There were no differences between the SPECT and NICE guideline-directed care groups in the incidence of MI (0.4 vs. 0.8 per 100 patients; RR 0.50, 95% CI 0.07 to 3.52), all-cause mortality (0.6 vs. 1.3 per 100 patients; RR 0.50, 95% CI 0.10 to 2.45), and cardiac mortality (0.6 vs. 0.4 per 100 patients; RR 1.50, 95% CI 0.16 to 14.31; Figure 30) over a median follow-up of 16 months.

Other Outcomes

There were no differences between the SPECT and NICE guideline-directed care groups in the incidence of MACE, a composite outcome of cardiovascular death, MI, unplanned revascularization or hospital admission for cardiac causes (3.1 vs. 2.5 per 100 patients; RR 1.24, 95% CI 0.49 to 3.17), heart failure (0.8 vs. 0 per 100 patients), stroke or TIA (0.2 vs. 0 per 100 patients), and arrhythmia (0.6 vs. 0.8 per 100 patients; RR 0.75, 95% CI 0.13 to 4.45) over a median follow-up of 16 months.

7.2.3.2 Key Question 2: Clinical decision making

Additional testing

SPECT was associated with a decreased incidence of ICA compared with NICE guideline-directed care up to 12 months of follow-up: 16.2 versus 42.5 per 100 patients; RR 0.38, 95% CI 0.30 to 0.49; RD –26.3%, 95% CI –33.4% to –19.2% (Figure 31). Unnecessary ICA (as described by the authors) was also less common following SPECT versus NICE guideline-directed care: 7.1 versus 28.8 per 100 patients; RR 0.25, 95% CI 0.17 to 0.36; RD –21.7%, 95% CI –27.9% to –15.5%. The primary reasons cited for an unnecessary ICA included a negative noninvasive test overruled by the attending physician (4.4 per 100 patients) and a false-positive test (2.5 per 100 patients) in the SPECT group, and direct referral to ICA (per algorithm) for patients with high pretest likelihood in the guideline-directed care group (24.6 per 100 patients). This trial did not report on additional noninvasive testing.

Treatment

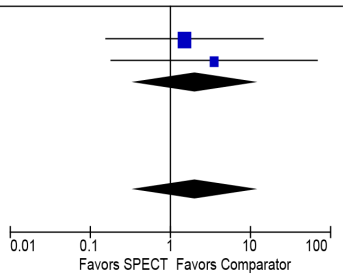
The frequency of any revascularization procedure over 12 months was similar between the SPECT and NICE guideline-directed care groups, respectively, (8.3 vs. 8.8 per 100 patients; RR 0.95, 95% CI 0.57 to 1.57), Figure 32, as was the frequency of PCI (5.6 vs. 5.8 per 100 patients; RR 0.96, 95% CI 0.51 to 1.80) and CABG (2.7 vs. 2.9 per 100 patients; RR 0.93, 95% CI 0.37 to 2.29) specifically. In both groups 0.8% of patients had an unplanned PCI over a median follow-up of 16 months (RR 1.0, 95% CI 0.18, to 5.41). There were no unplanned CABGs performed.

Hospitalization and ED visits

This trial did not report hospitalization or ED visits.

Figure 30. SPECT vs. NICE Guideline/Standard Care: Cardiac mortality

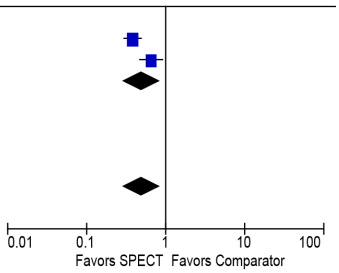
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs. NICE Guideline/Standard Care									
Greenwood 2017	16 months	OP, Stable	Suspected CAD	3	481	1	240	63.2%	1.50 [0.16, 14.31]
Lim 2013	12 months	ED/Hospital, Acute	Suspected ACS	3	1004	0	504	36.8%	3.52 [0.18, 67.96]
Subtotal (95% CI)					1485		744	100.0%	2.04 [0.25, 19.09]
Total events				6		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%									
Test for overall effect: Z = 0.78 (P = 0.43)									
Total (95% CI)					1485		744	100.0%	2.04 [0.25, 19.09]
Total events				6		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%									
Test for overall effect: Z = 0.78 (P = 0.43)									
Test for subgroup differences: Not applicable									



Greenwood = NICE guideline-directed care; Lim = Clinical assessment only.

Figure 31. SPECT vs. NICE Guideline/Standard Care: ICA

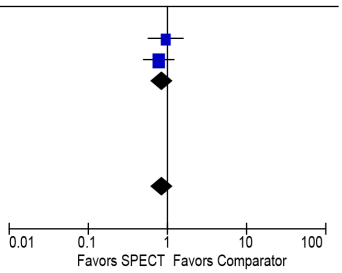
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs. NICE Guideline/Standard Care									
Greenwood 2017	16 months	OP, Stable	Suspected CAD	78	481	102	240	52.1%	0.38 [0.30, 0.49]
Lim 2013	12 months	ED/Hospital, Acute	Suspected ACS	73	1004	56	504	47.9%	0.65 [0.47, 0.91]
Subtotal (95% CI)					1485		744	100.0%	0.49 [0.26, 0.95]
Total events				151		158			
Heterogeneity: Tau² = 0.12; Chi² = 6.55, df = 1 (P = 0.01); I² = 85%									
Test for overall effect: Z = 2.60 (P = 0.009)									
Total (95% CI)					1485		744	100.0%	0.49 [0.26, 0.95]
Total events				151		158			
Heterogeneity: Tau² = 0.12; Chi² = 6.55, df = 1 (P = 0.01); I² = 85%									
Test for overall effect: Z = 2.60 (P = 0.009)									
Test for subgroup differences: Not applicable									



Greenwood = NICE guideline-directed care; Lim = Clinical assessment only.

Figure 32. SPECT vs. NICE Guideline/Standard Care: Any revascularization

Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs. NICE Guideline/Standard Care									
Greenwood 2017	16 months	OP, Stable	Suspected CAD	40	481	21	240	43.0%	0.95 [0.57, 1.57]
Lim 2013	12 months	ED/Hospital, Acute	Suspected ACS	48	1004	31	504	57.0%	0.78 [0.50, 1.21]
Subtotal (95% CI)					1485		744	100.0%	0.85 [0.57, 1.28]
Total events				88		52			
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.56); I² = 0%									
Test for overall effect: Z = 0.98 (P = 0.33)									
Total (95% CI)					1485		744	100.0%	0.85 [0.57, 1.28]
Total events				88		52			
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.56); I² = 0%									
Test for overall effect: Z = 0.98 (P = 0.33)									
Test for subgroup differences: Not applicable									



Greenwood = NICE guideline-directed care; Lim = Clinical assessment only.

7.3 SPECT versus ICA

One good-quality trial (N=446)[220,241] compared SPECT versus invasive coronary angiography (ICA) in patients with suspected or known (25% with prior MI) stable CAD referred for outpatient angiography (See Appendix Q). Referral to angiography was based on the results of an exercise ECG complete within 1 month of enrollment, the results of which were not available to the trial personnel. Patients in the SPECT arm were randomized to undergo rest and stress 99m Tc sestamibi SPECT with adenosine (or dobutamine if adenosine was contraindicated) while those randomized to the control arm underwent ICA as originally planned. Mean patient age was 61 years, and 69% were male. Patients were considered high-risk (69%) or low-risk (31%) according to the Pryor risk assessment and randomization was stratified based on pretest risk. Baseline cardiac risk factors included prior cerebrovascular accident (5%), peripheral vascular disease (9%), diabetes (12%), family history of CAD (26%), hypertension (56%), hyperlipidemia (75%), and smoking (44%). Patients were on a variety of cardiovascular related medications at baseline including antiplatelets, statins, and beta-blockers primarily as well as ACE inhibitors, calcium channel blockers, nicorandil, nitrates, diuretics, and angiotensin-II receptor antagonists. The primary follow-up period was 18 months. The secondary publication by Thom et al. (focused on cost-effectiveness) provided mortality data out to 72 months and post-index revascularization rates out to 32 months. This trial was conducted in the United Kingdom and funded by the National Institute for Health Research.

See Appendix D for details regarding study quality determination.

7.3.1 Summary of results

- There was insufficient evidence to draw conclusions regarding the risk of MI, all-cause mortality and cardiac mortality between groups. Over 18 months, the absolute risk was ≤2 per 100 patients across both test arms for all outcomes; at 72 months, the absolute risk of all-cause mortality was 3 per 100 patients. Given that these are rare events, the trial may not have been sufficiently powered to detect a difference (SOE Insufficient).
- Compared with ICA, SPECT was associated with a decreased risk of any revascularization after the index visit through 36 months (43.8 vs. 53.2 per 100 patients; RR 0.82, 95% CI 0.68 to 0.99; RD –9.4%, 95% CI –18.6% to –0.2%) (SOE Low). There was no difference in the risk of any hospitalization for chest pain (SOE Low).
- There was insufficient evidence to draw conclusions regarding impact of testing strategies on additional downstream NIT (SOE Insufficient).

Detailed results

7.3.2 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Myocardial infarction, all-cause mortality and cardiac mortality

Two patients randomized to SPECT compared with no patient randomized to ICA were admitted for acute MI over the 18-month follow-up (0.9 vs. 0 per 100 patients; p=0.16)[220], Table 49. There were no differences in the incidence of all-cause (1.8 vs. 1.8 per 100 patients) or cardiac (2.2 vs. 1.4 per 100 patients) mortality between diagnostic strategies by 18 months[220] or for all-cause mortality through 72 months (3.1 vs. 3.2 per 100 patients; RR 0.99, 95% CI 0.35 to 2.78)[241].

Other clinical outcomes

There was no difference between diagnostic strategies for the composite outcomes of any nonfatal event and any fatal plus nonfatal event at 18 months, or in the proportion of patents achieving a clinically significant improvement in Canadian Cardiovascular Society angina class (Table 49). There were no differences between SPECT and ICA on all subscales of the Seattle Angina Questionnaire or on the SF-36 health-related quality of life questionnaire at 6 and 18 months (Appendix Table O6).

7.3.3 Key Question 2: Clinical decision making

Additional testing

Most patients (78%) in the SPECT arm went on to get subsequent ICA during the 18-month follow-up. No patient in the ICA arm required repeat ICA. SPECT was associated with less additional noninvasive testing compared with ICA (0.4 vs. 3.6 per 100 patients; RR 0.12, 95% CI 0.02 to 0.98; RD –3.2%, 95% CI –5.8% to –0.6%)[220], Table 49; all but one additional test was SPECT imaging. The timing of additional noninvasive testing was unclear.

Treatment

Similar proportions of patients received revascularization following index testing with stress echocardiography versus ICA (30.4 vs. 34.2 per 100 patients, respectively; RR 0.89, 95% CI 0.68 to 1.16), to include rates of PCI and CABG.[220] However, SPECT was associated with a lower cumulative rate of revascularization over 36 months versus ICA (43.8 vs. 53.2 per 100 patients; RR 0.82, 95% CI 0.68 to 0.99; RD –9.4%, 95% CI –18.6% to –0.2%)[241], Table 49.

Hospitalization

There was no difference in the proportion of patients admitted for chest pain over 18 months in the stress echocardiography arm versus the ICA arm: 8.5 versus 6.3 per 100 patients, RR 1.35 (0.69 to 2.62)[220], Table 49.

Table 49. SPECT vs. ICA: Summary of primary and clinical decision making outcomes

Author, year RCT	Outcome	Timepoint	SPECT	ICA	Risk Ratio (95% CI)
Sharples 2007 Thom 2014 CECaT Suspected and known CAD Low (21%) and high (69%) risk.	**Admission for acute MI**	18 months	0.9% (2/224)	0% (0/222)	NC, p=0.16
	All-cause mortality	18 months	1.8% (4/224)	1.8% (4/222)	0.99 (0.25 to 3.91)
		72 months	3.1% (7/224)	3.2% (7/222)	0.99 (0.35 to 2.78)
	Cardiac mortality	18 months	2.2% (5/224)	1.4% (3/222)	1.65 (0.40 to 6.83)
	Total nonfatal events*	18 months	10.7% (24/224)	8.6% (19/222)	1.25 (0.71 to 2.22)
	Total nonfatal plus fatal events	18 months	16.4% (29/224)	10.8% (24/222)	1.20 (0.72 to 2.00)
	ICA/additional ICA	18 months	78.1% (175/224)	0% (0/222)	NC, p<0.001
	Additional noninvasive testing	18 months	0.4% (1/224)	3.6% (8/222)	0.12 (0.02 to 0.98)
	SPECT	18 months	0.4% (1/224)	3.2% (7/222)	0.14 (0.02 to 1.14)
	MRI	18 months	0% (0/224)	0.5% (1/222)	NC, p=0.32
	Revascularization (any)	Index Management	30.4% (68/224)	34.2% (76/222)	0.89 (0.68 to 1.16)
		36 months (cumulative)	43.8% (98/224)	53.2% (118/222)	0.82 (0.68 to 0.99)
	PCI	Index Management	17.4% (39/224)	24.8% (55/222)	0.70 (0.49 to 1.01)
	CABG	Index Management	12.9% (29/224)	9.5% (21/222)	1.37 (0.80 to 2.33)
	Unplanned PCI	18 months	0.4% (1/224)	1.8% (4/222)	0.25 (0.03 to 2.20)
	Unplanned CABG	18 months	0.4% (1/224)	1.4% (3/222)	0.33 (0.03 to 3.15)
	Admission for chest pain	18 months	8.5% (19/224)	6.3% (14/222)	1.35 (0.69 to 2.62)
	Significant improvement in CCS angina class (≥2 decrease)	6 months	33% (66/224)	32% (66/222)	0.99 (0.74 to 1.32)
		18 months	42% (87/224)	32% (65/222)	1.33 (1.02 to 1.72)

ACP = acute chest pain; ACS = acute coronary syndrome; Adj = adjusted statistically; CABG = coronary artery bypass graft; CCCS = Canadian Cardiovascular Society; CI = confidence interval; ICA = invasive coronary angiography; MD = mean difference; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SD = standard deviation; SF-36 = Short-Form 36 quality of life questionnaire.

*Includes admission for chest pain or acute MI, unplanned PCI or CABG, and other (other for the SPECT group = 1 post-CABG wound infection, 1 admission for breathlessness, 1 admission for ICD implant, 1 admission for suspected MI found to be muscular pain, 1 seen in A&E with chest pain in SPECT; and for the ICA group = 1 CVA post-ICA, observed overnight).

7.3.4 Key Question 3: Safety

Summary of results

- Test-related complications appear to be rare following SPECT in one good-quality trial (SOE Low).
- Data from one fair-quality trial was insufficient to draw conclusions regarding radiation exposure (SOE Insufficient). Mean exposure following SPECT was 14 mSv; exercise ECG does not use radiation.
- Adverse events from stress agents are relatively common and ranged from 2% to 13% of patients (5% to 37% of events) for dipyridamole and from 4% to 53% for regadenoson; the most

common events included headache, dyspnea, GI upset/nausea and dizziness or lightheadedness (SOE Low). Most reported symptoms are expected responses to the pharmacologic agents used.

Safety data were poorly reported by the included RCTs evaluating SPECT imaging as a first line diagnostic test. One fair-quality trial comparing SPECT with exercise ECG in a population of only women with stable angina and suspected CAD reported mean ionizing radiation exposure following index SPECT testing which was 14 mSv.[223] A second, good-quality trial comparing SPECT with NICE-guideline directed care reported that five test-related medical complications occurred, but none were following SPECT imaging.[88] The complications included one case of mild urticarial reaction following cardiac MRI, one vasovagal episode following cardiac CT, and one each of ventricular tachycardia, pseudo-aneurysm and popliteal deep venous thrombosis, and right coronary artery spasm and transient ST elevation following ICA. No further information was provided.

Given the lack of safety data reported by the included RCTs, additional studies reporting test-specific adverse events related to SPECT were evaluated for inclusion and are summarized below. See Appendix O for detailed results tables.

Adverse events related to Regadenoson and Dipyridamole

Three studies were identified that evaluated regadenoson or dipyridamole as stressor agents for SPECT MPI in patients with suspected or known CAD: two case series (one of regadenoson[134] and one of dipyridamole[158]) and one retrospective comparative cohort study comparing regadenoson versus dipyridamole.[13] For the purposes of this report, each arm of the comparative cohort was treated as a case series.

Across the two studies[13,158] reporting AEs following dipyridamole use for SPECT (N=284 patients in one study and N=604 adverse events in the other), the most common events included headache (13% of patients in one study; 37% of all AEs in the other), gastrointestinal upset/nausea (8% of patients; 11% of all AEs), chest pain (4% of patients; 12% of all AEs), dizziness or lightheadedness (6% of patients; 5% of all AEs), flushing (4% of patients; 8% of all AEs), and dyspnea (2% of patients; 5% of all AEs).

Across the two studies[13,134] reporting AEs following regadenoson use for SPECT (N=96 and 284), the most common events included dyspnea (30% and 53%), gastrointestinal upset/nausea (28% and 3%), chest pain (9% and 16%), dizziness or lightheadedness (8% and 13%), headache (7% and 12%), and flushing (4% and 6%).

Most reported symptoms are expected responses to the pharmacologic agents used. All reported side effects can be found in Appendix O, Table O26.

7.3.5 Key Question 4: Differential Effectiveness and Safety

None of the included trials evaluating SPECT versus stress echocardiography, exercise ECG, clinical assessment alone or NICE-guideline directed care reported safety or differential effectiveness or safety.

8 Positron Emission Tomography (PET) Results

8.1 PET versus SPECT

Two trials (total N=540) evaluated the effectiveness of PET compared with SPECT across different patient populations.

One trial (N=210)[168] randomized stable patients with a mixed of suspected (70%) or known (30%) CAD to initial diagnostic testing with PET versus SPECT in an outpatient setting. The mean patient age was 64 years, and 50% of patients were female. Presenting symptoms included any chest pain in 37%, shortness of breath in 16% and atypical angina in 15%. Baseline risk factors included high blood pressure in 49%, a family history of CAD in 19%, high cholesterol in 13% and congestive heart disease in 3%; in addition, 13% had undergone prior coronary angiography and 11% had a prior MI. PET imaging was performed using Rb-chloride for the radioactive tracer; all patients received dipyridamole as the stressor. SPECT imaging was performed using TI-chloride and Tc-labeled Sestamibi for radioactive tracers (dual-isotope technique); 94% of patients received dipyridamole as the stressor and 6% received dobutamine. Follow-up was a mean of 9 months (range, 6 to 12 months). This trial was conducted in the United States and funding was provided, in part, by industry (Bracco Diagnostics, Positron Corporation). This trial was rated as poor quality. Methodological limitations included unclear randomization and allocation concealment methods, lack of independent or blinded outcomes assessment, difference in sex (a key CAD risk factor) at baseline between treatment groups, and it was unclear whether there was comparable follow-up time between treatment groups.

The second trial (N=322)[189] randomized stable patients with known CAD presenting with new or worsening symptoms to receive PET versus SPECT in an outpatient setting. History of CAD was defined as presence of prior MI or prior coronary revascularization. The mean age of patients was 66 years, and 36% were female. Presenting symptoms included typical chest pain in 33%, atypical chest pain in 27%, non-anginal chest pain in 21%, and shortness of breath in 68%. Baseline cardiac risk factors included hyperlipidemia (99%), hypertension (90%), family history of cerebrovascular disease (43%), diabetes (28%), peripheral vascular disease (27%), smoking (18%), and prior cerebrovascular accident (15%). Sixteen percent of patients had atrial fibrillation. Regarding baseline medications, 89% of patients were taking aspirin, 78% were on 3 or more antianginal medications, 77% were on beta-blocker therapy, and 77% were on a statin. Both PET and SPECT imaging was performed using Tc-99m Sestamibi, RB-82 for the radioactive tracer and all patients in both groups received dipyridamole or regadenoson as the stressor. Follow-up was 12 months. This trial was conducted in the United States and funding was provided by Blue Cross Blue Shield. This trial was considered good quality.

8.1.1 Summary of results

- In the good-quality trial in patients with known CAD and new or worsening symptoms, the absolute risks of MI and all-cause mortality were ≤1 per 100 patients across both the PET and SPECT arms over 12 months, however the evidence was considered insufficient to draw conclusions (SOE Insufficient). There was no difference in the risk of ICA (29 vs. 28 per 100

patients); of diagnostic failure, defined as unnecessary ICA or additional confirmatory noninvasive testing within 2 months (2.0 vs. 2.5 per 100 patients); of any revascularization (16 vs. 15 per 100 patients); and of escalation in antianginal therapy (26 vs. 23 per 100 patients) (SOE Low for all).

- The only outcome reported by the older, poor-quality trial evaluating a mixed population of suspected and known CAD was cardiac mortality (absolute risk 3 vs. 4 in 100 patients over a mean 9 months) (SOE Insufficient).
- Neither trial reported on test safety or on differential effectiveness or safety.

Detailed results

Across both trials, there were no difference in any of the reported outcomes for patients randomized to PET versus SPECT (Table 50).

8.1.2 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

In the good-quality trial in patients with known CAD and new or worsening symptoms, the absolute risks of MI and all-cause mortality were ≤1 per 100 patients across both the PET and SPECT arms over 12 months.[189] The only outcome reported by the older, poor-quality trial evaluating a mixed population of suspected and known CAD was cardiac mortality (absolute risk 3 vs. 4 in 100 patients over a mean 9 months).[168] See **Error! Reference source not found.** for data.

8.1.3 Key Question 2: Clinical decision making

Over 12 months, the risk of ICA was 29 versus 28 per 100 patients; of any revascularization was 16 versus 15 per 100 patients; and of escalation in antianginal therapy was 26 versus 23 per 100 patients, for PET versus SPECT, respectively, in the good-quality trial.[189] The risk of diagnostic failure, defined as unnecessary ICA or additional confirmatory noninvasive testing within 2 months, was 2.0 versus 2.5 per 100 patients. See Table 50 for data. There was no difference on any of the SAQ subscales or in the Rose Dyspnea Score between test arms (Appendix H).

Table 50. Summary of primary clinical and decision-making outcomes for comparison of PET with SPECT

Study	Outcome	F/U	PET % (n/N)	SPECT % (n/N)	RR (95% CI)*
Mullani 2000 Mixed suspected or known CAD	Cardiac mortality†	Mean 9 (range 6-12) months	3% (3/105)	4% (4/105)	RR 0.75 (0.17, 3.27)
Patel 2019 Known CAD	MI (not specified)	12 months	0% (0/161)	1.2% (2/161)	NC, p=NS
	All-cause mortality	12 months	1% (1/161)	1.2% (2/161)	RR 0.50 (0.04, 5.46)
	Invasive coronary angiography	3 months	20.5% (33/161)	15.5% (25/161)	RR 1.32 (0.82, 2.11)
		6 months	22.4% (36/161)	18.6% (30/161)	RR 1.20 (0.78, 1.85)

		12 months	28.6% (46/161)	28.0% (45/161)	RR 1.02 (0.72, 1.45)
	Obstructive disease on angiography‡	3 months	15.5% (25/161)	10.6% (17/161)	RR 1.47 (0.83, 2.62)
	Diagnostic failure§	2 months	1.9% (3/161)	2.5% (4/161)	RR 0.75 (0.17, 3.30)
	Revascularization (PCI/CABG)	3 months	11.2% (18/161)	9.9% (16/161)	RR 1.13 (0.60, 2.13)
		6 months	12.4% (20/161)	11.8% (19/161)	RR 1.05 (0.58, 1.90)
		12 months	15.5% (25/161)	14.9% (24/161)	RR 1.04 (0.62, 1.74)
	Late revascularization after 3 months**	3 months	4.3% (7/161)	5.0% (8/161)	RR 0.88 (0.32, 2.36)
	Escalation in anti-anginal therapy††	3 months	25.5% (41/161)	23.0% (37/161)	RR 1.11 (0.75, 1.63)

CAD = coronary artery disease; MI = myocardial infarction; NC = not calculable; PET = positron emission tomography; RR = risk ratio; SPECT = single photon emission computed tomography

*Calculated unless otherwise indicated.

†2 of the deaths occurred in patients with prior history of CAD (3% [1/31] PET vs. 3% [1/31] SPECT), whereas 5 deaths occurred in patients with no prior history of CAD (3% [2/74] PET vs. 4% [3/73] SPECT).

‡Defined as stenosis of ≥ 50% of the left main coronary artery or ≥ 70% of a major epicardial or branch vessel or ≥ 70% of a graft vessel with occluded flow by native circulation for patients with history of coronary bypass graft surgery.

§Defined as unnecessary coronary angiography (i.e. absence of ≥ 50% stenosis in ≥1 vessels should the patient have undergone angiography) or additional confirmatory non-invasive testing such as repeat MPI, stress echo, of CCTA within 60 days of the baseline MPI

**Defined as the cumulative number of patients that had revascularization after 3 months.

††Defined as addition of another anti-anginal medication class or increase in dose or frequency of one or more of existing anti-anginal medications within 3 months post baseline MPI

8.1.4 Key Question 3: Safety

Neither trial reported on adverse events related to the diagnostic tests or radiation exposure.

8.1.5 Key Question 4: Differential Effectiveness and Safety

Neither trial reported differential effectiveness or safety.

9 Stress Echocardiography Results

Six trials (across 8 publications) evaluated the effectiveness and/or safety of stress echocardiography compared with exercise ECG (5 RCTs)[48,91,117,180,211,262], "standard care" (1 RCT)[180], and ICA (1 RCT)[220,241]. One trial included both an exercise ECG and a standard care comparison arm[180].

9.1 Stress Echocardiography versus Exercise ECG

Among the five trials comparing stress echocardiography with exercise ECG, two (total N=543) included stable patients with suspected CAD (known CAD was an exclusion criteria) treated on an outpatient basis (See Appendix Q). Mean patient age was 54 years in both trials. One trial enrolled only women[211] while in the second trial most of the population was male (68%). In the latter trial, patients' pre-test risk was considered low (41%), intermediate (34%), and high (25%); the other trial did not report pre-test risk. Regarding cardiac risk factors, there was a similar proportion of patients with diabetes in both trials (8% and 9%) but a greater proportion of patients with hypertension (49% and 18%), smoking history (21% and 8%), and family history of CAD (23% and 13%) in the trial enrolling women only. The latter trial, 42% of patients had hyperlipidemia and 76% were postmenopausal. Neither trial reported baseline pharmacological treatments. In one trial, patients in both arms underwent treadmill exercise using the standard Bruce protocol; in the echocardiography arm, intravenous contrast (Sonovue) was used as needed in technically difficult patients.[91,262] In the second trial, both treadmill exercise and pharmacological stressor (dobutamine) was used in the echocardiography arm depending on patient capability with no mention of whether contrast was used; treadmill exercise was used in the ECG arm. Mean follow-up periods were 28 and 36 months. One trial was conducted in the United Kingdom and the other in Canada. Both were funded by clinical research grants.

The remaining three trials (total N=854) comparing stress echocardiography with exercise ECG included patients with acute symptoms presenting to the ED or hospital (See Appendix Q). One RCT included low-risk patients with suspected ACS[180], one included patients with suspected or known CAD (27% with known ischemic heart disease) at primarily low (21%)-to-intermediate (69%) pretest risk[117], and the third (COSTAMI-II) included patients presenting with uncomplicated acute MIs.[48] Mean patient age ranged from 51 to 60 years across the trials. The majority of patients in all trials were male, with considerably more males in the trial evaluating those with uncomplicated MIs (57% to 61% vs. 87%). Regarding cardiac risk factors, the proportion of patients with prior MI ranged from 3% to 15%, prior revascularization from 3% to 25% (PCI, 2%–14% and CABG, 1%–11% in the 2 trials that reported it), hypertension from 36% to 66%, diabetes from 9% to 24%, and smoking from 44% to 63%. Pharmacological treatment at baseline varied across the populations. In the trial of low-risk patients with suspected ACS, 20% were taking antiplatelets, 13% beta-blockers, 11% calcium channel blockers, and 9% nitrates.[180] In the trial of low-to-intermediate risk patients with suspected or known CAD, 82% were taking aspirin, 52% statins, 41% beta-blockers and clopidogrel, 34% ACE inhibitors, and 23% calcium channel blockers.[117] The trial of uncomplicated MI patients did not report baseline medications. Two trials used dobutamine/atropine in the echocardiography arm while the third used either dobutamine or exercise as the stressor. Treadmill exercise was used in the ECG arms. Follow-up periods

ranged from 2 to 24 months. Two trials were conducted at multiple hospitals across several European countries[117,180] and one was conducted in the United Kingdom. One trial received support from professional societies[48] and the remaining two did not report any sources of funding.

One trial was considered good quality[91,262], one fair-quality[48] and three poor quality.[117,180,211] Methodological shortcomings in the fair quality trial included unclear allocation concealment methods, lack of blinding of outcome assessors and unclear attrition. Additional limitations in the poor-quality trials included unclear randomization sequence, between group differences at baseline on key CAD risk factors, and lack of a prespecified definition for a positive test in one trial. Both good-quality trials were in stable patients with suspected CAD. See Appendix D for details regarding study quality determination.

9.1.1 Summary of results

- There was insufficient evidence to draw conclusions regarding the risk of MI, all-cause mortality and cardiac mortality following stress echocardiography versus exercise ECG across the five trials. The absolute risks of MI and all-cause mortality across four trials were 1.3 vs. 0.9 and 0.6 vs. 0.9 per 100 patients, respectively, across follow-up periods ranging from 2 to 36 months. The absolute risk of cardiac mortality in one RCT was 0.5 vs. 0 at 36 months. Given that these are rare events, the trial may not have been sufficiently powered to detect a difference (SOE Insufficient).
- In stable patients with suspected CAD, stress echocardiography was associated with a reduced risk of ICA (1 good-quality RCT; 6.3 vs. 13.4 per 100 patients; RR 0.47, 95% CI 0.24 to 0.90; RD –7.1%, 95% CI –13.0 to –1.2%) (SOE Low) and additional downstream NIT (2 RCTs, 1 good and 1 poor quality; 5.8 vs. 42.7 per 100 patients; pooled RR 0.15, 95% CI 0.06 to 0.28, I^2=0%; pooled RD –31.6 (95% CI –49.3% to –14.0%, I^2=84%) (SOE Low) compared with exercise ECG over 28 to 36 months. Across the three trials in acute patients with a mix of known or suspected CAD, there was no difference between groups in either outcome, though one fair-quality trial tended to favor echocardiography for ICA (lower risk); heterogeneity was high possibly due to differences in populations, pretest risk and follow-up times (SOE Low for ICA; SOE Insufficient for additional NIT).
- Across trials in both stable (1 RCT) and acute patients (3 RCTs) with varying pretest risks of CAD, there were no differences between testing arms in the risk of revascularization (4 RCTs, 1 good, 2 fair and 1 poor quality) or (re)hospitalization (3 RCTs, 1 good, 1 fair and 1 poor quality) over follow-up periods ranging from 2 to 36 months (SOE Moderate for both).

Detailed results

9.1.2 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

9.1.2.1 Suspected CAD (stable, non-emergent, outpatient)

Myocardial infarction

One nonfatal MI occurred in both the stress echocardiography and the exercise ECG arms over a mean follow-up of 36 months in one good-quality trial[91,262] (N=385): 0.5% vs. 0.5 per 100 patients, RR 1.02 (95% CI 0.06 to 16.12), Figure 33. In the other poor-quality trial (n=158), which enrolled only women, there was also a total of two MIs (1.3 per 100 patients) over a mean follow-up of 28 months, however the authors did not report the incidence by study arm.[211]

All-cause and cardiac mortality

The good-quality trial[91,262] reported mortality, with a total of five all-cause deaths, one in the stress echocardiography arm versus four the exercise ECG arm: 0.5 vs. 2.1 per 100 patients; RR 0.25 (95% CI 0.03 to 2.25), Figure 34. The one death in the echocardiography arm was considered a cardiac death since evidence of coronary atherosclerosis was evident at autopsy (but no evidence of MI or acute coronary thrombosis). This patient was initially discharged based on a negative stress echocardiogram, re-admitted for urgent noncardiac surgery, and later died at home.

Other Outcomes

Both trials reported the incidence of MACE, with no difference between the stress echocardiography and the exercise ECG arms, respectively (Table 51). One good-quality RCT (N=385) defined MACE as death, nonfatal MI, late revascularization (>6 months), and hospitalization for chest pain [10.5 vs. 13.4 per 100 patients, mean follow-up 36 months][91,262] and the other poor-quality trial (N=158), in women only, did not define specific clinical events [7.7 vs. 7.4 per 100 patients, mean follow-up 28 months].[211] In the latter trial, the incidence of several other outcomes were reported for the overall population but not by test arm: unstable angina (1.3 per 100 patients), defined as prolonged or accelerating chest pain with EKG changes but no enzyme rise diagnostic of infarction; composite MI or unstable angina (2.5 per 100 patients overall); and acceleration of chest pain syndrome (9.5 per 100 patients), defined as symptoms not fulfilling criteria for MI or UA but resulted in frequency presentation to the clinic or ED. (See Appendix O, Tables O1 and O2 for other outcomes.)

9.1.2.2 Suspected or known CAD and suspected ACS (acute chest pain, ED/similar setting)

Myocardial infarction

There was no difference in the risk of MI across three trials[48,117,180] reporting various lengths of follow-up, both individually and when pooled (3 RCTs, N=707, 1.7 vs. 1.1 per 100 patients, pooled RR 1.52, 95% CI 0.18 to 8.52, I^2=8%), Figure 33. All MIs occurred in the two trials that included patients with either suspected or known CAD. In the poor-quality trial with 27% of patients with known ischemic heart

disease[117], there was one MI in the echocardiography group compared with two in the exercise ECG group over a mean follow-up period of 8.5 months. In the fair-quality trial evaluating uncomplicated MIs[48], nonfatal reinfarction occurred in five versus two patients, respectively, over 12 months (3.8 vs. 1.5 per 100 patients; RR 2.46, 95% CI 0.49 to 12.46). Of note, in the latter trial, four of the five MIs in the echocardiography group and both MIs in the exercise ECG group occurred following negative tests. The third, poor-quality trial in low-risk patients with suspected ACS which reported no MIs followed patients for only 2 months.[180]

All-cause mortality

There was no difference in the risk of all-cause mortality across three trials reporting various lengths of follow-up, both individually and when pooled (3 RCTs, N=707, 0.6 vs. 0.3 per 100 patients, pooled RR 1.60, 95% CI 0.13 to 21.89, I^2=0%)[48,117,180], Figure 34. All deaths occurred in the two trials that included patients with either suspected or known CAD. In the poor-quality trial with 27% of patients with known ischemic heart disease[117], there was one death in each group over a mean follow-up period of 8.5 months. In the fair-quality trial evaluating uncomplicated MIs[48], only one death occurred over 12 months and was in the echocardiography arm (0.8 vs. 0 per 100 patients; RR 2.95, 95% CI 0.12 to 71.88). The causes of death were not reported in either trial. The third, poor-quality RCT in low-risk patients with suspected ACS that reported no deaths followed patients for only 2 months.[180]

Cardiac mortality

None of the trials evaluating patients presenting to the ED or hospital with known or suspected CAD or suspected ACS reported on cardiac mortality.

Other Outcomes

There was no difference between stress echocardiography and exercise ECG in the frequency of MACE across two trials that included patients with either suspected or known CAD (Table 51). In the poor-quality trial with 27% of patients with known ischemic heart disease[117], the rate of the composite outcome of death, MI or revascularization, respectively, was 12.7 versus 16.6 per 100 patients (RR 0.77, 95% CI 0.44 to 1.34) and of death or MI was 1.4 versus 2.0 per 100 patients (RR 0.71, 95% CI 0.12 to 4.18) over a mean follow-up period of 8.5 months. In the fair-quality trial evaluating uncomplicated MIs[48], the frequency of death, nonfatal MI or unstable angina over 12 months was 19.7 versus 13.8 per 100 patients (RR 1.42, 95% CI 0.82 to 2.47). In the latter trial, the frequency of unstable angina requiring admission did not differ between those who received echocardiography versus exercise ECG, 15.2 versus 12.3 per 100 patients (16/130), RR 1.23 (95% CI 0.67 to 2.27). In a third trial[180], in patients with suspected ACS, there was no difference in quality of life at 2 months as measured by the Nottingham Health Profile (Appendix Table O2).

Table 51. MACE frequency in trials comparing stress echocardiography vs. exercise ECG
MACE frequency in trials comparing stress echocardiography vs. exercise ECG

Author, year RCT	Time point	MACE components	Echocardiography	Exercise ECG	Risk Ratio (95% CI)
Suspected CAD, stable outpatient					
Sanfilippo 2005	Mean 28 ± 14.2 months	"Clinical events" (NOS)	7.7% (8/104)	7.4% (4/54)	1.04 (0.33 to 3.29)
		MI or unstable angina	2.5% (4/158)*		NA
Zacharias 2017, Gurunathan 2018	Mean 36 ± 8.4 months	Death, nonfatal MI, late revascularization (>6 months), or hospitalization for chest pain	10.5% (20/191)	13.4% (26/194)	0.78 (0.45 to 1.35)
Suspected or Known CAD, ED/hospital					
Desideri 2005 COSTAMI-II Uncomplicated MI	12 months	Death, non-fatal MI, or unstable angina	19.7% (26/132)	13.8% (18/130)	1.42 (0.82 to 2.47)
Jeetley 2006 Suspected (63%), Known (27%) IHD	Mean 8.5 ± 4.9 months	Death, MI or revascularization	12.7% (18/142)	16.6% (25/151)	0.77 (0.44 to 1.34)
		Death or MI	1.4% (2/142)	2.0% (3/151)	0.71 (0.12 to 4.18)

ACS = acute coronary syndrome; adj. = adjusted; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ED = emergency department; HR = hazard ratio; IHD = ischemic heart disease; MACE = major adverse cardiac events; MI = myocardial infarction; NR = not reported; RCT = randomized controlled trial; UA = unstable angina.
*Not reported by test arm.

9.1.3 Key Question 2: Clinical decision making

9.1.3.1 Suspected CAD (stable, non-emergent, outpatient)

Additional testing

One good-quality trial[91] (N=385) reported that stress echocardiography was associated with a reduction in referral for ICA compared with exercise ECG over a mean of 36 months: 6.3 versus 13.4 per 100 patients, RR 0.47 (95% CI 0.24 to 0.90), RD –7.1% (95% CI –13.0 to –1.2), Figure 35; most ICAs occurred within 4 months as a direct consequence of the initial test [4.7 vs. 9.8 per 100 patients, RR 0.48 (95% CI 0.22 to 1.04)]. The second, poor-quality trial in women only did not report ICA rates.[211]

In both trials, compared with exercise ECG, stress echocardiography was associated with a reduction in any downstream noninvasive testing (i.e., stress echocardiography, cardiac MRI, SPECT or exercise ECG) (2 RCTs, N=543, 5.8 vs. 42.7 per 100 patients; pooled RR 0.15, 95% CI 0.06 to 0.28, I^2=0%, Figure 36; pooled RD –31.6%, 95% CI –49.3% to –14.0%, I^2=84%); results were similar for any downstream noninvasive testing requiring stress or imaging (i.e., stress echocardiography, cardiac MRI, SPECT) (2

RCTs, N=543, 5.4 vs. 40.7 per 100 patients, pooled RR 0.15, 95% CI 0.06 to 0.28, I^2=0%; pooled RD –30.7%, 95% CI –46.3% to –15.1%, I^2=80%), Figure 37. Only the good-quality trial[91] reported downstream noninvasive testing requiring radiation with no difference between the echocardiography and the ECG group, respectively: 0 versus 1.1 per 100 patients, RR 0.20 (95% CI 0.01 to 4.20); both additional tests were SPECT.

Treatment

There was no difference between groups in the subsequent rate of any revascularization in one good-quality trial with a mean follow-up of 36 months (N=385, 5.8 vs. 6.2 per 100 patients; RR 0.93, 95% CI 0.42 to 2.06)[91], Figure 38. The second, poor-quality trial in women only did not report revascularization rates.[211] Neither trial reported change in medication therapy based on initial diagnostic strategy.

Hospitalization and ED visits

One good-quality trial reported no difference between groups in subsequent hospitalization for chest pain over a mean 36 months (N=385, 7.9 vs. 9.8 per 100 patients; RR 0.80, 95% CI 0.42 to 1.53), Figure 39, but fewer ED visits in the stress echocardiography arm [14 (8 overnight stays) vs. 30 (29 overnight stays), p<0.01]; it was unclear from the article if the latter represented patients or events.[91]

9.1.3.2 Suspected or known CAD and suspected ACS (acute chest pain, ED/similar setting)

Additional testing

There was no difference in the frequency of referral to ICA across three trials with follow-up periods ranging from 2 to 12 months (3 RCTs, N=716, 24.4 vs. 28.4 per 100 patients, pooled RR 0.85 95% CI 0.36 to 1.33, I^2=64%)[48,117,180], Figure 35. Individually, only one poor-quality trial[117] showed a reduction in ICA referral favoring echocardiography (14.2 vs. 23.4 per 100 patients; RR 0.61, 95% CI 0.37 to 0.99) over a mean follow-up of 8.5 months, however, the estimate was marginally statistically significant. In this same trial, of those referred to ICA, more patients in the echocardiography versus exercise ECG arm showed significant coronary artery disease though the difference was not statistically significant (72.6 vs. 55.6 per 100 patients; RR 1.37, 95% CI 0.94 to 2.0).

Only poor-quality one trial[180] (N=152), in patients with suspected ACS, reported the frequency of additional noninvasive testing which was similar following stress echocardiography versus exercise ECG over 2 months: 10.3 versus 9.3 per 100 patients; RR 1.11 (95% CI 0.42 to 2.92), Figure 36. Noninvasive tests included primarily exercise ECG followed by transthoracic echocardiography.

Treatment

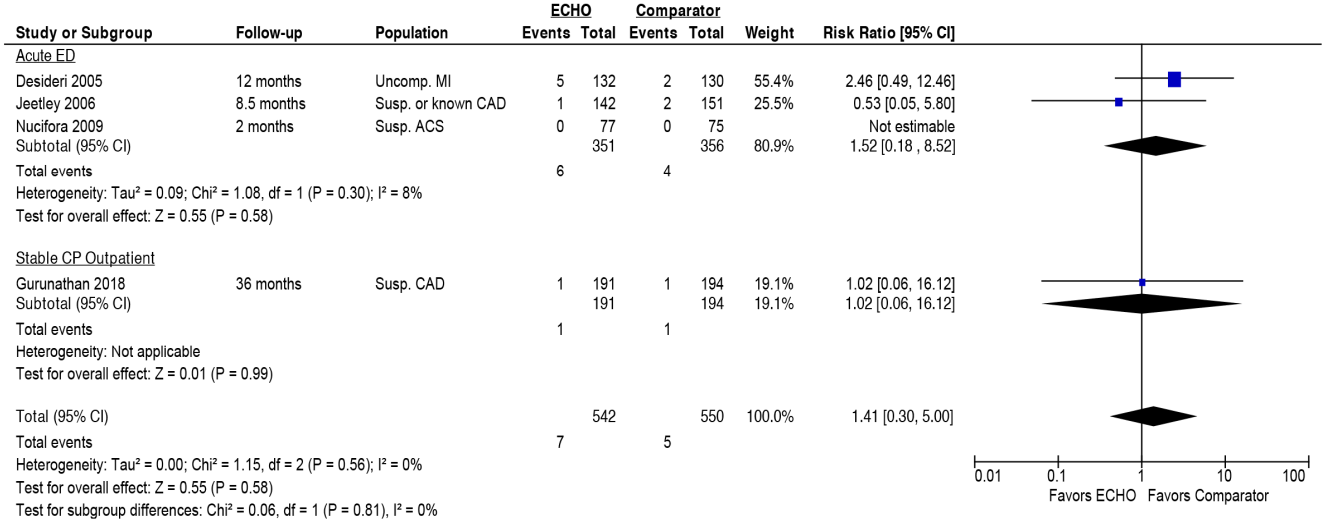
There was no difference in the incidence of any revascularization between diagnostic strategies across the same three trials, both individually and when pooled (3 RCTs, N=701, 19.1 vs. 20.2 per 100 patients; pooled RR 0.95, 95% CI 0.64 to 1.29, I^2=0%), Figure 38. Results were similar when just the better- (fair) quality trial was considered.[48] Results were similar when PCI and CABG were considered separately in two of these trials[48,180], one fair and one poor quality (Figure 40 and Figure 41).

One poor-quality trial in patients with suspected ACS reported pharmacological treatments prescribed at discharge which included nitrates in 14.5% (22/152), beta blockers in 21.7% (33/152), calcium channel blockers in 19.7% (30/152) and antiplatelets in 31.6% (48/152) of the population with similar prescribing patterns between diagnostic testing arms.[180] It was unclear, however, if these constituted only new medications for patients not taking them at baseline or whether/the degree to which patients' medications were discontinued and/or changed.

Hospitalization and length of stay

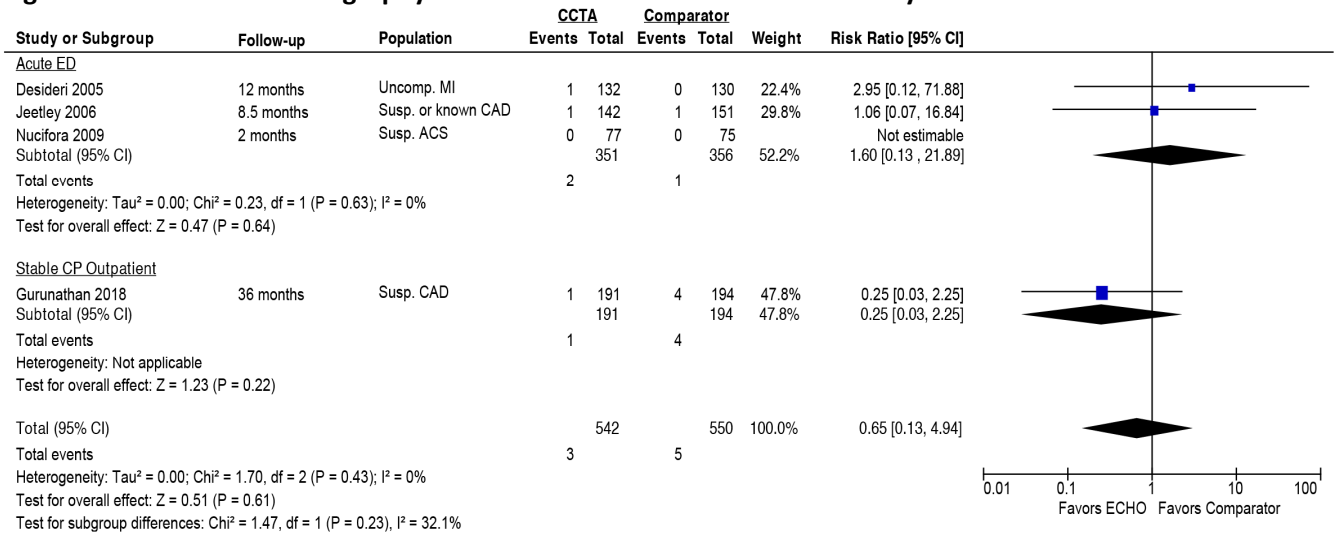
There was no difference in hospitalization rates across two trials, both individually and when pooled, with follow-up periods of 2 and 12 months (2 RCTs, N=414, 10.5 vs. 10.2 per 100 patients, pooled RR 1.07, 95% CI 0.26 to 2.29, I^2=42%)[48,180], Figure 39. Similarly, length of hospital stay was similar between groups in both trials: mean 9 versus 10 days in one fair-quality trial (patients with uncomplicated MI)[48] and 40 versus 39 hours in the other poor-quality trial (patients with suspected ACS)[180], Appendix O, Table O2.

Figure 33. Stress echocardiography versus exercise ECG: Myocardial infarction



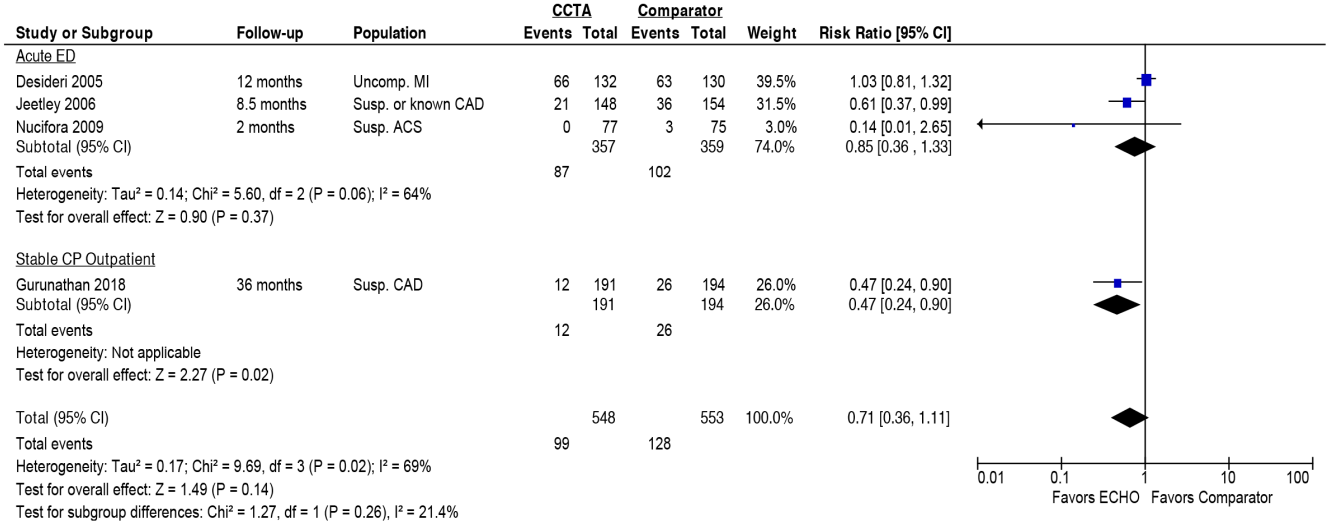
ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 34. Stress echocardiography versus exercise ECG: All-cause mortality



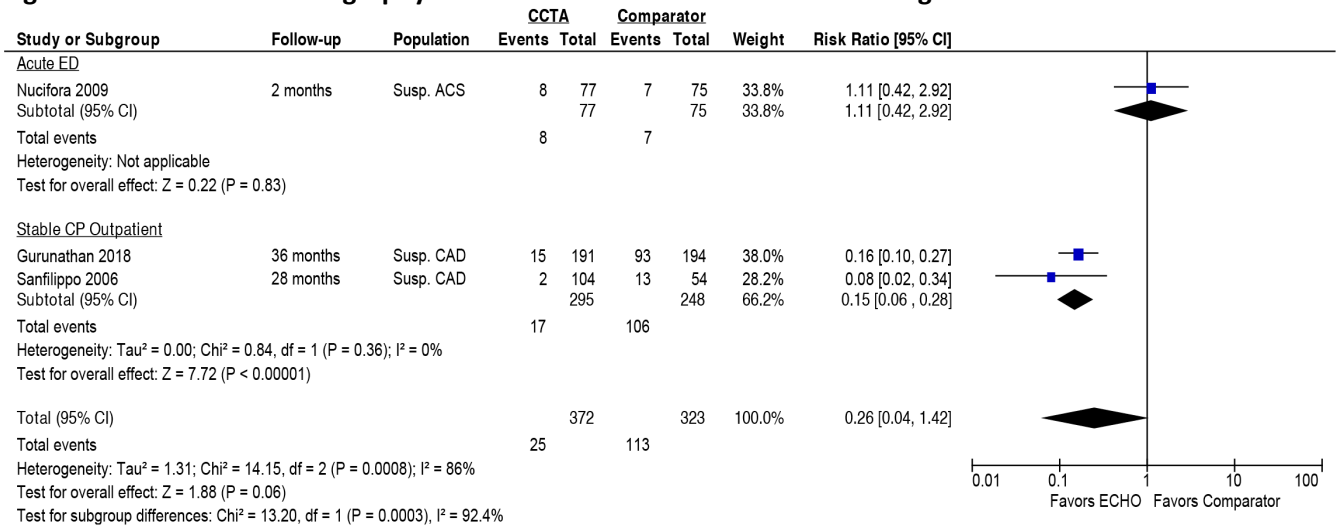
ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 35. Stress echocardiography versus exercise ECG: ICA



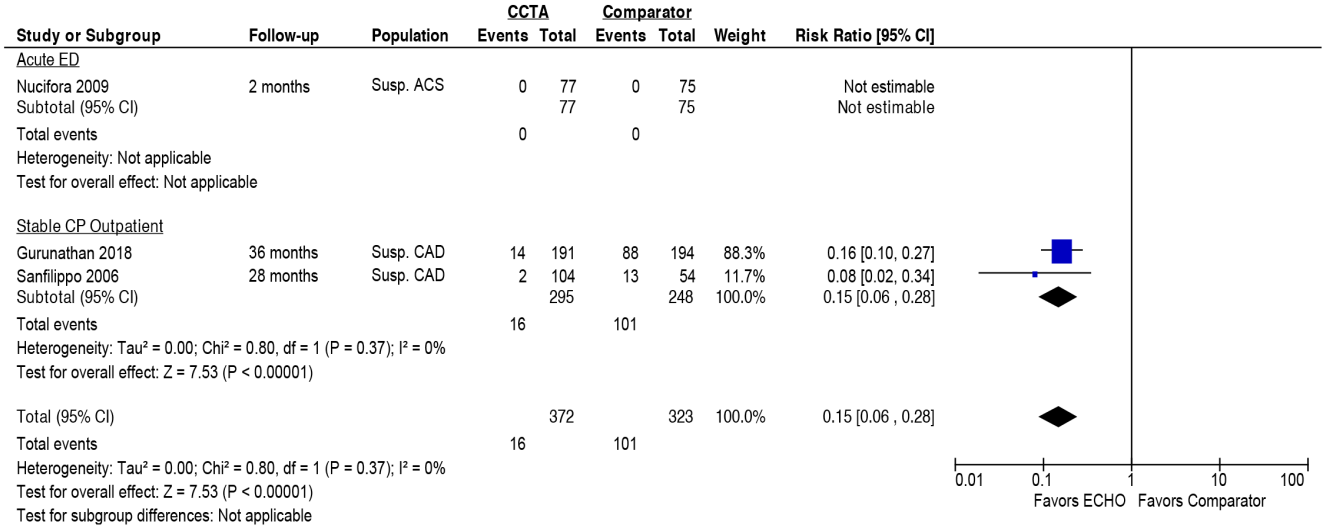
ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 36. Stress echocardiography versus exercise ECG: Noninvasive Testing



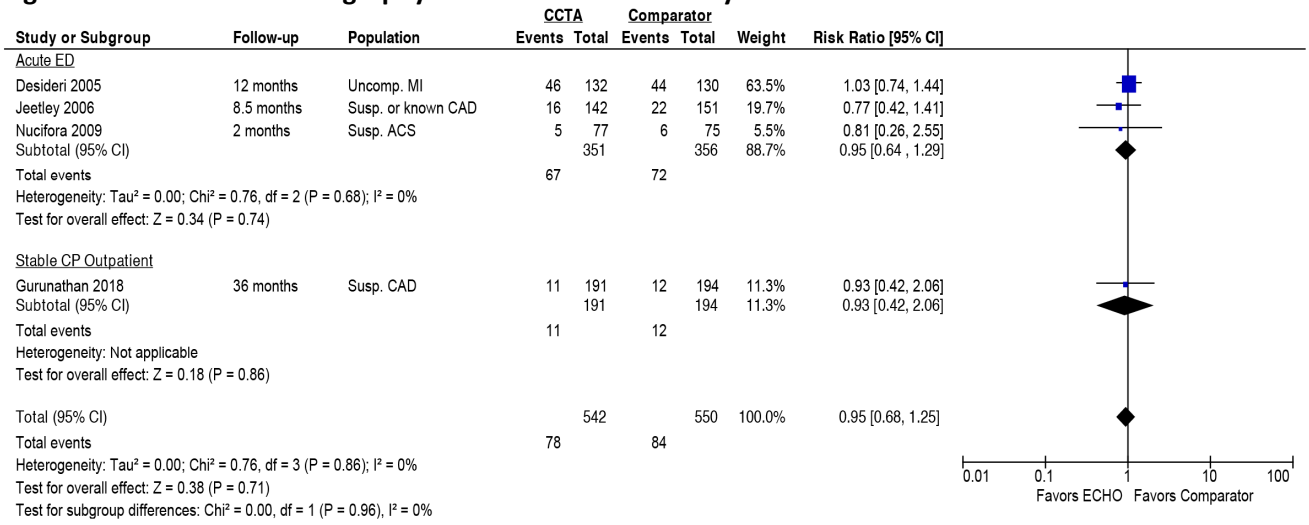
ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 37. Stress echocardiography versus exercise ECG: Any additional stress imaging NIT



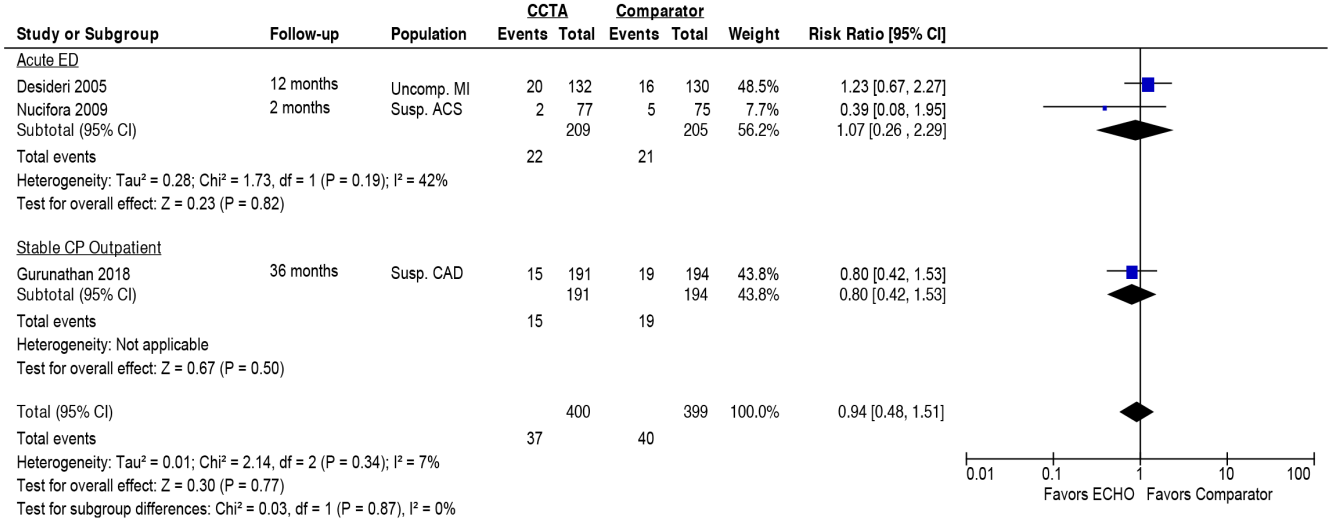
ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 38. Stress echocardiography versus exercise ECG: Any revascularization



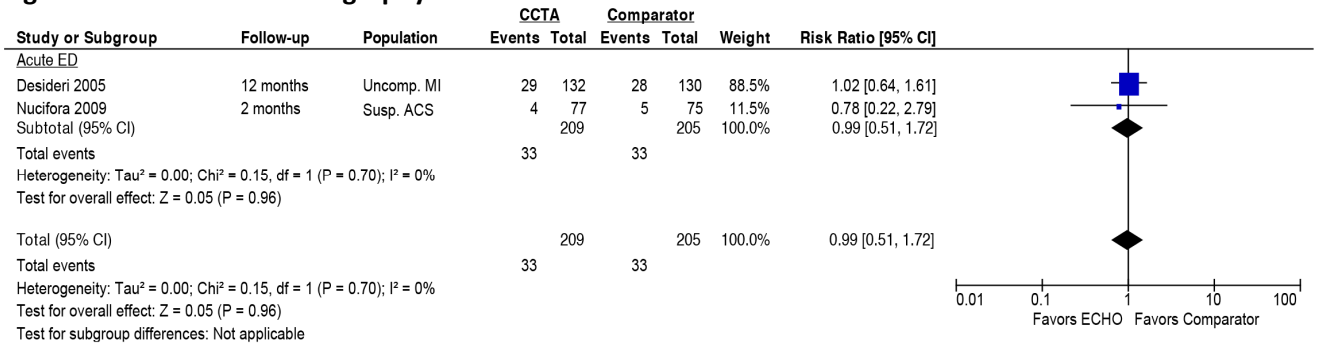
ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 39. Stress echocardiography versus exercise ECG: Hospitalization



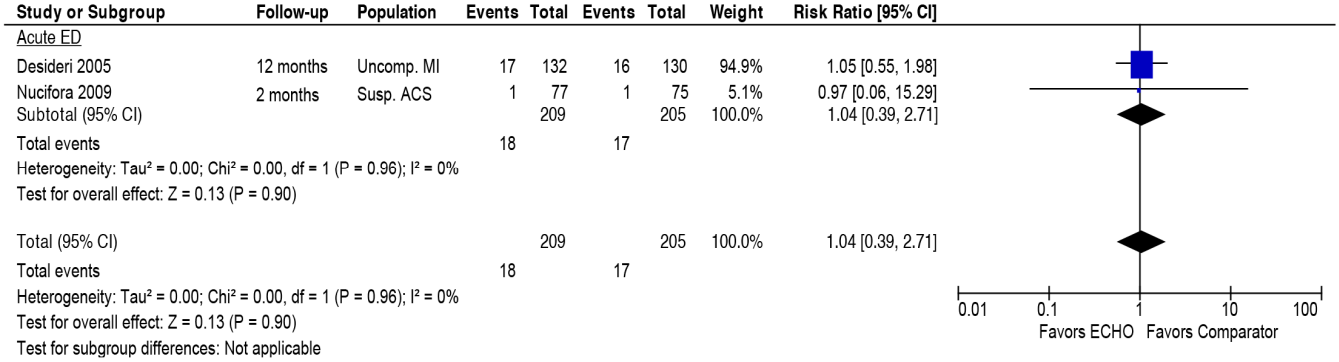
ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 40. Stress echocardiography versus exercise ECG: PCI



ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 41. Stress echocardiography versus exercise ECG: CABG



ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

9.2 Stress Echocardiography versus Standard Care

One trial (N=201)[180] compared stress echocardiography with "standard care" in low-risk patients with suspected ACS presenting to the ED (See Appendix Q). Mean patient age was 54 years and 46% were female. Twenty percent of patients presented with atypical ACS. Baseline cardiac risk factors included prior MI (2%), prior unstable angina (2%), prior revascularization (4%), diabetes (11%), hypercholesterolemia (39%), hypertension (42%), and smoking (48%). Pharmacological treatment at admission included antiplatelets (23%), beta-blockers (15%) calcium channel blockers (13%), and nitrates (10%). Patients randomized to echocardiography received dobutamine-atropine stress echocardiography; those with a negative test were immediately discharged. Patients randomized to standard care were hospitalized until a diagnosis was reached according to local protocols; the final diagnosis was achieved using clinical judgment only (i.e., no additional diagnostic examinations) in 71% of patients, exercise treadmill ECG in 13%, stress echocardiography in 11% and ICA in 5%. The follow-up period was 2 months. The trial was conducted across five European countries and did not report any sources of funding.

This trial was considered poor quality due to the following methodological shortcomings: unclear randomization and allocation concealment methods, lack of blinding of outcome assessors, lack of a prespecified definition for a positive test, and high attrition. See Appendix D for details regarding study quality determination.

9.2.1 Summary of results

- Data from one small, poor-quality trial (N=201) in acute patients with suspected ACS are insufficient to draw conclusions regarding the risk of MI, all-cause or cardiac mortality, ICA, additional downstream NIT, any revascularization and rehospitalization for acute chest pain following stress echocardiography versus standard care.
- No MIs and no deaths were reported in either test arm. Stress echocardiography resulted in fewer referrals for ICA and additional NITs, and fewer rehospitalizations for acute chest pain, but no difference in revascularization rates (SOE Insufficient).

Detailed results

9.2.2 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

No MIs and no deaths were reported over the 2-month follow-up period, Table 52.

9.2.3 Key Question 2: Clinical decision making

Compared with standard care, stress echocardiography was associated with fewer referrals to ICA (0% vs. 11%; RR 0.06, 95% CI 0.0 to 0.96; RD –10.9%, 95% CI –19.2% to –2.7%) and fewer additional noninvasive tests (10 vs. 49 per 100 patients; RR 0.21, 95% CI 0.10 to 0.43, RD –38.7%, 95% CI –53.6% to –23.8%) with no statistical difference between groups in revascularization rates (6.5 vs. 3.6 per 100

patients) or pharmacological treatments prescribed at discharge (Table 52). Fewer patients randomized to stress echocardiography were re-hospitalized for ACP over the 2-month follow-up period (3 vs. 15 per 100 patients; RR 0.18, 95% 0.04 to 0.81, RD –12.0%, 95% CI –21.9% to –2.0%) and length of hospital stay was significantly reduced in the echocardiography arm (MD –55 hours, 95% –75 to –35). The latter may in part be due to the design of trial/triage at presentation.

Table 52. Stress echocardiography vs. standard care

Author, year RCT	Outcome	Echocardiography	Standard care	Risk Ratio (95% CI)
Nucifora 2009 ASSENCE Suspected ACS Low risk Follow-up: 2 months	**All-cause mortality**	0% (0/77)	0% (0/55)	NC
	Nonfatal MI	0% (0/77)	0% (0/55)	NC
	ICA	0% (0/77)	11% (6/55)	**0.06 (0.0 to 0.96)**
	Revascularization	7% (5/77)	4% (2/55)	1.79 (0.36 to 8.87)
	PCI	5% (4/77)	2% (1/55)	2.86 (0.33 to 24.87)
	CABG	1% (1/77)	2% (1/55)	0.71 (0.05 to 11.17)
	Additional noninvasive testing	10% (8/77)	49% (27/55)	**0.21 (0.10 to 0.43)**
	Stress echocardiography	0% (0/77)	4% (2/55)	-----
	TE echocardiography	1% (1/77)	22% (12/55)	-----
	Electrocardiogram	9% (7/77)	24% (13/55)	-----
	Medications prescribed at discharge			
	Antiplatelet drugs	30% (23/77)	44% (24/55)	0.68 (0.43 to 1.08)
	Beta-blockers	21% (16/77)	29% (16/55)	0.71 (0.39 to 1.30)
	Calcium channel blockers	21% (16/77)	24% (13/55)	0.88 (0.46 to 1.68)
	Nitrates	13% (10/77)	22% (12/55)	0.59 (0.28 to 1.28)
	Rehospitalization for ACP	3% (2/77)	15% (8/55)	**0.18 (0.04 to 0.81)**
	Hospital length of stay (hours), mean ± SD	40 ± 42	95 ± 74	**MD –55 (–75.1 to –34.9)**

ACP = acute chest pain; ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CI = confidence interval; ICA = invasive coronary angiography; MD = mean difference; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SD = standard deviation.

9.3 Stress Echocardiography versus ICA

One good-quality trial (N=448)[220,241] compared stress echocardiography versus invasive coronary angiography (ICA) in patients with suspected or known (27% with prior MI) stable CAD referred for outpatient angiography (See Appendix Q). Referral to angiography was based on the results of an exercise ECG complete within 1 month of enrollment, the results of which were not available to the trial personnel. Patients in the echocardiography arm were randomized to undergo dobutamine-atropine stress echocardiography with contrast while those randomized to the control arm underwent ICA as originally planned. Mean patient age was 62 years, and 69% were male. Patients were considered high-risk (69%) or low-risk (31%) according to the Pryor risk assessment. Baseline cardiac risk factors included prior cerebrovascular accident (5%), peripheral vascular disease (8%), diabetes (12%), family history of CAD (27%), hypertension (55%), hyperlipidemia (77%), and smoking (45%). Patients were on a variety of cardiovascular related medications at baseline including antiplatelets, statins, and beta-blockers primarily as well as ACE inhibitors, calcium channel blockers, nicorandil, nitrates, diuretics, and

angiotensin-II receptor antagonists. The primary follow-up period was 18 months. The secondary publication by Thom et al. (focused on cost-effectiveness) provided mortality data out to 72 months and post-index revascularization rates out to 32 months. The trial was conducted at a single hospital in the United Kingdom and was funded by the National Institute for Health Research.

See Appendix D for details regarding study quality determination.

9.3.1 Summary of results

- There was insufficient evidence from one good-quality trial to draw conclusions regarding the risk of MI, all-cause mortality and cardiac mortality between groups. Over 18 months, the absolute risk was <3 per 100 patients across both test arms for all outcomes; at 72 months, the absolute risk of all-cause mortality was 4.9 vs. 3.2 per 100 patients. Given that these are rare events, the trial may not have been sufficiently powered to detect a difference (SOE Insufficient).
- There were no differences between stress echocardiography and ICA in the risk of additional downstream NIT (SOE Insufficient), any revascularization and hospitalization for chest pain across one trial (SOE Low for both).

9.3.2 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Myocardial infarction, all-cause mortality, cardiac death

Six patients randomized to stress echocardiography compared with no patient randomized to ICA were admitted for acute MI over the 18-month follow-up (2.7 vs. 0 per 100 patients; p=0.01), Table 53. There were no differences in the incidence of all-cause (2.7 vs. 1.8 per 100 patients) or cardiac (0.4 vs. 1.4 per 100 patients) mortality between diagnostic strategies by 18 months[220] or for all-cause mortality through 72 months (4.9 vs. 3.2 per 100 patients; RR 1.54, 95% CI 0.61 to 3.91).[241]

Other clinical outcomes

There was no difference between diagnostic strategies for the composite outcomes of any nonfatal event and any fatal plus nonfatal event at 18 months, or in the proportion of patents achieving a clinically significant improvement in Canadian Cardiovascular Society angina class (Table 53). There were no differences between stress echocardiography and ICA on all subscales of the Seattle Angina Questionnaire or on the SF-36 health-related quality of life questionnaire at 6 and 18 months (Appendix O).

9.3.3 Key Question 2: Clinical decision making

Additional testing

Most patients (75%) in the stress echocardiography arm went on to get subsequent ICA during the 18-month follow-up. No patient in the ICA arm required repeat ICA. No patient in the stress

echocardiography arm received additional noninvasive testing compared with eight patients in the ICA arm (0 vs. 3.6 per 100 patients, p=0.01), including seven SPECT and one cardiac MRI (Table 53). The timing of additional noninvasive testing was unclear.

Treatment

Similar proportions of patients received revascularization following index testing with stress echocardiography versus ICA (35.4 vs. 34.2 per 100 patients, respectively; RR 1.03, 95% CI 0.80 to 1.33), to include rates of PCI and CABG. The cumulative rates of revascularization remained similar over 36 months (53.5 vs. 53.2 per 100 patients; RR 1.01, 95% CI 0.85 to 1.20), Table 53.

Hospitalization

More patients were admitted for chest pain over 18 months in the stress echocardiography arm versus the ICA arm, however the difference was not significant: 10.6 versus 6.3 per 100 patients, RR 1.68 (0.89 to 3.17), Table 53.

Table 53. Stress echocardiography vs. ICA: Summary of primary clinical and decision-making outcomes

Author, year RCT	Outcome	Timepoint	Echocardiography % (n/N)	ICA % (n/N)	Risk Ratio (95% CI)*
Sharples 2007 **Thom 2014** CECaT Suspected and known CAD Low (21%) and high (69%) risk.	**All-cause mortality**	18 months	2.7% (6/226)	1.8% (4/222)	1.47 (0.42 to 5.15)
		72 months	4.9% (11/226)	3.2% (7/222)	1.54 (0.61 to 3.91)
	Cardiac mortality	18 months	0.4% (1/226)	1.4% (3/222)	0.32 (0.03 to 3.12)
	Admission for acute MI	18 months	2.7% (6/226)	0% (0/222)	NC, p=0.01
	Total nonfatal events†	18 months	13.7% (31/226)	8.6% (19/222)	1.60 (0.93 to 2.75)
	Total nonfatal plus fatal events	18 months	16.4% (37/226)	10.8% (24/222)	1.51 (0.94 to 2.45)
	ICA/additional ICA	18 months	74.8% (169/226)	0% (0/222)	NC, p<0.001
	Revascularization (any)	Index Management	35.4% (80/226)	34.2% (76/222)	1.03 (0.80 to 1.33)
		36 months (cumulative)	53.5% (121/226)	53.2% (118/222)	1.01 (0.85 to 1.20)
	PCI	Index Management	22.7% (51/226)	24.8% (55/222)	0.91 (0.65 to 1.27)
	CABG	Index Management	12.9% (29/226)	9.5% (21/222)	1.36 (0.80 to 2.31)
	Unplanned PCI	18 months	2.2% (5/226)	1.8% (4/222)	1.23 (0.33 to 4.51)
	Unplanned CABG	18 months	1.8% (4/226)	1.4% (3/222)	1.31 (0.30 to 5.79)
	Additional noninvasive testing	18 months	0% (0/226)	3.6% (8/222)	NC, p=0.01
	SPECT	18 months	0% (0/226)	3.2% (7/222)	NC, p=0.01
	MRI	18 months	0% (0/226)	0.5% (1/222)	NC, p=0.31
	Admission for chest pain	18 months	10.6% (24/226)	6.3% (14/222)	1.68 (0.89 to 3.17)
	Significant improvement in CCS angina class (≥2 decrease)	6 months	31% (67/226)	32% (66/222)	1.00 (0.75 to 1.33)
		18 months	34% (70/226)	32% (65/222)	1.06 (0.80 to 1.40)

ACP = acute chest pain; ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CI = confidence interval; ICA = invasive coronary angiography; MD = mean difference; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SD = standard deviation.
*Calculated by AAI
†Admission for chest pain or acute MI, unplanned PCI or CABG, and other (1 transient ischemic attack in echocardiography group; 1 cerebrovascular accident post-ICA, observed overnight in ICA group)

9.3.4 Key Question 3: Safety

Summary of results

- Data from one poor-quality trial is insufficient to draw conclusions regarding test-related complications.
- Across 11 case-series, the risk of major or life-threatening adverse events (e.g., death, MI, unstable angina, cerebrovascular accident, acute pulmonary edema) as a result of pharmacologic stress agents appears to be low: for dobutamine, ≤0.1% across all outcomes, and for dipyridamole and adenosine, no major adverse events were reported. Minor transient events (e.g., arrhythmias, chest pain, headache, dyspnea, nausea/vomiting) were not uncommon (SOE low for all); most reported symptoms are expected responses to the pharmacologic agents used.
- Definite or suspected contrast related adverse events and allergic reactions appear to be rare (≤2% across all studies/outcomes) (SOE Low)

Across all included trials and comparisons (stress echocardiography versus exercise ECG, "standard care" and ICA), only one trial comparing stress echocardiography with exercise ECG mentioned safety outcomes, the COSTAMI-II trials in patients with uncomplicated MIs presenting to the ED; the authors stated that no complications occurred during either test.[48]

Given the lack of safety data reported by the included RCTs, additional studies reporting test-specific adverse events related to stress echocardiography were evaluated for inclusion and are summarized below. Most identified studies were case series which are considered low quality (i.e., high risk of bias). See Appendix O (Tables O23-O25) for detailed results tables.

9.3.4.1 Adverse events related to Dobutamine (with or without atropine)

Eleven case series (N range, 86 to 2799), seven prospective and four retrospective, were identified that reported adverse events related to the use of dobutamine (with and without atropine) during stress echocardiography in patients with suspected or known CAD (10 studies)[20,45,87,122,155,164,181,191,193,229] and suspected ACS (one study).[77] The mean maximum dose of dobutamine ranged from 31.6 to 50.0 µg/kg/min. Six studies also used atropine (in 33% to 100% of the populations) to achieve target heart rate.

There were no deaths due to dobutamine as reported by six studies (total N=5512)[45,87,122,191,193,229] and the frequency of acute MI ranged from 0% to 0.1% across seven studies[45,87,122,155,191,193,229] (N range, 122

to 2799). One study reported a single case of unstable angina attributed to dobutamine (0.1%, N=802)[122] and another (N=1012) reported that no cerebrovascular accidents occurred.[45] The incidence of acute pulmonary edema was rare across two studies (0% [N=1012] and 0.1% [N=802]). Chest pain (not otherwise specified) was reported by three studies (N range, 86 to 1118) and ranged from 4.6% to 31.4%.

Arrythmia-related adverse events commonly reported across the studies included any arrhythmias or palpitations in six studies (range, 2.1% to 18.0%; N range, 122 to 1118), supraventricular or ventricular tachycardia in ten (range, 0% to 9.0%; N range, 86 to 2799), atrial or ventricular fibrillation in seven (range, 0% to 1.2%; N range 265 to 2799), and bradycardia in two large studies (≤0.2% in both). The occurrence of hypotension was reported in nine studies (range, 0.1% to 12.5%; N range, 86 to 2799) and hypertension in five studies (range, 0% to 7.5%; N range, 122 to 1118).

Other commonly reported side-effects included nausea and/or vomiting in six studies (range, 3.4% to 20.9%; N range, 86 to 1012), headache in four studies (0.8% to 13.6%; N range 122 to 1012), and dyspnea (range, 0% to 13.6%) and tremors (range, 0.4% to 2.4%) in three studies each (N range, 127 to 1012). Most studies reported that most events were minor and transient.

Most reported symptoms are expected responses to the pharmacologic agents used. All reported side effects can be found in Table O23 of the Appendix.

9.3.4.2 Adverse events related to Dipyridamole (with or without atropine) and Adenosine

Three case series (total N=946)[69,76,165], two prospective and one retrospective, were identified that reported adverse events related to the use of dipyridamole (with and without atropine) during stress echocardiography in patients with suspected or known CAD. In all studies the cumulative dose of dipyridamole was 0.84 mg/kg given over 4 min. No "major", severe, or life-threatening adverse events, to include death, MI and acute coronary syndrome, were reported by two studies (total N=837). All three studies (N range, 109 to 500) reported the frequency of hypotension/bradycardia which ranged from 0.8% to 6.4%, vomiting and nausea which ranged from 0.2% to 5.5%, and headache which ranged from 2.1% to 43%. Two studies reported the occurrence of arrythmias during stress testing which ranged from 2.7% (N=337) to 10.4% (N=550). Studies reported that most events were minor and transient.

One prospective case series (N=1429)[166] was identified that reported adverse events related to the use of adenosine during stress echocardiography in patients with suspected or known CAD. The most commonly occurring side-effects were hyperpnea (16.7%), atypical chest pain (9.9%), flushing (9.4%) and headache (6.6%).

Most reported symptoms are expected responses to the pharmacologic agents used. All reported side effects can be found in Tables O24 and O25 of the Appendix.

9.3.4.3 Adverse events due to non-iodinated contrast agent

Two retrospective comparative cohort studies (N=6,750)[15,119] and one retrospective non-comparative database study (N=3,071)[4] were identified that reported adverse events related to the use of non-iodinated contrast during stress echocardiography. One of the cohort studies presented results stratified by stable patients with suspected or known CAD and acute patients with suspected ACS[15] while the indications for stress echocardiography in the second cohort study were primarily ischemia assessment (80%) and heart transplantation (12.5%).[119] The database study used medical records to identify patients undergoing their first stress echocardiogram during a specific time period and the indication for the test was unclear. The contrast agents used varied across the studies and included Luminity (54%) and SonoVue (46%) in one cohort[15], Definity (100%) in the second cohort[119], and Definity (86%) and Opstison (14%) in the database study.[4]

One cohort study reported acute MI which was rare in both the contrast and non-contrast groups: 0% vs. 0.1%, respectively.[15] Across both comparative cohorts, the risk of allergic reaction to contrast agent was low and occurred in <0.5% of patients who received stress echocardiography with contrast.[15,119] There was a similar, low risk of arrythmias, hypotension, or severe hypertension between groups in one cohort study[15] while the second cohort study reported an increased risk of chest pain (23% vs. 17%; RR 1.35, 95% CI 1.12 to 1.62) in those who received contrast but a lower risk of palpitations (6% vs. 10%; RR 0.62, 95% CI 0.47 to 0.82) compared with those who did not received contrast; there was no difference between groups in other complications in the latter study.

The noncomparative database study reported definite and suspected contrast-related adverse events in 1.3% (41/3071) and 2.2% (68/3071) of patients[4], respectively. Backache, headache or both were rare (<1% each). Other adverse events that may be indicative of an allergic reaction were very rare and occurred in one patient (0.03%) each: transient wheezing without urticaria, urticaria or hives (limb and thorax) and swelling in the mouth, and throat tingling. Adverse reactions thought to be caused by concomitant infusion of contrast agent and dobutamine included chest pain (0.78%), nausea and vomiting (0.10%), and shivering and tremors (0.16%).

9.3.5 Key Question 4: Differential Effectiveness or Safety

None of the included trials comparing stress echocardiography with exercise ECG, “standard care” or ICA reported differential effectiveness or safety.

10 Strength of Evidence (SOE)

Table 10.1. Key Question 1: Strength of evidence: CCTA versus functional testing, primary clinical outcomes across patient populations

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Myocardial infarction Cumulative	Up to 58 months following index test	17 RCTs (N =22,328) **Suspected ACS** ACRIN-PA 2012 Hoffman 2012 Chang 2008 Dedic 2016 Goldstein 2007 Goldstein 2011 Hamilton-Craig 2014 Linde 2015 Levsky 2017 Uretsky 2017 Pineiro-Portela 2021 **Stable patients** Douglas 2915 Min 2012 Karthikeyan 2017 Stillman 2020 McKavanagh 2014 SCOT-HEART 2015	Yes (-1)	No	No	No	**CCTA vs. functional testing** Risk: 1.2 vs. 1.8 per 100 persons Pooled estimates (14 RCTs, N= 21,651) RR 0.70, 95% CI 0.56 to 0.89, I^2=0% RD 0.4, 95% CI 0.1 to 0.8 per 100; I^2=19% 3 smaller RCTs (N=667) reported no MI in either testing arm. **Conclusions:** Pooled estimates following exclusion of one trial in stable outpatients (SCOT-HEART) in which 85% of patients in the CCTA group also received functional testing (ETT) bordered the null (13 RCTS RR, 0.75, 95% CI 0.57 to 0.99) suggesting no clear association for reduction of MI with CCTA. Across all 14 trials, CCTA was associated with lower MI risk compared with functional testing based on pooled estimates; the RD (0.4 per 100 patients) was, however, small. Absolute MI risk was < 2 per 100 patients in both testing arms. Patients' pre-test risk across studies was predominately low to intermediate.	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Smaller trials may not have been sufficiently powered to detect a difference. **In patients with suspected ACS**, there was no difference in MI between tests at the time of index test, or at 1 to 6.5 months or ≥12 months after the index test. MI was most common around the time of index testing and occurred in 1.9 versus 2.8 per 100 patients. **In stable outpatients**, CCTA was associated with decreased risk of MI across 4 RCTS (pooled RR 0.64, 95% CI 0.44 to 0.87 I^2=0%) however following exclusion of the SCOT-HEART, results were no longer significant (3 RCTs pooled RR 0.69, 95% CI 0.27 to 1.14).	
All-cause Mortality Cumulative	Up to 58 months following index test	17 RCTs (N=21,680) **Suspected ACS** ACRIN-PA 2012 (Litt and Holland) Hoffman 2012 Chang 2008 Dedic 2016 Goldstein 2007 Goldstein 2011 Hamilton-Craig 2014 Linde 2015 Levsky 2015 Levsky 2018	Yes (-1)	No	No	No	**CCTA vs. functional testing** Risk: 1.2 vs. 1.3 per 100 persons Pooled estimate: 11 RCTs (N= 18,935) RR 0.99 95% CI 0.40 to 2.68, I^2=0% RD (not calculated, no association) 6 RCTs (N=2746) reported no mortality in either testing arm. **Conclusions:** CCTA was not associated with reduction in all-cause mortality compared with functional testing. The	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Uretsky 2017 Pineiro-Portela 2021 **Stable patients** Douglas 2015 Min 2012 Karthikeyan 2017 McKavanagh 2014 SCOT-HEART 2015					absolute risk was 1.2 per 100 patients across testing arms. Patients' pre-test risk across studies was predominately low to intermediate. Smaller trials may not have been sufficiently powered to detect a difference.	
Cardiac Mortality	Up to 58 months following index test	13 RCTs (N=11,647) **Suspected ACS** ACRIN-PA 2012 (Litt and Holland) Hoffman 2012 Goldstein 2007 Goldstein 2011 Nabi 2016 Hamilton-Craig 2014 Linde 2015 Levsky 2018 Uretsky 2017 **Stable patients** Min 2012 Stillman 2020 McKavanagh 2014 SCOT-HEART 2015	Yes (-1)	No	No	Yes (-2)	10 RCTs (N=5559) reported no cardiac mortality in either testing arm. 3 RCTs reported cardiac death **Stable patients:** 1 RCT CCTA 0.28% (5/2073) vs. ETT 0.28% (12/2073), RR 0.42, 95% CI 0.15 to 1.18) **Suspected ACS**: 2 RCTs (N=1942), 2 total events: 1 in CCTA (1 RCT), 1 in functional testing (1 RCT); RR 0.72, 95% CI 0.04 to 13.3) **Conclusions:** Firm conclusions regarding the impact of CCTA or functional testing on cardiac death are not possible. Cardiac death was rare. Sample sizes in individual trials may have been insufficient to detect cardiac death. Populations across trials were generally reported as low to intermediate CAD risk.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.2. Key Question 2: Strength of evidence: CCTA versus functional testing; decision-making, additional testing and management

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
ICA referral Cumulative	Up to 58 months	19 RCTs (N=22,335) **Suspected ACS** ACRIN-PA 2012 Hoffman 2012 Chang 2008 Dedic 2016 Goldstein 2007 Goldstein 2011 Hamilton-Craig 2014 Linde 2015 Levsky 2015 Uretsky 2017 Pineiro-Portela 2021 Levsky 2018 Nabi 2016 Miller 2011	Yes (-1)	No	No	No	**CCTA vs. functional testing** **Risk:** 14.4 vs. 12.0 per 100 persons **Pooled estimates** RR 1.25, 95% CI 1.09 to 1.47, I^2=67% RD 2.7, 95% CI 1 to 4 per 100, I^2=59% **Conclusions:** CCTA was associated with more frequent referral to ICA compared with functional testing across patient populations. Sensitivity analyses excluding outliers and poor-quality studies did not alter conclusions. However, in the stable population, exclusion of SCOT-HEART increased the effect size and strengthen the association between CCTA and ICA referral compared with functional testing and substantially reduced the heterogeneity (4 RCTS	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Stable patients Douglas 2015 Min 2012 Karthikeyan 2017 McKavanagh 2014 SCOT-HEART 2015					pooled RR 1.57, 95% CI 1.21 to 1.65, I2=0%, RD 4.1, 95% CI 3.0 to 5.2 per 100 patients).	
Any additional noninvasive testing	Up to 58 months	17 RCTs (N= 11,595) **Suspected ACS** ACRIN-PA 2012 Hoffman 2012 Chang 2008 Dedic 2016 Goldstein 2007 Goldstein 2011 Hamilton-Craig 2014 Linde 2015 Levsky 2015 Uretsky 2017 Pineiro-Portela 2021 Levsky 2018 Miller 2011 **Stable patients** Min 2012	Yes (-1)	Yes (-1)	No	Yes (-1)	**<u>CCTA vs. functional testing</u>** **Risk:** 7.2 vs. 7.6 per 100 persons **Pooled estimates** RR 0.82, 95% CI 0.53 to 1.28, I^2=83% RD (not calculated, no association) **<u>Conclusions</u>:** There was no difference in use of additional testing overall between CCTA and functional testing. Exclusion of poor-quality RCTs and outlying studies did not impact this conclusion. Substantial heterogeneity is noted and reasons are unclear.	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Karthikeyan 2017 McKavanagh 2014 SCOT-HEART 2015						
Any revascularization	55 days to 58 months	19 RCTs (N=23,124) **Suspected ACS** ACRIN-PA 2012 Hoffman 2012 Chang 2008 Dedic 2016 Goldstein 2007 Goldstein 2011 Hamilton-Craig 2014 Linde 2015 Levsky 2015 Uretsky 2017 Pineiro-Portela 2021 Levsky 2018 Nabi 2016 Miller 2011 **Stable patients** Douglas 2015 Min 2012 Karthikeyan 2017 McKavanagh 2014 SCOT-HEART 2015 Stillman 2020	Yes (-1)	Yes (-1)	No	No	**CCTA vs. functional testing** **Risk:** 9.5 vs. 7.1 per 100 persons **Pooled estimates** RR 1.52, 95% CI 1.26 to 1.90, I^2=66% RD 2.4, 95% CI 1.4 to 3.3 per 100, I^2=46% **Conclusions:** CCTA was associated with more frequent referral for revascularization. The conclusion did not change following exclusion of poor-quality RCTs or one RCT in which 85% of patients in the CCTA arm also received ETT.	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
PCI	Up to 58 months	12 RCTs (N=18,960) **Suspected ACS** Hoffman 2012 Dedic 2016 Miller 2011 Goldstein 2007 Goldstein 2011 Hamilton-Craig 2014 Linde 2015 Uretsky 2017 Levsky 2018 **Stable patients** Douglas 2015 McKavanagh 2014 SCOT-HEART 2015	Yes (-1)	Yes (-1)	No	No	**CCTA vs. functional testing** **Risk:** 8.2 vs. 6.0 per 100 persons **Pooled estimates** RR 1.63, 95% CI 1.22 to 2.35, I^2=74% RD 2.4, 95% CI 1.3 to 3.6 per 100, I^2=51% **Conclusions:** CCTA was associated with more frequent referral for PCI across populations. Exclusion of poor-quality and outlier trials had minimal effect on effect size or heterogeneity. Exclusion of the trial in which 85% of patients received ETT (SCOT-HEART) created a larger difference in risk between treatment groups (5.1 vs. 2.6 per 100 patients), substantially decreased heterogeneity and increased the effect size. (11 RCTs, pooled RR 1.89, 95% CI 1.38 to 2.43, I^2=36%); the conclusion remains the same.	⊕⊕⊕◯ MODERATE
Hospitalization ***Stable Outpatients***	Any	4 RCTs (N=14,810) Min 2012 Douglas 2015 McKavanagh 2014 SCOT-HEART 2015	Yes (-1)	Yes (-1)	No	No	**CCTA vs. functional testing** **Risk:** 4.3 vs. 4.5 per 100 patients, **RR** 1.00, 95% CI 0.29 to 1.75, I^2=77% **Conclusions: T**here was no difference in hospitalization between CCTA and functional testing. Heterogeneity is likely related to one RCTs which reported that CCTA was associated	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							with lower risk of hospitalization compared with ETT	
Hospitalization ***ED Patients with suspected ACS***	Index	8 RCTs (N=4,625) CCTA vs. any functional 4 RCTs (N=3,126) Litt 2012 Hoffman 2012 Chang 2008 Dedic 2016 CCTA vs. SPECT 2 RCTs (N=896) Goldstein 2007 Goldstein 2011 CCTA vs. Stress Echo 2 RCTs (N=603) Levsky 2018 Pineiro-Portela 2021	Yes (-1)	Yes (-2)	NO	No	**CCTA vs. (unspecified) functional tests** 4 RCTs 48 vs. 71 per 100 patients, pooled RR 0.69, 95% CI 0.60 to 0.85, RD –19.6 per 100, 95% CI –31.7 to –7.5 per 100 **CCTA vs. SPECT** 2 RCTs pooled RR 1.49, 95% CI 1.03 to 3.79 (NS) however the larger good-quality RCT (N= 699) in low pre-test risk patients, 27 per 100 patients in the versus 19 per 100 patients who received SPECT (RR 1.43, 95% CI 1.08 to 1.88) **CCTA vs. stress Echo** 2 RCTs (21.9 vs. 18.5 per 100 persons, pooled RR 1.18, 95% CI 0.48 to 3.00, NS). The largest RCT (N=400) CCTA (RR 1.76, 95% CI 1.08 to 2.85 **Conclusion:** Across comparators with CCTA at time of index testing, there is substantial heterogeneity and results are mixed. While 4 RCTs comparing CCTA with any functional test suggest that hospitalization is less common with CCTA, large studies of CCTA vs echocardiography and SPECT suggest	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							that hospitalization may be more common with CCTA	
	1 to 6.5 months after index	9 RCTs (N=5,144) Litt 2012 Hoffman 2012 Chang 2008 Dedic 2016 Goldstein 2007 Goldstein 2011 Linde 2015 Miller 2011 Nabi 2016	Yes (-1)	No	No	No	CCTA vs. functional testing 3.0 vs. 3.9 per 100 patients, pooled RR 0.76, 95% CI 0.49 to 1.1, I^2=18% **Conclusion**: There was no difference in hospitalization visits after index testing between CCTA and functional testing from 1 to 6.5 months post index visit.	⊕⊕⊕⊕ HIGH
	≥12 months after index	6 RCTs (N=3,624) Hollander 2016, Linde 2015 Levsky 2015 Levsky 2018, Uretsky 2017 Hamilton Craig 2014	Yes (-1)	No	No	No	14.9 vs. 17.4 per 100 patients, pooled RR 0.90, 95% CI 0.77 to 1.03, I^2=0%). **Conclusion: T**here was no difference in emergency department visits after index testing between CCTA and functional testing at ≥12 months after index visit	⊕⊕⊕⊕ HIGH
Subsequent ED visits	1 to 6.5 months after index	7 RCTs (N=4,294) **Acute ACS** Litt 2012, Miller 2011 Hoffmann 2012 Dedic 2016 Goldstein 2007 Goldstein 2011 Nabi 2016	Yes (-1)	No	No	No	5.9 vs. 6.7 per 100 patients pooled RR 0.84, 95% CI 0.66 to 1.06, I^2=0% **Conclusion**: There was no difference in emergency department visits after index testing between CCTA and functional testing	⊕⊕⊕⊕ HIGH

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
	≥12 months after index	5 RCTs (N=2,855) **Acute ACS** Hollander 2016 Levsky 2015 Levsky 2018 Pineiro-Portela 2021 Hamilton-Craig 2014	Yes (-1)	No	No	No	30.5 per 30.8 per 100 patients, pooled RR 1.06, 95% CI 0.93 to 1.56, I^2=16% **Conclusion**: There was no difference in emergency department visits after index testing between CCTA and functional testing	⊕⊕⊕⊕ HIGH
Medication changes	Any time	**Stable outpatients** 4 RCTs (N across 3 RCTs = 4,814; N unclear for PROMISE trial) PROMISE (Douglas 2015, Ladapo 2016), Min 2012, McKavanagh 2015 SCOT-HEART (2015, Williams 2018) **Acute ACS** 5 RCTs (N=3,157) Linde 2015, ACRIN-PA (Litt 2012, Hollander 2016), Levsky 2015, Levsky 2018, Uretsky 2017	Yes (-1)	Yes (-2)	No	No	CCTA was not consistently associated with initiation of, discontinuation of or changes in medications and results for many mediations were mixed. Evidence is insufficient to draw firm conclusions about the impact of testing on medication use. Medication use/change was documented differently across trials.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.3. Key Question 3: Strength of evidence: CCTA versus functional testing; Safety, harms and consequences of testing

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Any major test-related AE	Index test up to 24 hours	**3 RCTs (N= 10,270)** Stable outpatients (N=9,470) PROMISE (Douglas 2015) Suspected ACS (N=800) PROSPECT (Levsky 2015) Levsky 2018	Yes (-1)	No	No	Yes (-1)	**CCTA vs. Functional testing** 0% vs. 0% **Conclusion**: No major complications were observed in either arm in 3RCTs. Major complications were defined as death, renal failure requiring dialysis, or anaphylaxis requiring emergency respiratory and/or circulatory support in the PROMISE trial; stroke and cardiac arrest as part of MACE were considered in the other two. The two trials in patients with suspected ACS (N= 400 each) in particular may have been underpowered to detect rare events.	⊕⊕◯◯ LOW

Hospital admission for test-related complication	Index test up to 24 hours	**1 RCT (N=9,470)** **Stable outpatients** PROMISE/Douglas 2015	No	Unknown	No	Yes (-1)	**CCTA vs. any functional test** 0% vs. 0.1% (nuclear stress test)	⊕⊕◯◯ LOW
Any minor test-related AE		**12 RCTs (N=16,762)** **Stable outpatients (5 RCTs, N=12,978)** PROMISE/Douglas 2015, SCOT-HEART 2015 CAPP (McKavanagh 2015) IAEA-SPECT/CT (Karthikeyan 2017) RESCUE (Stillman 2020) **Suspected ACS (7 RCTs, N=3,784)** Chang 2008 ROMICAT-II (Hoffman 2012) ACRIN-PA (Litt 2012) BEACON (Dedic 2016) Goldstein 2007 PROSPECT (Levsky 2015) Levsky 2018	Yes (-1)	Yes (-1)	No	No	**CCTA:** 0% to 24% **Functional Testing:** 0% to 24% **Conclusions:** Risk of any minor test-related complication at time of index test or within 24 hours was <4% across treatment arms (10 RCT) Two RCTs in patients with suspected ACS which reported up to 24% of patients in both testing arms experienced minor events. These RCTs (Levsky 2015 and 2018) report a broader range of minor events including examination length and positional discomfort	⊕⊕◯◯ LOW

Contrast-related AEs Extravasation	Index test up to 24 hours	(CCTA arms only **Stable OP** (N=6,411) PROMISE (Douglas 2015, SCOT-HEART 2015 **Suspected ACS** 1 RCT (N=500) BEACON (Dedic 2016)	Yes (-1)	No	No	Yes (-1)	**CCTA only** **Conclusions:** Extravasation was rare (0.3% to 0.4%) in stable outpatients and 2% in patients with suspected ACS	⊕⊕◯◯ LOW
Nephropathy	Index test	Nephropathy 1 RCT (N=266) Chang 2008	Yes (-1)	unknown	No	Yes (-1)	Authors report that no cases of contrast-induced nephropathy occurred	⊕◯◯◯ **INSUFFICIENT**
Transient creatinine increase	Index test	**Suspected ACS** 2 RCTs (N=1,500) ROMICAT-II (Hoffman 2012) BEACON (Dedic 2016)	Yes (-1)	No	No	Yes (-1)	**CCTA** 0.2% to 1% **Functional test:** 0% to 0.4% **Conclusions:** Transient increases in creatinine not requiring dialysis were rare.	⊕⊕◯◯ LOW

Mild contrast-related reaction, allergic reaction, Skin rash/reaction, pruritis	Index test up to 24 hours	N for CCTA arms only **Stable outpatients** 2 RCTs (N=6,411) PROMISE (Douglas 2015, SCOT-HEART 2015 **Suspected ACS** 3 RCTs (N=596) Chang 2008 BEACON (Dedic 2016) PROSPECT (Levsky 2015	No	Yes	No	Yes (-2)	**CCTA arm only** **Stable outpatients:** **Stable OP**: 0.5% (35/6411) **Suspected ACS:** 1.2% (7/569) **Conclusions:** Contrast-related reactions were rare.	⊕⊕◯◯ LOW
Chest pain (CP), shortness of breath (SOB), or palpitations	Index test up to 24 hours	**2 RCTS (N=751)** **Suspected ACS** PROSPECT (Levsky 2015) Levsky 2018	Yes (-1)	No	No	Yes (-1)	**Suspected ACS (CP, SOB, palpitations)** **CCTA vs. SPECT** 1 RCT, 0.5% vs. 16% RR 0.03, 95% CI 0.004 to 0.24 **CCTA vs. Stress Echo** 1 RCT, 0% vs. 3%, p=0.03 **Conclusions:** CCTA was associated with lower risk of these symptoms, which are likely consistent with inducing cardiac stress	⊕⊕◯◯ LOW

Stress-Related symptoms and events (unspecified) and dipyridamole, adenosine-related events		**1 RCT (N=7,896)** **Stable outpatients** PROMISE (Douglas 2015)	No	Unknown	No	Yes (-1)	**CCTA vs. stress nuclear imaging** Stress-induced symptoms (unspecified) 0% vs. 0.1% Dipyridamole, adenosine related 0% vs. 0.2% **<u>Conclusions</u>:** The risk of symptoms and adverse events related to stress testing were confined to nuclear stress testing and were rare.	⊕⊕◯◯ LOW
Arrythmias: Rapid atrial fibrillation (AF) Ventricular tachycardia Bradyarrhythmia		**Stable outpatients** **1 RCT (N=7,896)** PROMISE (Douglas 2015) **Suspected ACS** **1 RCT (N=1,370)** ACRIN-PA (Litt 2012)	Stable No Suspected ACS Yes (-1)	Unknown	No	Yes (-1)	**CCTA vs. functional testing** **Stable outpatients** Rapid AF 0% vs. 0% Ventricular Tachycardia: 0% vs. 0.2% (nuclear stress test) **Suspected ACS** Bradyarrhythmia: 0.1% vs. 0.2%	⊕◯◯◯ INSUFFICIENT

Radiation exposure	Index Test	**5 RCTs total** **CCTA vs. SPECT** **Stable OP** 3 RCTs (N=6,832) PROMISE (Douglas 2015) IAEA-SPECT/CTA (Karthikeyan 2017) Min 2012 **Suspected ACS** 2 RCTs (N=1,297) CT-STAT (Goldstein 2011) Nabi 2016	Yes (-1)	Yes (-1)	No	No	Across five RCTs comparing CCTA specifically with SPECT, four reported that CCTA was associated with a lower effective radiation dose for the index test (estimated range 1.30 mSv to 11.9 mSv); the fifth trial reported that CCTA was associated with slightly higher radiation (estimated difference 1.8 mSv). **Conclusion:** CCTA may be associated with lower radiation exposure at index test compared with SPECT specifically. It is unclear if some of the differences between arms would impact clinical decision making.	⊕⊕◯◯ LOW

Radiation exposure	Cumulative	9 RCTs total **Stable OP** 3 RCTs (N=10,486) PROMISE (Douglas 2015) IAEA-SPECT/CTA (Karthikeyan 2017) Min 2012 **Suspected ACS** 6 RCTs (N=3,498) CATCH (Linde 2013) ROMICAT-II (Hoffman 2012) BEACON (Dedic 2016) PROSPECT (Levksy 2015) Nabi 2016 Levksy 2018	Yes (-1)	Yes (-1)	No	No	Range of rough estimated differences between arms reported higher for CCTA 1.9 mSv to 9.0 mSv **<u>Conclusions</u>:** Across nine RCTs, results are somewhat mixed, but suggest that cumulative radiation may be higher when CCTA is the initial test. It is unclear if some of the differences between arms would impact clinical decision making.	⊕⊕◯◯ LOW

Incidental findings: "potentially serious" or requiring additional imaging	Any time	3 RCTs (N=12,295) **Stable patients** Lu2017 (PROMISE) Williams 2018 (SCOT-HEART) Stillman 2020 (RESCUE) 2 systematic reviews (N=27,580) Karius 2014 Flor 2013 4 Retrospective cohorts (N=9,090) Karius 2019 Bendix 2011 Erol 2014 Ramanathan 2019	Yes (-2)	Yes (-1)	No	No	**CCTA only** **"**Any" incidental finding range: (28% to 44%) Findings that are "potentially significant" "clinically significant" or "required follow-up" range: 4.9% to 16% **Conclusion**: Incidental findings are common with CCTA with pulmonary findings being most common. There is wide range of findings that were considered potentially important that would likely result in the need to follow-up and/or require additional testing.	⊕⊕◯◯ LOW

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.4. Key Question 4: Strength of evidence: CCTA versus functional testing: Differential efficacy or safety for primary outcomes*

Outcome(s)	Subgroups	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Risk, Effect Estimate (95% CI), p for interaction	Quality (SOE)
Primary clinical outcomes								
Myocardial infarction **Median 3.2 years**	NICE classification of chest pain (non-anginal vs. possibly anginal)	1 RCT (N=3,370) **Stable outpatients** SCOT-HEART, 2018	Yes (-2)	Unknown	No	Yes (-1)	**CCTA vs. functional testing** **Nonanginal** 1.0 % vs. 1.5 %, HR 0.65 (95% CI 0.25 to 1.69) **Anginal** 1.9% vs. 3.2%, HR 0.58 (95% CI 0.34 to 0.99) *p=0.836* **Conclusions:** Although the effect of CCTA does not appear to vary based on anginal classification, it is not clear that this study was sufficiently powered for this evaluation.	⊕⊕◯◯ LOW
All-Cause mortality **Median 3.2 years**			Yes (-2)	Unknown	No	Yes (-2)	**CCTA vs. functional testing** **Nonanginal** 0.1% vs. 0.7%, HR 1.81 (95% CI 0.53 to 6.18) **Anginal** 0.5% vs. 0.5%, HR 0.82 (95% CI 0.44 to 1.53) *p=0.200* **Conclusions:** Although the effect of CCTA does not appear to vary based on anginal classification, it is not clear that this study was sufficiently powered for this evaluation. Authors do not state if subgroup analysis was planned a priori or conducted post hoc and do not describe specific hypotheses tested.	⊕◯◯◯ INSUFFICENT
CAD death			Yes (-2)	Unknown	No	Yes (-2)	**CCTA vs. functional testing**	⊕◯◯◯

Outcome(s)	Subgroups	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Risk, Effect Estimate (95% CI), p for interaction	Quality (SOE)
Median 3.2 years							**Nonanginal** 0% vs 0.3%, HR 0 (95% CI 0 to Infinity) **Anginal** 0.3% vs. 0.3%, HR 0.78 (95% CI 0.17 to 3.48) *p=0.998* **<u>Conclusions</u>:** Although the effect of CCTA does not appear to vary based on anginal classification, it is not clear that this study was sufficiently powered for this evaluation. Authors do not state if subgroup analysis was planned a priori or conducted post hoc and do not describe specific hypotheses tested.	INSUFFICENT
Decision making								
Downstream Testing	Diabetes Sex Race	1 RCT (N= 1,000) **Suspected ACS** ROMICAT-II trial (Hoffman 2012)	Yes (-2)	Unknown	No	No	**CCTA vs. functional testing** (no effect sizes provided) ***Index visit*** **Diabetes:** 38% vs. 5% **No diabetes:** 20% vs. 12% *p=0.0001* ***28-day follow-up*** **Diabetes:** 42% vs. 7% **No diabetes:** 23% vs. 13% *p=0.002* **Sex p-value for interaction** Index visit, p=0.08	⊕⊕◯◯ LOW

Outcome(s)	Subgroups	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Risk, Effect Estimate (95% CI), p for interaction	Quality (SOE)
							28-day follow-up, p=0.23 **Race p-value for interaction** Index visit, p=0.16 28-day follow-up, p=0.18 **Conclusions:** Diabetes status may modify the effect of CCTA: more downstream testing occurred with CCTA in patients with diabetes at index visit and by 28-day follow-up Downstream testing. No interaction (differential effect) by sex or race was seen. (See full report)	
ICA referral	Diabetes Sex Race	**Stable OP** 1 RCT (N= 8,966) PROMISE (good quality) **Suspected ACS** 1 RCT (N= 1,000) ROMICAT-II trial (fair quality)	Diabetes Yes (-1) Sex, Race Yes (-2)	No Sex, Race Unknown	No	No	**Conclusions:** Across two RCTs, one in stable outpatients and the other in patients with suspected ACS the effect of CCTA versus functional testing on ICA referral did not vary by diabetes status (p-values 0.596 and 0.06) There was no effect modification in the trial in patients with suspected ACS by sex or race at index visit or by 28-day follow-up. P-values for interaction across all subgroups were not statistically significant. (See full report.)	Diabetes ⨁⨁◯◯ LOW Sex, Race ⨁◯◯◯ INSUFFICIENT
Revascularization	Diabetes Sex Angina classification	Stable OP 2 RCTs PROMISE (N=8,966)	Diabetes Yes (-1)	Diabetes Yes (-1)	No	No	**Diabetes** (2 RCTs, PROMISE, ROMICAT-II) The effect of CCTA versus functional testing on revascularization did not vary by diabetes status within 30 days of ICA (PROMISE) or 28 days of	Diabetes ⨁⨁◯◯ LOW

Outcome(s)	Subgroups	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Risk, Effect Estimate (95% CI), p for interaction	Quality (SOE)
		SCOT-HEART (N=3,770) **Suspected ACS** 1 RCT (N= 1,000) ROMICAT-II trial	Sex Yes (-2) Angina Yes (-1)	Sex, angina Unknown		Sex Yes (-1) Angina Yes (-1)	follow-up (ROMICAT) (p-values, 0.372 and 0.26). **Sex:** (ROMICAT-II) The effect of CCTA versus functional testing on revascularization was not modified by sex (p=0.33) **Angina classification**: (SCOT-HEART) The effect of CCTA versus functional testing on revascularization was not modified by angina classification (p=0.938) See full report	Sex, ⨁◯◯◯ INSUFFICIENT Anginal classification ⨁◯◯◯ INSUFFICIENT
Safety								
Radiation Exposure (mSv) (cumulative) ≤90 days	Age (N=6355) Sex (N=6626) BMI (N=6301) Heart Rate (N=NR)	**Stable OP** 1 RCT (N= 8,966) PROMISE	Yes (-2) (Population subset)	Unknown	No	No	**Age** (<65**,** ≥65 years), p= 0.72 **Sex** (Male, female), p=0.82 **BMI** (<30 kg/m^2, ≥30 kg/m^2), p=0.10 **Heart rate** (<75 bpm, ≥75 bpm), p =0.04 See full report **Conclusion:** CTTA cumulative radiation may vary based on baseline heart rate. Patients with ≥75 bpm may have higher cumulative radiation with CCTA compared with functional testing. Tests for interaction by Age, sex and BMI were not significant.	⨁◯◯◯ INSUFFICIENT
Radiation Exposure (mSv) Index test	Sex	Suspected ACS ROMICAT-II trial (N=NR)	Yes (-2)	Unknown	No	Yes -1	**CCTA vs. functional testing (mSv mean (SD)** **Female** 10.8 (8.7) vs. 4.7 (8.1) **Male**1 14.2 (11.2) vs. 4.7 (8.7) p= 0.003	⨁◯◯◯ INSUFFICIENT

Outcome(s)	Subgroups	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Risk, Effect Estimate (95% CI), p for interaction	Quality (SOE)
							Conclusion: Mean radiation dose at index varied by sex. Doses were higher for men receiving CCTA vs. functional testing.	
Radiation Exposure (mSv) (cumulative) To 28 days	Sex Diabetes Race	Suspected ACS ROMICAT-II trial (N=NR)	Yes (-2)	Unknown	No	Yes -1	**CCTA vs. functional testing (mSv mean (SD)** **Female** 11.0 (8.9) 6.0 (8.2) **Male** 14.7 (12.0) vs. 5.6 (10.7) p= 0.002 **Diabetes** 18.4 (14.7) 6.6 (10.4) **No diabetes** 13.4 (9.8) 5.1 (9.5) P=0.04 Median, IQR **White** 12.0 (7.9 to 17.2) vs 0.0 (0.0 to 12.4) **Black** 11.7 (8.6 to 16 vs. 0.0 (0.0 to 0.0) P=0.60 **Conclusion:** Mean cumulative radiation dose by 28 days varied by sex and diabetes status but not by race for CCTA vs. functional testing. Higher doses in the CCTA groups were seen for men and patients with diabetes. Race did not modify the relationship between testing and dose.	⊕◯◯◯ INSUFFICIENT

*Strength of evidence for evaluation of differential efficacy or safety considers of the overall study risk of bias (study quality) as well as whether subgroup variables and analyses were specified a priori, number of subgroups tested, the hypothesized impact and direction of a subgroup and sample size as evaluation of interaction requires greater sample size.

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice; For HTE evaluation this may be down-graded an additional level based on failure to specify subgroup analysis *a priori* or if the subgroup hypothesis was not one of a smaller number tested and/or not stated (i.e. large number of subgroups tested)
2. Inconsistency: differing estimates of effects across trials

3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with TT
5. Imprecise effect estimate for a dichotomous outcome: small sample size, rare outcome
6. Serious risk of bias in evaluation of HTE: the subgroup variables were specified at randomization, however the hypothesized direction was not stated; the subgroup hypothesis was not one of a smaller number tested

Table 10.5. Key Question 1, 2 and 3: Strength of evidence: CCTA vs. ICA

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction Cumulative **Mortality, all-cause** Cumulative **Mortality, cardiac** Cumulative	12 months, median 40 months	2 RCTs (N=1,832) **Chang 2019** Suspected CAD, stable outpatients **Dewey 2016** Suspected CAD, stable and acute, atypical chest pain	No	No	No	Yes (-2)	**MI** Risk: 0.3 vs. 0.2 per 100 patients Pooled estimates (2 RCTs, N=1,832): RR 1.26 (95% CI 0.24 to 6.67), I^2=0% RD (not calculated, no association) **All-cause mortality** Risk: 0.2 vs. 0.2 per 100 patients Pooled estimates (2 RCTs, N=1,832): RR 1.03 (95% CI 0.06 to 11.08), I^2=0% RD (not calculated, no association) **Cardiac mortality** Risk: 0 vs. 0.6 per 100 patients 1 RCT (N=329) **Conclusions:** There was no difference in the risk of MI or all-cause mortality for CCTA vs. ICA, despite difference in populations and follow-up duration across the trials. Firm conclusions	MI, all-cause mortality ⊕⊕◯◯ LOW Cardiac mortality ⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							regarding the impact of CCTA or ICA on cardiac death are not possible. Cardiac death was rare. Sample sizes in individual trials may have been insufficient to detect cardiac death.	
Key Question 2: Clinical Decision-Making Outcomes								
ICA not showing obstructive CAD	12 months, median 40 months	2 RCTs (N=1,832) **Chang 2019** Suspected CAD, stable outpatients **Dewey 2016** Suspected CAD, stable and acute, atypical chest pain	No	No	No	Yes (-1)	Risk: 22 vs. 65 per 100 patients Pooled estimates (2 RCTs, N=1,019): RR 0.32 (95% CI 0.18 to 0.51), I^2=0% RD –48% (95% CI –67% to –29%), I^2=73% **Conclusions:** CCTA was associated with a decreased risk of ICA showing no obstructive CAD compared with direct referral to ICA.	⊕⊕⊕◯ MODERATE
Additional NIT (any)	12 months	1 RCT (N=1,503) **Chang 2019** Suspected CAD, stable outpatients	No	Unknown	No	Yes (-1)	Risk: 53 vs. 27 per 100 patients RR 1.96 (95% CI 1.71 to 2.25) RD 26.0% (95% CI 21.1% to 30.7%) **Conclusions:** CCTA was associated with an increased risk of additional downstream testing compared with direct referral to ICA.	⊕⊕⊕◯ MODERATE
Revascularization (any)	12 months, median 40 months	2 RCTs (N=1,832) **Chang 2019** Suspected CAD,	No	No	No	Yes (-1)	Risk: 13 vs. 18 per 100 patients Pooled estimates (2 RCTs, N=1,832): RR 0.71 (95% CI 0.55 to 0.96), I^2=0% RD –5.0% (95% CI –8.0% to –2.0%),	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		stable outpatients **Dewey 2016** Suspected CAD, stable and acute, atypical chest pain					I^2=0% **Conclusions:** CCTA was associated with a decreased risk of revascularization compared with direct referral to ICA.	
Hospitalization, cardiac causes	12 months	1 RCT (N=1,503) **Chang 2019** Suspected CAD, stable outpatients	No	Unknown	No	Yes (-1)	Risk: 4 vs. 4 per 100 patients RR 0.98 (95% CI 0.60 to 1.58) RD (not calculated, no association) **Conclusions:** There was no difference in the risk of cardiac hospitalization with CCTA compared with direct referral to ICA.	⊕⊕⊕◯ MODERATE
Key Question 3: Safety								
Major adverse events	≤48 hours, median 12 months	2 RCTs (N=1,832) **Chang 2019** Suspected CAD, stable outpatients **Dewey 2016** Suspected CAD, stable and acute, atypical chest pain	No	No	No	Yes (-2)	**Any complications prolonging hospital stay** Risk: no events in either test arm 1 RCT (N=327) **Major bleeding** Risk: 0 vs. 0.3 per 100 patients 1 RCT (N=1,503) **Conclusions:** There was no difference in the risk of major adverse events between CCTA and ICA. Given that the events are rare, trials may have been	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							under powered to detect a difference.	
Minor adverse events	≤48 hours after last procedure	2 RCTs (N=327) **Dewey 2016** Suspected CAD, stable and acute, atypical chest pain	No	Unknown	No	Yes (-1)	**Any minor procedural complication** Risk: 4 vs. 11 per 100 patients RR 0.35 (0.14 to 0.86) RD –6.9% (–12.4% to –1.3%) **Hematoma at puncture site** Risk: 1 vs. 9 per 100 patients RR 0.07 (0.01 to 0.53) RD –8.0% (–12.5% to –3.6%) **Bradycardia** Risk: 1 vs. 0 per 100 patients **Other minor adverse events** Risk: <1 per 100 patients for each arm: Secondary bleeding at puncture site, angina without MI, allergic reaction to contrast agent, hypotension requiring treatment, stent migration **Conclusions:** CCTA was associated with a reduced risk of any minor procedural adverse event compared with ICA, driven by the frequency of hematoma at the puncture site. There was no difference in the risk of other specific minor events.	⊕⊕◯◯ LOW

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;

2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.6. Key Questions 1, 2 and 3: Strength of evidence: CCTA FFR versus any functional and versus ICA

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction cumulative	3, 12 months	1 prospective cohort (N=584) **Planned noninvasive test cohort (N=204)** CCTA FFR vs. any noninvasive test **Planned ICA cohort (N=380)** CCTA FFR vs. ICA	Yes (-1)	Unknown	No	Yes (-2)	**CCTA FFR vs. any noninvasive test** 3 months: No MIs in either arm 12 months: Risk: 0 vs. 1 per 100 patients **CCTA FFR vs. ICA** 3 months: Risk: 1 vs. 0 per 100 patients 12 months: Risk: 1 vs. 1 per 100 patients **Conclusion**: Firm conclusions regarding the impact of CCTA FFR vs. any noninvasive test or vs. ICA on MI are not possible. MI was rare (≤1 per 100 patients [3 MIs total] across both arms of both cohorts through 12 months). The sample size may have been insufficient to detect MI.	⨁◯◯◯ INSUFFICIENT
Mortality, all-cause cumulative	3, 12 months						**CCTA FFR vs. any noninvasive test** 3 and 12 months: No deaths in either arm **CCTA FFR vs. ICA** 3 months: No deaths in either arm 12 months: Risk: 0 vs. 1 per 100 patients	

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Conclusion: Firm conclusions regarding the impact of CCTA FFR vs. any noninvasive test or vs. ICA on all-cause mortality are not possible. All-cause mortality was rare (1 death [planned ICA cohort] over 12 months across both cohorts). The sample size may have been insufficient to detect all-cause mortality.	
Key Question 2: Clinical Decision-Making Outcomes								
ICA	3, 12 months	1 prospective cohort (N=584) **Planned noninvasive test cohort (N=204)** CCTA FFR vs. any noninvasive test **Planned ICA cohort (N=380)** CCTA FFR vs. ICA	Yes (-1)	Unknown	No	Yes (-1)	**CCTA FFR vs. any noninvasive test** 3 months: Risk: 18 vs. 12 per 100 patients RR 1.52 (0.78 to 2.97) 12 months: Risk: 21 vs. 16 per 100 patients RR 1.32 (0.74 to 2.37) **CCTA FFR vs. ICA** 3 months: Risk: 39 vs. 100 per 100 patients RR 0.39 (0.33 to 0.47) 12 months: Risk: 51 vs. 100 per 100 patients • RR 0.51 (0.45 to 0.59)No events in the 61% of CCTA with FFR patients in whom ICA was cancelled **Conclusion**: Firm conclusions regarding the impact of CCTA FFR vs. any noninvasive test or vs. ICA on referral to ICA are not possible.	⨁◯◯◯ INSUFFICIENT
ICA without obstructive CAD (core lab quantitative analysis)	3 months						**CCTA FFR vs. any noninvasive test** 3 months: Risk: 13 vs. 6 per 100 patients RR 2.08 (0.82 to 5.27) **CCTA FFR vs. ICA**	⨁◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							3 months: Risk: 39 vs. 100 per 100 patients RR 0.39 (0.33 to 0.47) **Conclusion**: Firm conclusions regarding the impact of CCTA FFR vs. any noninvasive test or vs. ICA on the frequency of ICA without obstructive CAD are not possible.	
Revascularization (any)	3, 12 months						**CCTA FFR vs. any noninvasive test** 3 months: Risk: 10 vs. 5 per 100 patients RD (not calculated, no association) 12 months: Risk: 10 vs. 7 per 100 patients RR 1.37 (0.54 to 3.47) **CCTA FFR vs. ICA** 3 months: Risk: 29 vs. 32 per 100 patients RR 0.90 (0.66 to 1.23) 12 months: Risk: 34 vs. 36 per 100 patients RR 0.94 (0.71 to 1.24) **Conclusion**: Firm conclusions regarding the impact of CCTA FFR vs. any noninvasive test or vs. ICA on any revascularization are not possible.	⨁◯◯◯ INSUFFICIENT
Hospitalization (with urgent revascularization)	3, 12 months						**CCTA FFR vs. any noninvasive test** 3 and 12 months: No events in either arm **CCTA FFR vs. ICA** 3 and 12 months: Risk: 1 vs. 0 per 100 patients **Conclusion**: Firm conclusions regarding the	⨁◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							impact of CCTA FFR vs. any noninvasive test or vs. ICA on hospitalization with urgent revascularization are not possible. There was one hospitalization with urgent revascularization over 12 months across both cohorts which occurred in a patient who received CCTA with FFR rather than being referred directly to ICA (planned ICA cohort). Given that these likely are rare events (there was 1 event in a patient who received CCTA with FFR rather than direct ICA [planned ICA cohort]), the study may not have been sufficiently powered to detect them.	
Key Question 3: Safety								
Test-related AEs	12 months	1 prospective cohort (N=584) **Planned noninvasive test cohort (N=204)** CCTA FFR vs. any noninvasive test **Planned ICA cohort (N=380)** CCTA FFR vs. ICA	Low	Unknown	No	Yes (-2)	One mild contrast reaction from CCTA testing; no other information provided. <u>**Conclusion**</u>: Data are insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT
Cumulative radiation exposure (mSv)	12 months						**CCTA FFR vs. any noninvasive test** <u>3 months</u>: 8.8 vs. 5.8 mSv MD 3.0 (0.6 to 5.4) <u>12 months</u>: 9.6 vs. 6.4 mSv MD 3.1 (0.6 to 5.7) **CCTA FFR vs. ICA** <u>3 months</u>: 9.9 vs. 9.4 mSv MD 0.50 (–0.93 to 1.93) <u>12 months</u>: 10.7 vs. 10.4 mSv MD 0.36 (–1.32 to 2.04)	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Conclusion: Patients who received CCTA with FFR had significantly greater cumulative radiation exposure over 12 months compared to those who received any noninvasive test (planned noninvasive test cohort); there was no difference for CCTA with FFR versus direct referral to ICA (planned ICA cohort).	

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.7. Key Questions 1 and 2: Strength of evidence: SPECT versus any functional

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction cumulative	30 days to mean 24 months	4 RCTs (N=1,908) **SPECT vs. Echo (Suspected or**	Yes (-1)	No	No	Yes (-2)	Risk: 0.3 vs. 1.3 per 100 patients Pooled estimates (2 RCTs, N=907): RR 0.32 (95% CI 0.05 to 1.96), I^2=0.0% RD (not calculated, no association)	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		known CAD) 2 RCTs (N=679) Sharples 2007 (stable, OP) Salame 2018 (acute, ED) **SPECT vs. ECG (Suspected CAD)** 2 RCT (N=1,229) Sabharwal 2007 Shaw 2011 (stable, OP)					1 RCT, SPECT vs. Echo (N=229): no events in either group 1 RCT, SPECT vs. ECG (N=772): 0.4 per 100 patients (not reported by test group) **Conclusions:** Firm conclusions regarding the impact of SPECT or functional testing (echocardiography or exercise ECG) on MI are not possible. MI was rare. Sample sizes in individual trials may have been insufficient to detect MI.	
Mortality, all-cause cumulative	30 days to 72 months	4 RCTs (N=1,908) **SPECT vs. Echo (Suspected or known CAD)** 2 RCTs (N=679) Sharples 2007 (stable, OP) Salame 2018 (acute, ED) **SPECT vs. ECG (Suspected CAD)** 2 RCT (N=1,229) Sabharwal 2007 Shaw 2011	Yes (-1)	No	No	Yes (-1)	Risk: 1.4 vs. 1.6 per 100 patients Pooled estimates (4 RCTs, N=1,908): RR 0.89 (95% CI 0.42 to 2.57), I^2=0.0% RD (not calculated, no association) **Conclusions**: There was no difference for SPECT versus stress echocardiography or exercise ECG in the risk of all-cause mortality, despite difference in populations and follow-up duration across the trials. Since this is a rare event, trials may not have been sufficiently powered to detect a difference.	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		(stable, OP)						
Mortality, cardiac cumulative	18 to 24 months	3 RCTs (N=1,679) **SPECT vs. Echo (Suspected or known CAD)** 1 RCT (N=450) Sharples 2007 (stable, OP) **SPECT vs. ECG (Suspected CAD)** 2 RCT (N=1,229) Sabharwal 2007 Shaw 2011 (stable, OP)	Yes (-1)	Yes (-1)	No	Yes (-1)	1.1 vs. 0.5 per 100 patients Pooled estimates (2 RCTs, N=907): RR 2.21 (95% CI 0.05 to 35.30), I^2=0.0% RD (not calculated, no association) 1 RCT, SPECT vs. ECG (N=772): 0.1 per 100 patients (not reported by test group) **Conclusions:** Firm conclusions regarding the impact of SPECT or functional testing (echocardiography or exercise ECG) on cardiac mortality are not possible. Cardiac mortality was rare. Sample sizes in individual trials may have been insufficient to detect events.	⊕◯◯◯ INSUFFICIENT
Key Question 2: Clinical Decision-Making Outcomes								
ICA	30 days to 24 months	4 RCTs (N=1,908) **SPECT vs. Echo (Suspected or known CAD)** 2 RCTs (N=679) Sharples 2007 (stable, OP) Salame 2018 (acute, ED)	Yes (-1)	Yes (-1)	No	No	Risk: 24.5 vs. 31.9 per 100 patients Pooled estimates (4 RCTs, N=1,908) RR 0.64 (95% CI 0.31 to 1.22), I^2=86.5% RD (not calculated, no association) 1 RCT (N=457), SPECT vs. ECG 16.4 versus 47.3 per 100 patients RR 0.35 (95% CI 0.25 to 0.47) RD –30.9%, 95% CI –39.2% to –22.7%)	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		SPECT vs. ECG (Suspected CAD) 2 RCT (N=1,229) Sabharwal 2007 Shaw 2011 (stable, OP)					**Conclusion:** There was no difference for SPECT versus stress echocardiography or exercise ECG in the risk of ICA across all 4 trials, however, there was substantial heterogeneity. Individually, only one fair-quality trial comparing SPECT with exercise ECG in stable patients at mixed pretest risk for CAD reported a statistically significant difference which favored SPECT (30% reduction in ICA). Differences in patient populations and/or pretest risk may have played a role in these findings.	
Additional NIT (any)	18 to 24 months	3 RCTs (N=1,679) **SPECT vs. Echo (Suspected or known CAD)** 1 RCT (N=450) Sharples 2007 (stable, OP) **SPECT vs. ECG (Suspected CAD)** 2 RCT (N=1,229) Sabharwal 2007 Shaw 2011	Yes (-1)	Yes (-1)	No	Yes (-1)	Risk: 4.3 vs. 14.6 per 100 patients Pooled estimates (3 RCTs, N=1,679) RR 0.24 (95% CI 0.01 to 8.67), I^2=70.0% RD (not calculated, no association) **SPECT vs. Echo** Risk: 0.4 vs. 0 per 100 patients 1 RCT (N=450) RR 3.03 (95% CI 0.12 to 73.90) RD (not calculated, no association) **SPECT vs. ECG** 5.7 vs. 20.2 per 100 patients Pooled estimate (2 RCTs, N=1,229) RR 0.11 (95% CI 0.00 to 8.87), I^2=93%	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							RD (not calculated, no association) 1 RCT (N=772): Risk: 9.4 vs. 18.6 per 100 patients RR 0.51 (95% CI 0.35 to 0.73) RD –8.2% (95% CI –14.0 to –4.3%) 1 RCT (N=457): Risk: 0 vs. 23.2 per 100 patients RR 0.01 (95% CI 0.00 to 0.14) RD –23.2% (95% CI –29.0 to –17.4%) **Conclusion:** It is difficult to draw firm conclusions across trials due to lack of precision and inconsistency. While both trials comparing SPECT with exercise ECG showed a reduction in risk of downstream NIT with SPECT, heterogeneity was substantial resulting in a pooled estimate that was not statistically significant. Differences in testing protocols, populations (1 trial was in women only), and pre-test risks may partly explain the heterogeneity.	
Revascularization (any)	30 days to 36 months	4 RCTs (N=1,908) **SPECT vs. Echo (Suspected or known CAD)** 2 RCTs (N=679)	Yes (-1)	Yes (-1)	No	No	Risk: 13.7 vs. 17.5 per 100 patients Pooled estimates (4 RCTs, N=1,908): RR 0.80 (95% CI 0.60 to 1.09), I^2=0.0% RD (not calculated, no association) **Conclusion:** There was no difference	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Thom 2014 (stable, OP) Salame 2018 (acute, ED) **SPECT vs. ECG (Suspected CAD)** 2 RCT (N=1,229) Sabharwal 2007 Shaw 2011 (stable, OP)					for SPECT versus stress echocardiography or versus exercise ECG in the risk of revascularization, despite difference in populations and follow-up duration across the trials. Two trials in stable patients reported a lower risk of revascularization following SPECT, however, the differences were only marginally significant: 1 good-quality trial comparing SPECT with echocardiography (RR 0.82, 95% CI 0.67 to 0.99) and 1 fair-quality trial comparing SPECT with ECG (RR 0.60 (95% CI 0.38 to 0.96). There were no differences when PCI and CABG were considered separately.	
Hospitalization	30 days to 24 months	3 RCTs (N=1,451) **SPECT vs. Echo (Suspected or known CAD)** 2 RCTs (N=679) Sharples 2007 (stable, OP) Salame 2018 (acute, ED) **SPECT vs. ECG (Suspected CAD)** 1 RCT (N=772)	Yes (-1)	No	No	Yes (-1)	Risk: 5.4 vs. 5.9 per 100 patients Pooled estimates (3 RCTs, N=1,451): RR 0.89 (95% CI 0.54 to 2.14), I^2=0.0% RD (not calculated, no association) **Conclusions:** There was no difference for SPECT versus stress echocardiography or versus exercise ECG in the risk of hospitalization for cardiac causes, despite difference in populations and follow-up duration across the trials.	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Shaw 2011 (stable, OP)						
ED revisit	30 days	1 RCT (N=229) **SPECT vs. Echo (Suspected or known CAD)** Salame 2018 (acute, ED)	Yes (-1)	Unknown	No	Yes (-1)	Risk: 2.6 vs. 2.7 per 100 patients RR 0.97 (95% CI 0.20 to 4.73) **Conclusions:** There was no difference for SPECT versus stress echocardiography in the risk of re-presentation to the ED within 30 days.	⊕⊕◯◯ LOW

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.8. Key Questions 1 and 2: Strength of evidence: SPECT versus NICE guideline-directed care and versus clinical assessment alone

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction	Median 16 months	1 RCT (N=721)	No	Unknown	No	Yes (-2)	Risk: 0.4 vs. 0.8 per 100 patients, RR 0.50 (95% CI 0.07 to 3.52)	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
cumulative		**NICE guideline-directed care** Greenwood 2017 Suspected CAD (stable, OP)					RD (not calculated, no association) **Conclusions:** Firm conclusions regarding the impact of SPECT or NICE guideline-directed care on MI are not possible. MI was rare. The sample size may have been insufficient to detect MI.	
Mortality, all-cause cumulative							Risk: 0.6 vs. 1.3 per 100 patients, RR 0.50 (95% CI 0.10 to 2.45) RD (not calculated, no association) **Conclusions:** Firm conclusions regarding the impact of SPECT or NICE guideline-directed care on all-cause mortality are not possible. All-cause mortality was rare. The sample size may have been insufficient to detect events.	⨁◯◯◯ INSUFFICIENT
Cardiac mortality cumulative	12, 16 months	2 RCTs (N=2,229) **Clinical assessment alone** Lim 2013 Suspected ACS (acute, ED) **NICE guideline-directed care** Greenwood 2017	Yes (-1)	No	No	Yes (-2)	Risk: 0.4 vs. 0.1 per 100 patients Pooled estimates (2 RCTs, N=2,229): RR 2.04 (95% CI 0.25 to 19.09), I^2=0% RD (not calculated, no association) **Conclusions:** Firm conclusions regarding the impact of SPECT or NICE guideline-directed care or clinical assessment alone on cardiac mortality are not possible. Cardiac mortality was rare. Sample sizes in individual	⨁◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Suspected CAD (stable, OP)					trials may have been insufficient to detect events.	
Key Question 2: Clinical Decision-Making Outcomes								
ICA	12, 16 months	2 RCTs (N=2,229) **Clinical assessment alone** Lim 2013 Suspected ACS (acute, ED) **NICE guideline-directed care** Greenwood 2017 Suspected CAD (stable, OP)	Yes (-1)	Yes (-1)	No	No	Risk: 10.2 vs. 21.1 per 100 patients Pooled estimates (2 RCTs, N=2,229): RR 0.49 (95% CI 0.26 to 0.95), I^2=85% RD –11.1% (95% CI –14.4% to –7.8%) **SPECT vs. Clinical assessment alone**: 1 RCT, N=1,508 Risk: 7 vs. 11 per 100 patients RR 0.65 (95% CI 0.47 to 0.91) **SPECT vs. NICE guideline-directed care**: 1 RCT, N=721 Risk: 16 vs. 43 per 100 patients RR 0.38 (95% CI 0.30 to 0.49) **Conclusions:** SPECT was associated with a decreased risk of ICA vs. clinical assessment alone and vs. NICE guideline-directed care, however heterogeneity was substantial, driven by the stronger association found for SPECT vs. NICE guideline-directed care due to the direct referral to ICA of patients with high pretest risk per the NICE guideline algorithm.	⊕⊕◯◯ LOW
ICA showing no obstructive CAD	12 months	1 RCT (N=1,508)	Yes (-1)	Unknown	No	No	Risk: 21.9 vs. 39.3 per 100 patients, RR 0.56 (95% CI 0.32 to 0.96)	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Clinical assessment alone Lim 2013 Suspected ACS (acute, ED)					RD –17.4% (95% CI –33.3% to –1.4%) **Conclusions:** SPECT was associated with a decreased risk of ICA showing no obstructive disease, compared with clinical assessment alone.	
Unnecessary ICA*	16 months	1 RCT (N=721) **NICE guideline-directed care** Greenwood 2017 Suspected CAD (stable, OP)	No	Unknown	No	Yes (-1)	Risk: 7.1 vs. 28.8 per 100 patients, RR 0.25 (95% CI 0.17 to 0.36), RD –21.7% (95% CI –27.9% to –15.5%) **Conclusions:** SPECT was associated with a decreased risk of unnecessary ICA compared with NICE-guideline directed care.	⊕⊕◯◯ LOW
Additional NIT (any)	12 months	1 RCT (N=1,508) **Clinical assessment alone** Lim 2013 Suspected ACS (acute, ED)	Yes (-1)	Unknown	No	No	Risk: 12.1 vs. 68.3 per 100 patients, RR 0.18 (95% CI 0.15 to 0.21), RD –56.2% (95% CI –60.7% to –51.7%) **Conclusions:** SPECT was associated with a decreased risk of additional downstream NIT compared with clinical assessment alone.	⊕⊕◯◯ LOW
Revascularization (any)	12, 16 months	2 RCTs (N=2,229) **Clinical assessment alone** Lim 2013 Suspected ACS (acute, ED)	Yes (-1)	Unknown	No	No	Risk: 5.9 vs. 7.0 per 100 patients Pooled estimates (2 RCTs, N=2,229): RR 0.85 (95% CI 0.57 to 1.28), I^2=0% RD (not calculated, no association) **Conclusions:** There was no difference between SPECT and clinical assessment alone or NICE guideline-	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		NICE guideline-directed care Greenwood 2017 Suspected CAD (stable, OP)					directed care in the risk of any revascularization.	
Hospitalization	Index	1 RCT (N=1,508) **Clinical assessment alone** Lim 2013 Suspected ACS (acute, ED)	Yes (-1)	Unknown	No	No	Risk: 10.2 vs. 18.5 per 100 patients, RR 0.55 (95% CI 0.42 to 0.71), RD –8.3% (95% CI –12.2% to –4.4%) **Conclusions:** SPECT was associated with a decreased risk of hospitalization at the index visit compared with clinical assessment alone. Subsequent hospitalization following the index visit was not reported.	⊕⊕◯◯ LOW

*As described by the authors. Primary reasons cited for an unnecessary ICA included negative noninvasive test overruled by the attending physician (4.4 per 100 patients) and a false-positive test (2.5 per 100 patients) in the SPECT group, and direct referral to ICA (per algorithm) for patients with high pretest likelihood in the guideline-directed care group (24.6 per 100 patients).

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.9. Key Questions 1 and 2: Strength of evidence: SPECT versus ICA

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Primary clinical outcomes								
Myocardial infarction cumulative	18 months	1 RCT (N=446) Sharples 2007/Thom 2017 (Stable OP, suspected CAD)	No	Unknown	No	Yes (-2)	0.9 vs. 0 per 100 patients; all admissions for acute MI **Conclusions:** Firm conclusions regarding the impact of SPECT or ICA on MI are not possible. MI was rare. The sample size may have been insufficient to detect events.	⊕◯◯◯ INSUFFICIENT
All-cause mortality cumulative	72 months						**18 months** 1.8 vs. 1.8 per 100 patients, RR 0.99 (95% CI 0.25 to 3.91) RD (not calculated, no association) **72 months** 3.1 vs. 3.2 per 100 patients, RR 0.99 (95% CI 0.35 to 2.78) RD (not calculated, no association) **Conclusions:** Firm conclusions regarding the impact of SPECT or ICA on all-cause mortality are not possible. All-cause mortality was rare. The sample size may have been insufficient to detect events.	⊕◯◯◯ INSUFFICIENT
Cardiac mortality cumulative	18 months						2.2 vs. 1.4 per 100 patients, RR 1.65 (95% CI 0.40 to 6.83) RD (not calculated, no association) **Conclusions:** Firm conclusions	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							regarding the impact of SPECT or ICA on cardiac mortality are not possible. Cardiac mortality was rare. The sample size may have been insufficient to detect events	
Clinical Decision-Making Outcomes								
Additional NIT (any)	Unclear	1 RCT (N=448) Sharples 2007 (Stable OP, suspected CAD)	No	Unknown	No	Yes (-1)	0.4 vs. 3.6 per 100 patients, RR 0.12 (95% CI 0.02 to 0.98), RD –3.2% (95% CI –5.8% to –0.6%) **Conclusions:** Firm conclusions regarding the impact of SPECT or ICA on additional NITs are not possible.	⊕◯◯◯ INSUFFICIENT
Revascularization (any)	36 months						**Index** 30.4 vs. 34.2 per 100 patients, RR 0.89 (95% CI 0.68 to 1.16) RD (not calculated, no association) **36 months (cumulative)** 43.8 vs. 53.2 per 100 patients, RR 0.82 (95% CI 0.68 to 0.99) RD –9.4% (95% CI –18.6% to –0.2%) **Conclusions:** SPECT was associated with a decreased risk of any revascularization following the index visit through 36 months compared with ICA.	⊕⊕◯◯ LOW
Hospitalization for chest pain	18 months						8.5 vs. 6.3 per 100 patients, RR 1.35 (95% CI 0.69 to 2.62) RD (not calculated, no association)	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Conclusions: There was no difference between SPECT and ICA in the risk of hospitalization for chest pain.	

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.10. Key Questions 3: Strength of evidence: SPECT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Safety								
Test-related adverse events,	Median 16 months,	1 RCT (N=721) Greenwood 2016 Stable	No	Unclear	No	Yes	**Test-related medical complications** SPECT vs. NICE guideline-directed care: • 5 test-related medical complications occurred; none were following SPECT imaging; no other information was provided **Conclusions**: Test-related complications appear to be rare following SPECT in one good-quality trial.	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Radiation exposure	24 months	1 RCT (N=722) Shaw 2011 (women only) Stable	Yes (-1)	Unclear	No	Yes (-2)	**Radiation exposure** SPECT vs. exercise ECG: • Mean ionizing radiation exposure following index SPECT was 14 mSv **Conclusions**: Insufficient evidence to draw conclusions.	⊕◯◯◯ INSUFFICIENT
AEs related to regadenoson and dipyridamole	NR	3 studies (N=380 patients, 604 adverse events) 1 case series 1 retrospective cohort Amer 2017 Koutsikos 2017 Meyer 2000 Suspected or known CAD	Yes	No	No	Yes	**Dipyridamole** (2 studies, N=284 patients and N=604 events), the most common events included: • Headache (13% of patients; 37% of all AEs), • GI upset/nausea (8% of patients; 11% of AEs) • Chest pain (4% of patients; 12% of AEs) • Dizziness or lightheadedness (6% of patients; 5% of AEs) • Flushing (4% of patients; 8% of AEs) • Dyspnea (2% of patients; 5% of AEs). **Regadenoson** (2 studies; N=96, 284), the most common events included: • Dyspnea (30% and 53%) • GI upset/nausea (28% and 3%) Chest pain (9% and 16%) • Dizziness or lightheadedness (8% and 13%) • Headache (7% and 12%) • Flushing (4% and 6%). **Conclusions:** AE's from stress agents	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							are relatively common and ranged from 2% to 13% of patients (5% to 37% of AEs) for dipyridamole and from 4% to 53% for regadenoson.	

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.11. Key Questions 1 and 2: Strength of evidence: Stress echocardiography versus ECG

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction cumulative	2 to 36 months	5 RCTs (N=1,250) **Stable OP (suspected CAD)** 2 RCT (N=543) Gurunathan 2018 Sanfilippo 2006	Yes (-1)	No	No	Yes (-2)	Risk: 1.3 vs. 0.9 per 100 patients Pooled estimate (3 RCTs, N=940): RR 1.41 (95% CI 0.30 to 5.00), I^2=0% RD (not calculated, no association) 1 RCT (N=152) reported no events in either arm	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Acute, ED/hospital (known or suspected CAD and suspected ACS) 3 RCTs (N=707) Desideri 2005 Jeetley 2006 Nucifora 2009					1 RCT (N=158) did not report MI by testing arm (Risk: 1.3 per 100 patents) **Conclusions:** There is insufficient evidence to draw conclusions about the risk of MI following echocardiography versus exercise ECG. MI was rare. Except for one newer, good-quality trial in stable outpatients, trials were older and of primarily poor-quality. Smaller trials may not have been sufficiently powered to detect a difference.	
Mortality, all-cause cumulative	2 to 36 months	4 RCTs (N=1,092) **Stable OP (suspected CAD)** 1 RCT (N=385) Gurunathan 2018 **Acute, ED/hospital (known or suspected CAD and suspected ACS)** 3 RCTs (N=707) Desideri 2005 Jeetley 2006 Nucifora 2009	Yes (-1)	No	No	Yes (-2)	Risk: 0.6 vs. 0.9 per 100 patients; Pooled estimate (3 RCTs, N=940): RR 0.65 (95% CI 0.13 to 4.94), I^2=0% RD (not calculated, no association) 1 RCT (N=152) reported no events in either arm **Conclusions:** There is insufficient evidence to draw conclusions about the risk of all-cause mortality following echocardiography versus exercise ECG. All-cause mortality was rare. Except for one newer, good-quality trial in stable outpatients, trials were older and of primarily poor-quality. Smaller trials may not have been sufficiently powered to	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							detect a difference	
Mortality, cardiac cumulative	36 months	1 RCT (N=385) Gurunathan 2018 (Stable OP, suspected CAD)	No	Unknown	No	Yes (-2)	Risk: 0.5 vs. 0 per 100 patients **Conclusions:** There is insufficient evidence from one good-quality trial to draw conclusions regarding the risk of cardiac mortality following echocardiography versus exercise ECG. Cardiac mortality was rare. Smaller sample size may have precluded identification of rare events.	⨁◯◯◯ INSUFFICIENT
Key Question 2: Clinical Decision-Making Outcomes								
ICA	2 to 36 months	4 RCTs (N=1,101) **Stable OP (suspected CAD)** 1 RCT (N=385) Gurunathan 2018 **Acute, ED/hospital (known or suspected CAD and suspected ACS)** 3 RCTs (N=716) Desideri 2005 Jeetley 2006 Nucifora 2009	Yes (-1) Yes (-2)	Unknown No	No No	No No	**Stable patients** Risk: 6.3 vs. 13.4 per 100 patients 1 RCT (N=385): RR 0.47 (95% CI 0.24 to 0.90) RD –7.1% (95% CI –13.0 to –1.2%) **Acute patients** Risk: 24.4 vs. 28.4 per 100 patients; Pooled estimate (3 RCTs, N=716): RR 0.85 (95% CI 0.36 to 1.33), I^2=64.3% RD (not calculated, no association) **Conclusions:** In one good-quality trial in stable patients, echocardiography was associated with a reduced risk of ICA versus exercise ECG over 36	⨁⨁◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							months. Across 3 trials in acute patients, there was no difference between groups, though one fair-quality trial tended to favor echocardiography; heterogeneity was high possibly due to differences in populations, pretest risk and follow-up times.	
Additional NIT (any)	2 to 36 months	3 RCTs (N=695) **Stable OP (suspected CAD)** 2 RCT (N=543) Gurunathan 2018 Sanfilippo 2006 **Acute, ED/hospital (known or suspected CAD and suspected ACS)** 1 RCT (N=152) Nucifora 2009	Yes (-1) Yes (-2)	No	No	Yes (-1)	**Stable patients** Risk: 5.8 vs. 42.7 per 100 patients Pooled estimate (2 RCTs, N=543): RR 0.15 (95% CI 0.06 to 0.28), I^2=0% RD –31.6 (95% CI –49.3% to –14.0%), I^2=84% **Acute patients** Risk: 10.4 vs. 9.3 per 100 patients 1 RCT (N=152): RR 1.11 (95% CI 0.42 to 2.92) RD (not calculated, no association) **Conclusions:** In stable patients, but not acute patients, echocardiography was associated with a reduced risk of additional downstream NIT compared with exercise ECG; follow-up was 28 to 36 months. The trial in acute patients was considered poor-quality and only followed patients for 2 months; evidence from this trial was considered insufficient to draw	Stable ⊕⊕◯◯ LOW Acute ⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							conclusions in this population.	
Revascularization (any)	2 to 36 months	4 RCTs (N=1,092) **Stable OP (suspected CAD)** 1 RCT (N=385) Gurunathan 2018 **Acute, ED/hospital (known or suspected CAD and suspected ACS)** 3 RCTs (N=707) Desideri 2005 Jeetley 2006 Nucifora 2009	Yes (-1)	No	No	No	Risk: 14.4 vs. 15.3 per 100 patients Pooled estimate (4 RCTs, N=1,092): RR 0.95 (95% CI 0.68 to 1.25), I^2=0% RD (not calculated, no association) **Conclusions:** There was no difference in the risk of revascularization between the echocardiography and exercise ECG groups.	⊕⊕⊕◯ MODERATE
Hospitalization	2 to 36 months	3 RCTs (N=799) **Stable OP (suspected CAD)** 1 RCT (N=385) Gurunathan 2018 **Acute, ED/hospital (known or suspected CAD**	Yes (-1)	No	No	No	Risk: 9.3 vs. 10.0 per 100 patients Pooled estimate (3 RCTs, N=799): RR 0.94 (95% CI 0.48 to 1.51), I^2=6.5% RD (not calculated, no association) **Conclusions:** There was no difference in the risk of (re)hospitalization between the echocardiography and exercise ECG groups.	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		and suspected ACS) 2 RCTs (N=414) Desideri 2005 Nucifora 2009						

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.12. Key Questions 1 and 2: Strength of evidence: Stress echocardiography versus standard care

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction, All-cause mortality, Cardiac mortality cumulative	2 months	1 RCT (N=132) Nucifora (suspected ACS, ED)	Yes (-1)	Unknown	No	Yes (-2)	No MIs and no deaths reported in either group. **Conclusions:** There is insufficient evidence from one small, poor-quality trial in low-risk patients to draw conclusions regarding the impact of stress echocardiography or standard care on MI, all-cause mortality, or cardiac mortality. No events were reported. The sample size and follow-up period may have been insufficient to detect events.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 2: Clinical Decision-Making Outcomes								
ICA; Additional NIT (any); Revascularization (any); Rehospitalization for ACP	2 months	1 RCT (N=132) Nucifora (suspected ACS, ED)	Yes (-1)	Unknown	No	Yes (-2)	**ICA**: Risk: 0 vs. 11 per 100 patients RR 0.06 (95% CI 0.0 to 0.96) RD –10.9% (95% CI –19.2% to –2.7%) **Any additional NIT:** Risk: 10 vs. 49 per 100 patients RR 0.21 (95% CI 0.10 to 0.43) RD –38.7% (95% CI –53.6% to –23.8%) **Any revascularization:** Risk: 7 vs. 4 per 100 patients RR 1.79 (95% CI 0.36 to 8.87) RD (not calculated, no association) **Rehospitalization for ACP:** Risk 3 vs. 15 per 100 patients RR 0.18 (95% CI 0.04 to 0.81) RD –12.0% (95% CI –21.9% to –2.0%) **Conclusions:** There is insufficient evidence from one small, poor-quality trial in low-risk patients to draw conclusions regarding the impact of stress echocardiography or standard care on referral to ICA, additional NIT, revascularization or rehospitalization.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.13. Key Questions 1 and 2: Strength of evidence: Stress echocardiography versus ICA

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction cumulative	18 months	1 RCT (N=448) Sharples 2007/Thom 2017 (Stable OP, suspected CAD)	No	Unknown	No	Yes (-2)	Risk: 2.7 vs. 0 per 100 patients, p=0.01; all admission for acute MI **Conclusion**: The risk of MI following stress echocardiography appears to be low; however, the evidence is considered insufficient to draw firm conclusions.	⊕⊕⊕◯ INSUFFICIENT
All-cause mortality cumulative	72 months						**18 months** Risk: 2.7 vs. 1.8 per 100 patients, RR 1.47 (95% CI 0.42 to 5.15) RD (not calculated, no association) **72 months** Risk: 4.9 vs. 3.2 per 100 patients, RR 1.54 (95% CI 0.61 to 3.91) RD (not calculated, no association)	

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Conclusion: The risk of all-cause mortality did not differ between stress echocardiography and ICA; however, the evidence is considered insufficient to draw firm conclusions.	
Cardiac mortality cumulative	18 months						Risk 0.4 vs. 1.4 per 100 patients, RR 0.33 (95% CI 0.03 to 3.12) RD (not calculated, no association) **Conclusion**: The risk of cardiac mortality was low and did not differ between stress echocardiography and ICA; however the evidence is considered insufficient to draw firm conclusions.	
Key Question 2: Clinical Decision-Making Outcomes								
Additional NIT (any)	Unclear	1 RCT (N=448) Sharples 2007 (Stable OP, suspected CAD)	No	Unknown	No	Yes (-2)	Risk: 0 vs. 3.6 per 100 patients, p=0.01 **Conclusion**: Firm conclusions regarding the impact of stress echocardiography or ICA on additional NITs are not possible.	⊕◯◯◯ INSUFFICIENT
Revascularization	36 months						**Index** Risk: 35.4 vs. 34.2 per 100 patients, RR 1.03 (95% CI 0.80 to 1.33) RD (not calculated, no association) **36 months** Risk: 53.5 vs. 53.2 per 100 patients, RR 1.01 (95% CI 0.85 to 1.20) RD (not calculated, no association)	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Conclusion: There was no difference between stress echocardiography and ICA in the risk of revascularization.	
Hospitalization for chest pain	18 months						Risk: 10.6 vs. 6.3 per 100 patients, RR 1.68 (95% CI 0.89 to 3.17) RD (not calculated, no association) **Conclusion**: There was no difference between stress echocardiography and ICA in the risk of hospitalization for chest pain.	⊕⊕◯◯ LOW

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.14. Key Question 3: Strength of evidence: Stress echocardiography

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Any complication	2 months	1 RCT (N=152)	Yes (-1)	Unknown	No	Yes (-1)	No test-related complications occurred in 1 RCT comparing stress	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Nucifora 2009 Uncomplicated MI					echocardiography versus stress ECG. **Conclusions:** Insufficient evidence to draw conclusions.	
Dobutamine-related adverse events		11 case series (N range, 86–2799)* Baudhuin 1993 Dakik 1996 Geleijnse 2000 Gordon 1995 Karabinos 2004 Mertes 1993 Minardi 2007 Poldermans 1994 Picano 1994 O'Driscoll 2014 Sitges 2000 Stable, suspected or known CAD (10 studies) Suspected ACS (1 study)	Yes (-2)	Unknown	No	No	<u>Potentially life threatening, major adverse events</u> • **Mortality** (6 studies, N=5,512): No deaths • **MI** (7 studies, N range 122 to 2,799): range, 0% to 0.1% • **UA** (1 study, N=802): 0.1% • **CVA** (1 study, N=1,012): No CVAs • **Acute pulmonary edema** (2 studies, N=1,012, 802): 0% and 0.1% **Conclusion:** The risk of potentially life-threatening adverse event with dobutamine appears to be low, ≤0.1% across all outcomes.	⊕⊕◯◯ LOW
							<u>Arrythmia-related AEs</u> • **Any arrhythmias or palpitations** (6 studies, N range 122 to 1,118): range, 2.1% to 18.0% • **Supraventricular or ventricular tachycardia** (10 studies, N range 86 to 2,799): range, 0% to 9.0% • **Atrial or ventricular fibrillation** (7 studies, N range 265 to 2,799): range, 0% to 1.2% • **Bradycardia** (2 large studies,	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							N=3,917): ≤0.2% in both. **Conclusion:** The frequency of any arrhythmia (not well defined) and tachycardias ranged from 0% to 18%. Atrial fibrillation and bradycardia appear to be infrequent events.	
							<u>Hypotension and Hypertension</u> • **Hypotension** (9 studies; N range 86 to 2799): range, 0.1% to 12.5% • **Hypertension** (5 studies; N range 122 to 1118): range, 0% to 7.5% **Conclusion:** Hypo- and hypertension were not uncommon with dobutamine for stress echocardiography. The severity of the events was not reported.	⊕⊕◯◯ LOW
							<u>Other, general adverse events</u> • **Chest pain (NOS)** (3 studies, N range 86 to 1,118): range, 4.6% to 31.4% • **Nausea and/or vomiting** (6 studies, N range 86 to 1012): range, 3.4% to 20.9% • **Headache** (4 studies, N range 122 to 1012): 0.8% to 13.6% • **Dyspnea** (3 studies, N range 127 to 1012): range, 0% to 13.6% • **Tremors** (3 studies, N range 127 to 1012): range, 0.4% to 2.4%	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Conclusions: The frequency of other adverse events, such as chest pain, nausea/vomiting, headache, dyspnea and tremors ranged from 0% to 31%; most authors reported that events were mild and transient.	
Dipyridamole and Adenosine		**Dipyridamole** 3 case series (N=946) Minardi 2002 Ferrara 1991 Gaibazzi 2009 **Adenosine** 1 case series (N=1429) Montisci 2017 Suspected or known CAD for all	Yes (-2)	Unknown	No	No	**Dipyridamole** 2 studies (total N=837): • No "major", severe, or life-threatening adverse events, to include death, MI and ACS 3 studies (N range, 109 to 500): • Hypotension/bradycardia: range, 0.8% to 6.4% • Vomiting and nausea: range, 0.2% to 5.5% • Headache: range, 2.1% to 43% **Adenosine** The most commonly occurring side-effects were hyperpnea (16.7%), atypical chest pain (9.9%), flushing (9.4%) and headache (6.6%). **Conclusions**: There were no major or life-threatening adverse events after dipyridamole administration. Minor adverse events with the use of these stressor agents for echocardiography	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							are not uncommon and occurred with variable frequency and ranged from 0.2% to 43%.	
Noniodinated contrast		3 studies (N=9,821) 2 comparative cohorts (N=6,750) Anantharam 2009 Jin 2019 1 database study (N=3,071) Abdelmoneim 2009	Yes (-2)	Unknown	No	No	**Definite or suspected contrast-related adverse events** 1 database study: 1.3% (41/3071) and 2.2% (68/3071) **Allergic reaction to contrast** • 2 cohort studies: <0.5% of patients who received stress echocardiography with contrast • 1 database study: 0.03% each for transient wheezing without urticaria, urticaria or hives (limb and thorax) and swelling in the mouth, and throat tingling **Conclusions**: Definite or suspected contrast related adverse events and allergic reactions appear to be rare.	⊕⊕◯◯ LOW

CAD = coronary artery disease; CI = Confidence Interval; ECG = electrocardiography; ED = emergency department; OP = outpatient; RCT = randomized controlled trial; SOE = strength of evidence.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.

3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.15. Key Questions 1 and 2: Strength of evidence: PET vs. SPECT

Outcome	Follow-up	Studies	Study Limitations	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction Cumulative; **Mortality, all-cause** cumulative	12 months	1 RCT (N=322) Patel 2019 Known CAD, new or worsening symptoms	No	Unknown	No	Yes (-2)	**MI:** Risk: 0 vs. 1.2 per 100 patients **All-cause mortality:** Risk: 1 vs. 1.2 per 100 patients RR 0.50 (95% CI 0.04 to 5.46) RD (not calculated, no association) **Conclusion:** Firm conclusions regarding the impact of PET or SPECT on MI and all-cause mortality are not possible. Both outcomes were rare. The sample size may have been insufficient to detect events.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Study Limitations	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Mortality, cardiac cumulative	Mean 9 months	1 RCT (N=210) Mullani 2000 Stable, mixed suspected or known CAD	Yes (-1)	Unknown	No	Yes (-2)	Risk: 3 vs. 4 per 100 patients RR 0.75 (95% CI 0.17 to 3.27) RD (not calculated, no association) **Conclusion:** Data from one poor-quality trial were insufficient to draw conclusions.	⨁◯◯◯ INSUFFICIENT
Key Question 2: Clinical Decision-Making Outcomes								
ICA	3, 6, 12 months	1 RCT (N=322) Patel 2019 Known CAD, new or worsening symptoms	No	Unknown	No	Yes (-1)	**3 months** Risk: 20.5 vs. 15.5 per 100 patients RR 1.32 (95% CI 0.82 to 2.11) RD (not calculated, no association) **6 months** Risk: 22.4 vs. 18.6 per 100 patients RR 1.20 (95% CI 0.78 to 1.85) RD (not calculated, no association) **12 months** Risk: 28.6 vs. 28.0 per 100 patients RR 1.02 (95% CI 0.72 to 1.45) RD (not calculated, no association) **Conclusion:** No difference between PET and SPECT in the risk of ICA at any timepoint.	⨁⨁◯◯ LOW
Revascularization (any)							**3 months** Risk: 11.2 vs. 9.9 per 100 patients RR 1.13 (95% CI 0.60 to 2.13) RD (not calculated, no association) **6 months** Risk: 12.4 vs. 11.8 per 100 patients RR 1.05 (95% CI 0.58 to 1.90) RD (not calculated, no association) **12 months**	⨁⨁◯◯ LOW

Outcome	Follow-up	Studies	Study Limitations	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Risk: 15.5 vs. 14.9 per 100 patients RR 1.04 (95% CI 0.62 to 1.74) RD (not calculated, no association) **Conclusion:** No difference between PET and SPECT in the risk of any revascularization at any timepoint.	
Medication change*							Escalation in antianginal therapy* at **3 months** Risk: 26 vs. 23 per 100 patients RR 1.11 (95% CI 0.75, 1.63) RD (not calculated, no association)	

CI = Confidence Interval; NR = Not Reported; NS = Not significant;

*Footnote: Defined as addition of another anti-anginal medication class or increase in dose or frequency of one or more of existing anti-anginal medications within 3 months post baseline MPI

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

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