Annals of Internal Medicine REVIEW

Diagnostic Strategies for the Assessment of Suspected Stable Coronary Artery Disease

A Systematic Review and Meta-analysis

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Background: There is uncertainty about which diagnostic strategy for detecting coronary artery disease (CAD) provides better outcomes.

Purpose: To compare the effect on clinical management and subsequent health effects of alternative diagnostic strategies for the initial assessment of suspected stable CAD.

Data Sources: PubMed, Embase, and Cochrane Central Register of Controlled Trials.

Study Selection: Randomized clinical trials comparing diagnostic strategies for CAD detection among patients with symptoms suggestive of stable CAD.

Data Extraction: Three investigators independently extracted study data.

Data Synthesis: The strongest available evidence was for 3 of the 6 comparisons: coronary computed tomography angiography (CCTA) versus invasive coronary angiography (ICA) (4 trials), CCTA versus exercise electrocardiography (ECG) (2 trials), and CCTA versus stress single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) (5 trials). Compared with direct ICA referral, CCTA was associated with no difference in cardiovascular death and myocardial infarction (relative risk [RR], 0.84 [95% CI, 0.52 to 1.35]; low certainty) but less index ICA (RR, 0.23 [CI, 0.22 to 0.25]; high certainty) and index revascularization (RR, 0.71 [CI, 0.63 to 0.80]; moderate certainty). Moreover, CCTA was associated with a reduction in cardiovascular death and myocardial infarction compared with exercise ECG (RR, 0.66 [CI, 0.44 to 0.99]; moderate certainty) and SPECT-MPI (RR, 0.64 [CI, 0.45 to 0.90]; high certainty). However, CCTA was associated with more index revascularization (RR, 1.78 [CI, 1.33 to 2.38]; moderate certainty) but less downstream testing (RR, 0.56 [CI, 0.45 to 0.71]; very low certainty) than exercise ECG. Low-certainty evidence compared SPECT-MPI versus exercise ECG (2 trials), SPECT-MPI versus stress cardiovascular magnetic resonance imaging (1 trial), and stress echocardiography versus exercise ECG (1 trial).

Limitation: Most comparisons primarily rely on a single study, many studies were underpowered to detect potential differences in direct health outcomes, and individual patient data were lacking.

Conclusion: For the initial assessment of patients with suspected stable CAD, CCTA was associated with similar health effects to direct ICA referral, and with a health benefit compared with exercise ECG and SPECT-MPI. Further research is needed to better assess the relative performance of each diagnostic strategy.

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Coronary artery disease (CAD) is a leading cause of death worldwide (1, 2). Although acute coronary syndromes require prompt invasive management, chronic coronary syndromes (CCSs) are usually managed through a stepwise diagnostic and therapeutic approach to rule out noncardiac causes of chest pain and improve patients' quality of life and prognosis (3). Invasive coronary angiography (ICA) is the benchmark in the diagnostic assessment of CAD. However, its cost, invasiveness, potential complications, and low diagnostic yield in the clinical setting of suspected CCS have called its large-scale use into question (4). For this reason, noninvasive diagnostic tests have been developed to accurately detect obstructive CAD and identify patients with suspected CCS requiring invasive evaluation. These tests differ in their availability, requirements, costs, and diagnostic performance (5). Functional diagnostic strategies have been the cornerstone of noninvasive CAD testing and can detect several signs of myocardial ischemia provoked by exercise or pharmacologic agents: electrocardiography (ECG) changes by exercise ECG, wall motion abnormalities by stress cardiac magnetic resonance (CMR) imaging or stress echocardiography, and perfusion changes by stress single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) (6). On the other hand, coronary computed tomography angiography (CCTA) allows noninvasive anatomical assessment of the coronary arteries and has emerged as an alternative diagnostic strategy (7).

Because diagnostic pathways may affect subsequent patient management and clinical outcomes, evidence on the long-term health effects of alternative diagnostic pathways has been requested (8). Several randomized clinical trials (RCTs) have compared the clinical outcomes of various invasive and noninvasive diagnostic techniques for

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CAD detection in patients with suspected CCS, but they cannot provide clear evidence because they had inadequate statistical power due to lower-than-expected incidence of cardiovascular events in 2 landmark trials (9, 10) and small sample sizes in most of the other trials. On this background, we did a meta-analysis of all randomized evidence to assess the effect on clinical management and subsequent health effects of alternative diagnostic strategies for the initial assessment of patients with symptoms suggestive of stable CAD.

METHODS

This systematic review and meta-analysis was carried out in accordance with guidelines from the Cochrane Collaboration and PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (**Supplement Table 1**, available at Annals.org) (11). The protocol was registered in PROSPERO (CRD42022329635).

Data Sources and Searches

A systematic literature search using PubMed, Embase, and Cochrane Central Register of Controlled Trials was initially made from inception to 16 March 2022 and subsequently updated on 21 March 2023. In addition, we did backward snowballing research (that is, a review of references from identified articles). We used a combination of terms related to CCTA, functional tests, and CAD. An experienced medical librarian reviewed the literature search terms. The full search strategy is available in **Supplement Table 2** (available at Annals.org).

Study Selection

We included RCTs comparing any invasive and noninvasive diagnostic strategies for CAD detection among patients with symptoms suggestive of stable CAD. Studies that did not report clinical outcomes or did not assess the diagnostic and therapeutic pathway secondary to the index test were excluded. To assess the performance of individual diagnostic strategies, we excluded trials (or groups) evaluating a combination of at least 2 strategies among functional testing, CCTA, and direct ICA referral. In addition, we excluded trials enrolling patients with previously known CAD (>10% of the total population) or evaluating diagnostic algorithms for CAD risk stratification (for example, selective CCTA after calcium score). We applied no restrictions on study language, follow-up duration, or publication date. Three investigators (A.Z., M.G., and G.P.) independently screened all records retrieved and examined titles and abstracts for eligibility. They assessed potentially suitable articles for inclusion by inspecting full-text and supplementary material. Discrepancies were resolved by collegial discussion.

Data Extraction and Quality Assessment

Three investigators (A.Z., M.G., and G.P.) extracted data on study design and features, patients' baseline characteristics, and outcomes. When different follow-up durations were reported for the same trial, the longest was included in the analysis. The SCOT-HEART (Scottish Computed Tomography of the Heart) trial compared CCTA plus standard of care versus standard of care alone, and the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial compared CCTA versus functional testing. For these 2 trials, we included only data from the most commonly used functional test in the quantitative analysis: exercise ECG (85%) for the SCOT-HEART trial (12) and SPECT-MPI (67%) for the PROMISE trial (13). In addition to data extracted from the main and subsequent publications of the included trials, unpublished outcome data from PROMISE were obtained and included in the analyses.

The same 3 investigators independently assessed risk of bias using the Cochrane Risk of Bias Tool, composed of the following 5 domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The certainty of each estimate was rated as high, moderate, low, or very low according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group frameworks (14) based on specific criteria concerning study limitations, inconsistency, indirectness, imprecision, and the likelihood of publication bias (**Supplement Table 3**, available at Annals.org).

The primary direct health outcome was a composite of cardiovascular death and myocardial infarction. Secondary direct health outcomes included all-cause death, cardiovascular death, and myocardial infarction. The primary clinical management outcome was index ICA (defined as the number of ICA procedures done secondary to the index test for noninvasive diagnostic strategies and the number of initial ICA procedures done for direct ICA referral). Secondary clinical management outcomes included index revascularization (defined as the number of revascularization procedures done secondary to the index test) and downstream testing (defined as all additional noninvasive testing and ICA done secondary to the index test). Outcome definitions of each study are reported in **Supplement Table 4** (available at Annals.org).

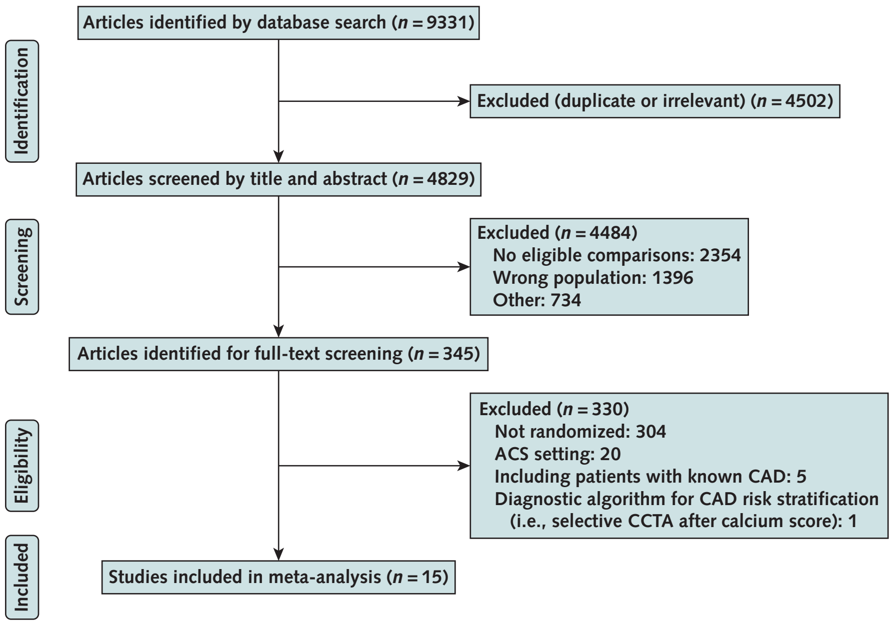
Data Synthesis and Analysis

We did multiple pairwise meta-analyses according to individual test comparisons. Relative risks (RRs) were calculated using the random-effects model with inverse variance weighting and the restricted maximum likelihood estimator of variance. We used the modified Knapp–Hartung–Sidik–Jonkman method with the DerSimonian–Laird estimator to calculate 95% CIs of the random-effects estimate. Statistical heterogeneity was evaluated using the Cochran *Q* test, whereas consistency was measured using Higgins and Thompson I^2. The potential presence of publication bias was assessed by visual inspection of funnel plots for comparisons pooling at least 2 studies. We did sensitivity analyses using the leave-one-out approach for comparisons pooling at least 2 studies by sequentially removing each study to investigate its influence on the main results. Statistical analysis was done using the "meta" package in R, version 4.1.2 (R Foundation).

Role of the Funding Source

There was no funding source for this study.

Figure 1. Evidence search and selection.



ACS = acute coronary syndrome; CAD = coronary artery disease; CCTA = coronary computed tomography angiography.

Results

After screening the 9331 citations retrieved, we identified 15 RCTs for inclusion in the analysis (**Figure 1**). The following comparisons were available (**Table**): CCTA versus ICA (4 trials; 5752 patients; mean follow-up, 2 years), CCTA versus exercise ECG (2 trials; 3783 patients; mean follow-up, 3 years), CCTA versus SPECT-MPI (5 trials; 10 195 patients; mean follow-up, 1 year), SPECT-MPI versus exercise ECG (2 trials; 1229 patients; mean follow-up, 2 years), SPECT-MPI versus CMR imaging (1 trial; 962 patients; mean follow-up, 1 year), and stress echocardiography versus exercise ECG (1 trial; 385 patients; mean follow-up, 3 years). The Table and **Supplement Tables 5** and **6** (available at Annals.org) summarize key features of included trials. Baseline characteristics of patients are summarized and illustrated with violin and box-and-whisker plots for each comparison in **Supplement Table 7** and **Supplement Figure 1** (available at Annals.org). The risk-of-bias assessment identified 8 studies at low risk of bias, 4 with some concerns, and 3 at high risk of bias (**Supplement Figure 2**, available at Annals.org). **Supplement Table 8** (available at Annals.org) provides a GRADE evidence profile for all outcomes.

CCTA Versus ICA

The analysis included 4 trials comprising 5752 patients and a mean follow-up of 2 years. The mean age of the patients was 61 years, 51% were women, and the mean pretest likelihood of CAD was 41%.

Compared with direct ICA referral, CCTA was associated with similar risks for cardiovascular death and myocardial infarction (RR, 0.84 [95% CI, 0.52 to 1.35]; low certainty), all-cause death (RR, 0.82 [CI, 0.54 to 1.25]; moderate certainty), cardiovascular death (RR, 0.47 [CI, 0.20 to 1.13]; moderate certainty), and myocardial infarction (RR, 1.09 [CI, 0.63 to 1.90]; low certainty) (**Figure 2**; **Supplement Figures 3** to **6**, available at Annals.org).

Patients referred to initial CCTA were less likely to undergo index ICA (RR, 0.23 [CI, 0.22 to 0.25]; high certainty) and index revascularization (RR, 0.71 [CI, 0.63 to 0.80]; moderate certainty) than patients initially referred to ICA (**Figure 3**; **Supplement Figures 7** and **8**, available at Annals.org).

CCTA Versus Exercise ECG

The analysis included 2 trials comprising 3783 patients and a mean follow-up of 3 years. The mean age of the patients was 57 years, 44% were women, and the mean pretest likelihood of CAD was 46% (available only from the CAPP [Cardiac CT for the Assessment of Pain and Plaque] trial [19]).

Compared with exercise ECG, CCTA was associated with a reduction in the risk for cardiovascular death and myocardial infarction (RR, 0.66 [CI, 0.44 to 0.99]; moderate certainty) (**Figure 2**; **Supplement Figure 3**). However, CCTA did not significantly reduce the risks for all-cause death (RR, 1.00 [CI, 0.06 to 15.90]; very low certainty) or myocardial infarction (RR, 0.50 [CI, 0.05 to 5.48]; very low certainty) compared with exercise ECG (**Figure 2**; **Supplement Figures 4** and **6**). No data were available for the individual outcome of cardiovascular death. Of note, data from the SCOT-HEART trial (12) were included in the analyses for the composite outcome of cardiovascular death and myocardial infarction, whereas no data were available for the individual outcomes of all-cause

Table. Key Features of RCTs Included in the Meta-analysis

Study, Year (Reference)	Sample Size, *n*	Comparison	Available Outcomes	Follow-up, *y*	Pretest Likelihood of CAD, %
CAD-Man, 2016 (15)	340	CCTA (*n* = 168) vs. ICA (*n* = 172)	Cardiovascular death and myocardial infarction, cardiovascular death, myocardial infarction, index ICA, index revascularization	3.3	34.6*
CONSERVE, 2019 (16)	1631	CCTA (*n* = 823) vs. ICA (*n* = 808)	All-cause death, myocardial infarction, index ICA, index revascularization	1	51.5†
DISCHARGE, 2022 (17)	3561	CCTA (*n* = 1808) vs. ICA (*n* = 1753)	Cardiovascular death and myocardial infarction, all-cause death, cardiovascular death, myocardial infarction, index ICA, index revascularization	3.5	37.2‡
Reis et al, 2022 (18)	220	CCTA (*n* = 115) vs. ICA (*n* = 105)	Cardiovascular death and myocardial infarction, all-cause death, cardiovascular death, myocardial infarction, index ICA, index revascularization	1	33.8*
CAPP, 2015 (19)	500	CCTA (*n* = 250) vs. exercise ECG (*n* = 250)	Cardiovascular death and myocardial infarction, all-cause death, cardiovascular death, myocardial infarction, index ICA, index revascularization, downstream testing	1	46.4§
SCOT-HEART, 2018 (9, 20)	4146	CCTA + standard of care (*n* = 2073) vs. standard of care (*n* = 2073)‖	Cardiovascular death and myocardial infarction, index ICA, index revascularization	5	–
CARE-CCTA, 2019 (21)	903	CCTA (*n* = 460) vs. SPECT-MPI (*n* = 443)	All-cause death, myocardial infarction, index ICA, index revascularization, downstream testing	1	44.4§
IAEA-SPECT/CTA, 2016 (22)	303	CCTA (*n* = 152) vs. SPECT-MPI (*n* = 151)	All-cause death, myocardial infarction, index ICA, index revascularization, downstream testing	1	–
Min et al, 2012 (23)	180	CCTA (*n* = 91) vs. SPECT-MPI (*n* = 89)	Cardiovascular death and myocardial infarction, all-cause death, cardiovascular death, myocardial infarction, index ICA, index revascularization, downstream testing	0.2	–
PROMISE, 2015 (10)	10 003	CCTA (*n* = 4996) vs. functional testing (*n* = 5007)¶	Cardiovascular death and myocardial infarction, all-cause death, cardiovascular death, myocardial infarction, index ICA, index revascularization, downstream testing	2.1	53.3**
RESCUE, 2020 (24)	1050	CCTA (*n* = 518) vs. SPECT-MPI (*n* = 532)	Cardiovascular death and myocardial infarction, cardiovascular death, myocardial infarction	1.4	–
Sabharwal et al, 2007 (25)	457	SPECT-MPI (*n* = 250) vs. exercise ECG (*n* = 207)	All-cause death, cardiovascular death, index ICA, index revascularization, downstream testing	1.6	–
WOMEN, 2011 (26)	772	SPECT-MPI (*n* = 388) vs. exercise ECG (*n* = 384)	Index ICA, index revascularization	2	–
CE-MARC 2, 2016 (27)	962	CMR imaging (*n* = 481) vs. SPECT-MPI (*n* = 481)	Cardiovascular death and myocardial infarction, all-cause death, cardiovascular death, myocardial infarction, index ICA, index revascularization, downstream testing	1.3	49.3†
Gurunathan et al, 2018 (28)	385	Stress echocardiography (*n* = 191) vs. exercise ECG (*n* = 194)	All-cause death, myocardial infarction, index ICA, index revascularization, downstream testing	3	34.5*

CAD = coronary artery disease; CAD-Man = Coronary Artery Disease Management; CAPP = Cardiac CT for the Assessment of Pain and Plaque; CARE-CCTA = Comparison of the Cost-Effectiveness of Coronary CT Angiography Versus Myocardial SPECT in Patients With Intermediate Risk of Coronary Heart Disease; CCTA = coronary computed tomography angiography; CE-MARC 2 = Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease 2; CMR = cardiovascular magnetic resonance; CONSERVE = Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization; DISCHARGE = Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease; ECG = electrocardiography; IAEA-SPECT/CTA = Stress Testing Compared to Coronary Computed Tomographic Angiography in Patients With Suspected Coronary Artery Disease; ICA = invasive coronary angiography; PROMISE = Prospective Multileft Imaging Study for Evaluation of Chest Pain; RCT = randomized clinical trial; RESCUE = Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Noninvasive Examinations; SCOT-HEART = Scottish Computed Tomography of the Heart; SPECT-MPI = single-photon emission computed tomography myocardial perfusion imaging; WOMEN = What Is the Optimal Method for Ischemia Evaluation in Women.

* Duke score (29).

† Not reported.

‡ Diamond–Forrester updated score (31).

§ Diamond–Forrester score (30).

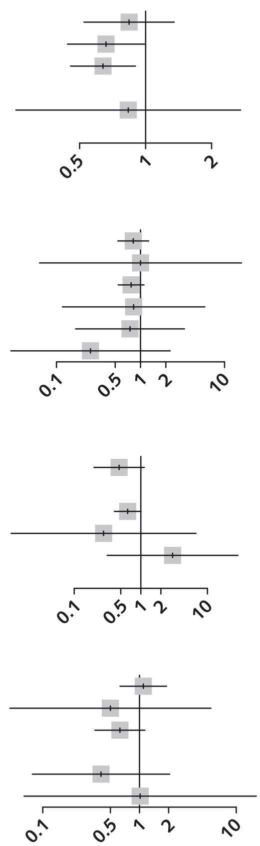
‖ Only the subgroups of patients who had exercise ECG alone (standard of care group, *n* = 1632) or in combination with CCTA (CCTA + standard of care group, *n* = 1651) were included in the quantitative analysis (12).

¶ Only the subgroup of patients in the functional testing group who had SPECT-MPI (*n* = 3218) was included in the quantitative analysis (13).

** Combined Diamond–Forrester and Coronary Artery Surgery Study risk score (32).

Figure 2. Direct health outcomes for all diagnostic comparisons.

Comparison	Studies, *n*	RR (95% CI)	Certainty of Evidence
Cardiovascular death and myocardial infarction			
CCTA vs. ICA	3	0.84 (0.52–1.35)	Low
CCTA vs. exercise ECG	2	0.66 (0.44–0.99)	Moderate
CCTA vs. SPECT-MPI	2	0.64 (0.45–0.90)	High
SPECT-MPI vs. exercise ECG	0	–	–
SPECT-MPI vs. CMR imaging	1	0.83 (0.26–2.71)	Very low
Stress echocardiography vs. exercise ECG	0	–	–
All-cause death			
CCTA vs. ICA	2	0.82 (0.54–1.25)	Moderate
CCTA vs. exercise ECG	1	1.00 (0.06–15.90)	Very low
CCTA vs. SPECT-MPI	3	0.77 (0.54–1.10)	Moderate
SPECT-MPI vs. exercise ECG	1	0.83 (0.12–5.83)	Very low
SPECT-MPI vs. CMR imaging	1	0.75 (0.17–3.33)	Very low
Stress echocardiography vs. exercise ECG	1	0.25 (0.03–2.25)	Very low
Cardiovascular death			
CCTA vs. ICA	2	0.47 (0.20–1.13)	Moderate
CCTA vs. exercise ECG	0	–	–
CCTA vs. SPECT-MPI	1	0.63 (0.40–1.00)	Low
SPECT-MPI vs. exercise ECG	1	0.28 (0.01–6.74)	Very low
SPECT-MPI vs. CMR imaging	1	3.00 (0.31–28.74)	Very low
Stress echocardiography vs. exercise ECG	0	–	–
Myocardial infarction			
CCTA vs. ICA	4	1.09 (0.63–1.90)	Low
CCTA vs. exercise ECG	1	0.50 (0.05–5.48)	Very low
CCTA vs. SPECT-MPI	2	0.63 (0.35–1.14)	Moderate
SPECT-MPI vs. exercise ECG	0	–	–
SPECT-MPI vs. CMR imaging	1	0.40 (0.08–2.05)	Very low
Stress echocardiography vs. exercise ECG	1	1.02 (0.06–16.12)	Very low



The column for numbers of studies refers to studies with a weight in the analysis, and studies with 0 events were not counted. CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance; ECG = electrocardiography; ICA = invasive coronary angiography; RR = relative risk; SPECT-MPI = single-photon emission computed tomography myocardial perfusion imaging.

death, cardiovascular death, and myocardial infarction (Table).

Compared with patients initially referred to exercise ECG, those referred to initial CCTA had no difference in index ICA (RR, 1.09 [CI, 0.86 to 1.38]; low certainty) but were more likely to undergo index revascularization (RR, 1.78 [CI, 1.33 to 2.38]; moderate certainty) and less likely to undergo downstream testing (RR, 0.56 [CI, 0.45 to 0.71]; very low certainty) (Figure 3; Supplement Figures 7 to 9, available at Annals.org).

CCTA Versus SPECT-MPI

The analysis included 5 trials comprising 10 195 patients and a mean follow-up of 1 year. The mean age of the patients was 61 years, 52% were women, and the mean pretest likelihood of CAD was 52% (available only from the CARE-CCTA [Comparison of the Cost-Effectiveness of Coronary CT Angiography Versus Myocardial SPECT in Patients With Intermediate Risk of Coronary Heart Disease] [21] and PROMISE [10] trials).

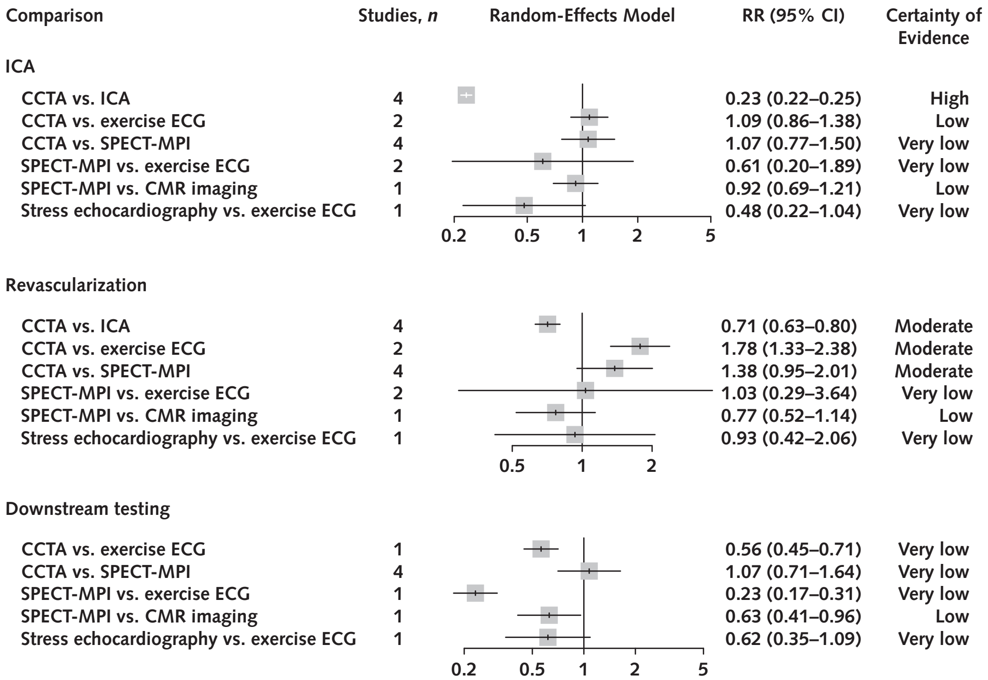
Compared with SPECT-MPI, CCTA was associated with a reduction in the risk for cardiovascular death and myocardial infarction (RR, 0.64 [CI, 0.45 to 0.90]; high certainty) (Figure 2; Supplement Figure 3). It did not significantly reduce the risks for all-cause death (RR, 0.77 [CI, 0.54 to 1.10]; moderate certainty) or myocardial infarction (RR, 0.63 [CI, 0.35 to 1.14]; moderate certainty) (Figure 2; Supplement Figures 4 and 6). However, it provided a marginal, nonsignificant reduction in the risk for cardiovascular death (RR, 0.63 [CI, 0.40 to 1.00]; low certainty) compared with SPECT-MPI (Figure 2; Supplement Figure 5).

Patients referred to initial CCTA had no difference in index ICA (RR, 1.07 [CI, 0.77 to 1.50]; very low certainty), index revascularization (RR, 1.38 [CI, 0.95 to 2.01]; moderate certainty), or downstream testing (RR, 1.07 [CI, 0.71 to 1.64]; very low certainty) compared with patients referred to initial SPECT-MPI (Figure 3; Supplement Figures 7 to 9).

SPECT-MPI Versus Exercise ECG

The analysis included 2 trials comprising 1229 patients and a mean follow-up of 2 years. The mean age of the patients was 62 years, 79% were women, and the pretest likelihood of CAD was not reported, although the

Figure 3. Clinical management outcomes for all diagnostic comparisons.



The column for numbers of studies refers to studies with a weight in the analysis, and studies with 0 events were not counted. CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance; ECG = electrocardiography; ICA = invasive coronary angiography; RR = relative risk; SPECT-MPI = single-photon emission computed tomography myocardial perfusion imaging.

WOMEN (What Is the Optimal Method for Ischemia Evaluation in Women) trial (26) included patients with an intermediate likelihood of CAD.

Compared with exercise ECG, SPECT-MPI was associated with similar risks for all-cause death (RR, 0.83 [CI, 0.12 to 5.83]; very low certainty) and cardiovascular death (RR, 0.28 [CI, 0.01 to 6.74]; very low certainty) (Figure 2; Supplement Figures 4 and 5). No data were available for the composite outcome of cardiovascular death and myocardial infarction or for the individual outcome of myocardial infarction.

Compared with patients referred to initial exercise ECG, those initially referred to SPECT-MPI had no difference in index ICA (RR, 0.61 [CI, 0.20 to 1.89]; very low certainty) or index revascularization (RR, 1.03 [CI, 0.29 to 3.64]; very low certainty) and were less likely to undergo downstream testing (RR, 0.23 [CI, 0.17 to 0.31]; very low certainty) (Figure 3; Supplement Figures 7 to 9).

SPECT-MPI Versus CMR Imaging

The analysis included 1 trial with 962 patients and a mean follow-up of 1 year. The mean age of the patients was 56 years, 59% were women, and the pretest likelihood of CAD was 49%.

Compared with CMR imaging, SPECT-MPI was associated with similar risks for cardiovascular death and myocardial infarction (RR, 0.83 [CI, 0.26 to 2.71]; very low certainty), all-cause death (RR, 0.75 [CI, 0.17 to 3.33]; very low certainty), cardiovascular death (RR, 3.00 [CI, 0.31 to 28.74]; very low certainty), and myocardial infarction (RR, 0.40 [CI, 0.08 to 2.05]; very low certainty) (Figure 2; Supplement Figures 3 to 6).

Compared with patients referred to initial CMR imaging, those referred to initial SPECT-MPI had no difference in index ICA (RR, 0.92 [CI, 0.69 to 1.21]; low certainty) or index revascularization (RR, 0.77 [CI, 0.52 to 1.14]; low certainty) and were less likely to undergo downstream testing (RR, 0.63 [CI, 0.41 to 0.96]; low certainty) (Figure 3; Supplement Figures 7 to 9).

Stress Echocardiography Versus Exercise ECG

The analysis included 1 trial with 385 patients and a mean follow-up of 3 years. The mean age of the patients was 55 years, 32% were women, and the pretest likelihood of CAD was 35%.

Compared with exercise ECG, stress echocardiography was associated with similar risks for all-cause death (RR, 0.25 [CI, 0.03 to 2.25]; very low certainty) and myocardial infarction (RR, 1.02 [CI, 0.06 to 16.12]; very low certainty) (Figure 2; Supplement Figures 4 and 6). No data were available for the composite outcome of cardiovascular death and myocardial infarction or for the individual outcome of cardiovascular death.

Compared with patients referred to initial exercise ECG, those initially referred to stress echocardiography had no difference in index ICA (RR, 0.48 [CI, 0.22 to 1.04]; very low certainty), index revascularization (RR, 0.93 [CI, 0.42 to 2.06]; very low certainty), or downstream testing

(RR, 0.62 [CI, 0.35 to 1.09]; very low certainty) (Figure 3; Supplement Figures 7 to 9).

Leave-One-Out Sensitivity Analyses

In the comparison of CCTA versus ICA (Supplement Figure 10, available at Annals.org), the omission of each trial provided results consistent with the main analyses for all outcomes. In the comparison of CCTA versus exercise ECG (Supplement Figure 11, available at Annals.org), the risk for cardiovascular death and myocardial infarction was no longer significantly reduced when the SCOT-HEART trial (12) was omitted (RR, 0.50 [CI, 0.05 to 5.48]) and was marginally nonsignificantly reduced when the CAPP trial was omitted (RR, 0.66 [CI, 0.44 to 1.00]). In the comparison of CCTA versus SPECT-MPI (Supplement Figure 12, available at Annals.org), the risk for cardiovascular death and myocardial infarction was no longer reduced when the PROMISE trial (13) was omitted (RR, 0.29 [CI, 0.06 to 1.41]), the incidence of referral to index ICA was significantly higher when the CARE-CCTA trial (21) was omitted (RR, 1.25 [CI, 1.10 to 1.42]), and the incidence of referral to index revascularization was significantly higher when the IAEA-SPECT/CTA (Stress Testing Compared to Coronary Computed Tomographic Angiography in Patients With Suspected Coronary Artery Disease) trial (22) was omitted (RR, 1.50 [CI, 1.02 to 2.21]). In the comparison of SPECT-MPI versus exercise ECG (Supplement Figure 13, available at Annals.org), the incidence of referral to index ICA (RR, 0.35 [CI, 0.25 to 0.47]) and index revascularization (RR, 0.60 [CI, 0.38 to 0.96]) was significantly reduced when the WOMEN trial (26) was omitted.

DISCUSSION

This systematic review and meta-analysis of 15 diagnostic RCTs assessed the effect on clinical management and subsequent health effects of alternative diagnostic strategies for the initial assessment of patients with suspected stable CAD. The main findings can be summarized as follows. Compared with direct ICA referral, CCTA was associated with no difference in direct health outcomes but less index ICA and index revascularization. Compared with exercise ECG, CCTA was associated with a reduction in the risk for cardiovascular death and myocardial infarction, no difference in index ICA, more index revascularization, and less downstream testing. Compared with SPECT-MPI, CCTA was associated with a reduction in the risk for cardiovascular death and myocardial infarction and no difference in clinical management outcomes. Finally, direct health and clinical management outcomes did not differ significantly between functional tests, except for a reduction in downstream testing with SPECT-MPI in comparison with exercise ECG and CMR imaging. The uncertainty surrounding available data should be considered when these findings are interpreted. In fact, comparisons among functional tests were sparse and imprecise. In addition, the health benefit of CCTA compared with exercise ECG and SPECT-MPI was mainly driven by subgroup data from SCOT-HEART (12) and PROMISE (13), respectively.

The diagnostic assessment of stable chest pain is a public health and economic challenge. Although functional testing has been the mainstay in the initial evaluation of patients with suspected stable CAD, its poor sensitivity in detecting obstructive CAD has given way to the advent of alternative diagnostic strategies (5). Over the past 2 decades, CCTA has emerged as a useful diagnostic test with high sensitivity and negative predictive value in detecting CAD (5), and its clinical performance has been compared with that of functional testing and direct ICA referral in the landmark trials PROMISE (10), SCOT-HEART (9, 20), and DISCHARGE (Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease) (17).

The principal goals of CCS treatment are to reduce risk for cardiovascular events and to enhance quality of life by reducing angina symptoms (3). Although revascularization may play a role in angina relief (33), its effect on cardiovascular outcomes is still debated (3, 34, 35). Among diagnostic comparisons, we found no clear association between the incidence of referral to index revascularization and direct health outcomes. Of note, despite leading to fewer index revascularizations, CCTA provided similar health effects to direct ICA referral. Thus, the health benefit of some diagnostic strategies is likely to reflect their greater effectiveness in identifying at-risk patients with CAD who would benefit from targeted medical and, eventually, invasive therapeutic management. In fact, CCTA was shown to provide better prognostic information than functional testing due to the identification of patients with nonobstructive CAD at risk for future cardiovascular events, whereas functional testing detects CAD at a later stage (13). Besides, functional tests are useful to identify ischemia in the absence of obstructive CAD, a cause of stable CAD symptoms that should be suspected after the exclusion of obstructive CAD by anatomical testing (36). Of note, functional tests have varying sensitivity to detect ischemia in the absence of obstructive CAD; the main tests that perform reliably are stress positron emission tomography with MPI and CMR imaging (37).

Given the excellent medium-term prognosis of the research population (38), demonstrating a difference in direct health outcomes of patients with suspected stable CAD using alternative diagnostic strategies is ambitious and requires a large sample size, which is often achievable only with meta-analyses; however, previous meta-analyses had conflicting results (39–41). Two pairwise meta-analyses (39, 40) found that, compared with functional testing, CCTA is associated with reduced risk for myocardial infarction and an increase in index ICA and index revascularization. On the other hand, a network meta-analysis (41) found no difference in direct health outcomes and confirmed a significant increase in index ICA and index revascularization with CCTA in comparison with functional testing, while finding no clear discrimination in the analyses considering individual functional tests separately. Our findings expand previous evidence by providing comparisons between individual diagnostic strategies with the selection of a composite primary direct health outcome, which provided adequate statistical power to detect potential differences in the health effects of alternative diagnostic strategies.

Mostly based on diagnostic accuracy data, European and U.S. guidelines recommend the use of either CCTA or functional imaging for the initial evaluation of patients with stable chest pain and intermediate pretest likelihood of obstructive CAD (6, 42). Conversely, guidelines from the National Institute for Health and Care Excellence in the United Kingdom advise CCTA as a first-line diagnostic strategy, with subsequent functional testing reserved in case of inconclusive CCTA results (43). Exercise ECG has controversial recommendations, and our results corroborate the European and U.K. guidelines, which do not advise its use for detecting (or excluding) CAD (6, 43), while contradicting U.S. guidelines that deem it reasonable as a first choice if the patient can attain maximum exercise levels (42). As a result of these conflicting recommendations, the selection of a diagnostic test currently depends on locally available resources and expertise.

Because included trials mainly focused on patients with intermediate pretest likelihood of obstructive CAD, our results should be applied to this target population. However, given the burden of CAD testing (44), our findings have major implications for health care providers and will help determine the relevance of various tests in the diagnostic pathways of CCS symptoms. In the coming years, CCTA may gain a main role in the initial assessment of suspected stable CAD, with functional tests potentially reserved for identifying ischemia in the absence of obstructive CAD in selected, persistently symptomatic patients without obstructive CAD on CCTA. A noninvasive anatomical evaluation with CCTA may enable a personalized risk assessment, detecting various stages of atherosclerosis ranging from early subclinical disease to flow-limiting lesions and plaque rupture, thus aiming for targeted preventive and invasive management (7). Furthermore, modern processing technology allows CCTA to characterize high-risk plaque features and assess the functional significance of stenoses using estimations from CT-derived fractional flow reserve, potentially improving its predictive accuracy and favoring a combined anatomical and functional imaging approach (45–47). Coronary CT angiography with selective CT-derived fractional flow reserve estimations was randomly compared with standard clinical pathways in the trials FORECAST (Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain) (48), PRECISE (Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization) (49), and TARGET (Role of On-site CT-derived Fractional Flow Reserve in the Management of Suspect CAD Patients) (50); results suggested a reduction in index ICA without obstructive CAD but no significant health benefits at about 1 year of follow-up. Despite the widespread applications of CCTA, interobserver variability in visual plaque assessment remains a challenge (7). Artificial intelligence and machine-learning systems may address this issue, improving the reliability of image analysis (51, 52).

Our study has some limitations. First, the lack of individual patient data has foreclosed the assessment of potential treatment modifiers, such as revascularization strategy and CAD severity. Second, comparisons primarily based on a single study should be interpreted with caution. Third, many of the included studies have inadequate sample size or follow-up to detect potential differences in direct health outcomes, which are relatively rare in patients with suspected stable CAD. Fourth, although all trials have been conducted over the past 15 years, revascularization techniques have improved during the past few years. Fifth, we could not assess the performance of positron emission tomography with MPI because no randomized trials have compared it with any other diagnostic strategy. Sixth, we could not fully evaluate cost-effectiveness because most of the studies did not report data on the costs of the diagnostic pathways.

In conclusion, this meta-analysis provides comparative evidence of the relative performance of individual diagnostic strategies for the initial assessment of patients with suspected stable CAD. Coronary CT angiography was associated with similar risk for cardiovascular death and myocardial infarction compared with direct ICA referral, and with a reduction in the risk for cardiovascular death and myocardial infarction compared with exercise ECG and SPECT-MPI. Results' uncertainty calls for further research to better assess the relative performance of each diagnostic strategy.

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