SUPPLEMENTAL MATERIALS*

Zito A, Galli M, Biondi-Zoccai G, et al. Diagnostic strategies for the assessment of suspected stable coronary artery disease, A systematic review and meta-analysis. Ann Intern Med. 6 June 2023. [Epub ahead of print]. doi:10.7326/M23-0231

* This supplementary material was provided by the authors to give readers further details on their article. The material was not copyedited.

Supplement Table 1. PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5-6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6-7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6-7, Supplement Table 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7-8, Supplement Table 4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6-8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6-8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6-8

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6-8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6-8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6-8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7, Supplement Table 3
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	8-9, Table 1, Supplement Table 4, Supplement Table 5, Supplement Table 6, Supplement Table 7, Supplement Figure 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9, Supplement Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9-12, Figure 2, Figure 3, Supplement Figure 3, Supplement Figure 4, Supplement Figure 5, Supplement Figure 6, Supplement Figure 7, Supplement Figure 8, Supplement Figure 9, Supplement Figure 10
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-12, Figure 2, Figure 3

Section and Topic	Item #	Checklist item	Location where item is reported
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9-12, Figure 2, Figure 3, Supplement Figure 3, Supplement Figure 4, Supplement Figure 5, Supplement Figure 6, Supplement Figure 7, Supplement Figure 8, Supplement Figure 9, Supplement Figure 10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9-12, Figure 2, Figure 3, Supplement Figure 3, Supplement Figure 4, Supplement Figure 5, Supplement Figure 6, Supplement Figure 7, Supplement Figure 8, Supplement Figure 9, Supplement Figure 10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	12-13, Supplement Figure 10, Supplement Figure 11, Supplement Figure 12, Supplement Figure 13
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplement Figure 14, Supplement Figure 15, Supplement Figure 16, Supplement Figure 17
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	9-12, Figure 2, Figure 3, Supplement Table 8
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13-16

Section and Topic	Item #	Checklist item	Location where item is reported
	23b	Discuss any limitations of the evidence included in the review.	13-16
	23c	Discuss any limitations of the review processes used.	13-16
	23d	Discuss implications of the results for practice, policy, and future research.	13-16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	6
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	8
Competing interests	26	Declare any competing interests of review authors.	17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	17

Supplement Table 2. Full electronic search strategy

Search strategy on PubMed

("computed tomography"[Title/Abstract] OR "CT angiography"[Title/Abstract] OR "computed tomography angiography"[Title/Abstract] OR "computed tomographic angiography"[Title/Abstract] OR "functional test"[Title/Abstract] OR "functional testing"[Title/Abstract] OR "exercise electrocardiography"[Title/Abstract] OR “exercise ECG”[Title/Abstract] OR "exercise test"[Title/Abstract] OR “stress electrocardiography”[Title/Abstract] OR "nuclear stress testing"[Title/Abstract] OR "stress SPECT"[Title/Abstract] OR “single photon emission CT”[Title/Abstract] OR “myocardial perfusion scintigraphy”[Title/Abstract] OR "stress echocardiography"[Title/Abstract] OR "stress imaging"[Title/Abstract] OR “CMR”[Title/Abstract] OR “cardiac magnetic resonance”[Title/Abstract] OR “MPI”[Title/Abstract] OR “myocardial perfusion imaging”[Title/Abstract]) AND ("chest pain"[Title/Abstract] OR “angina pectoris”[Title/Abstract] OR "coronary artery disease"[Title/Abstract] OR "ischemic heart disease"[Title/Abstract] OR “acute coronary syndrome”[Title/Abstract]) AND ("trial" OR "random*") NOT "review"

Search strategy on Embase

(‘computed tomography’:ab,ti OR ‘CT angiography’:ab,ti OR ‘computed tomography angiography’:ab,ti OR ‘computed tomographic angiography’:ab,ti OR ‘functional test’:ab,ti OR ‘functional testing’:ab,ti OR ‘exercise electrocardiography’:ab,ti OR ‘exercise ECG’:ab,ti OR ‘exercise test’:ab,ti OR ‘stress electrocardiography’:ab,ti OR ‘nuclear stress testing’:ab,ti OR ‘stress SPECT’:ab,ti OR ‘single photon emission CT’:ab,ti OR ‘myocardial perfusion scintigraphy’:ab,ti OR ‘stress echocardiography’:ab,ti OR ‘stress imaging’:ab,ti OR ‘CMR’:ab,ti OR ‘cardiac

magnetic resonance’:ab,ti OR ‘MPI’:ab,ti OR ‘myocardial perfusion imaging’:ab,ti) AND (‘chest pain’:ab,ti OR ‘angina pectoris’:ab,ti OR ‘coronary artery disease’:ab,ti OR ‘ischemic heart disease’:ab,ti OR ‘acute coronary syndrome’:ab,ti) AND (‘trial’ OR ‘random*’) AND 'article'/it

Search strategy on Cochrane Central Register of Controlled Trials

("computed tomography" OR "CT angiography" OR "computed tomography angiography" OR "computed tomographic angiography" OR "functional test" OR "functional testing" OR "exercise electrocardiography" OR “exercise ECG” OR "exercise test" OR “stress electrocardiography” OR "nuclear stress testing" OR "stress SPECT" OR “single photon emission CT” OR “myocardial perfusion scintigraphy” OR "stress echocardiography" OR "stress imaging" OR “CMR” OR “cardiac magnetic resonance” OR “MPI” OR “myocardial perfusion imaging”) AND ("chest pain" OR “angina pectoris” OR "coronary artery disease" OR "ischemic heart disease" OR “acute coronary syndrome”) AND ("trial" OR "random*") NOT "review"

Supplement Table 3. GRADE assessment criteria

GRADE domain	Rules to decrease certainty
Study limitations (53)	Do not downgrade if studies with "high risk" of bias contributed <50% to the effect estimate. ↓1 level if studies with "high risk" of bias or "some concerns" contributed >50% of the effect estimate. ↓2 levels if all studies were "high risk" of bias or "some concerns".
Indirectness (54)	Do not downgrade if interventions, populations, and outcomes were consistent across studies. ↓1 level if substantial differences exist between interventions, populations, outcomes, or time-points of measurement across studies.
Imprecision (55)	Do not downgrade if the total sample size was >2000 and the CI of estimate does not cross 1.0. ↓1 level if the total sample size was <2000. ↓1 level if the total sample size was >2000 but CI of the overall estimate crosses 1.0 (i.e., the no effect line) and includes an important benefit or harm (RR reduction or increase >30%). ↓2 levels if CI of the overall estimate include both important benefit and harm (potential RR reduction or increase >30%).
Inconsistency (56)	Do not downgrade if I^2<75% and CIs of individual studies overlap or are in the same direction (supporting harms or benefits). ↓1 level if I^2>70%, CIs of individual studies don't overlap and few (<30%) are in complete opposite directions. ↓2 levels if I^2>70%, CIs of individual studies don't overlap and many (>30%) are in complete opposite directions.
Publication bias (57)	Do not downgrade if evidence includes large studies and funnel plots do not suggest publication bias. ↓1 level if the evidence consists of a single study or a number of small studies or funnel plots indicates asymmetry.

Supplement Table 4. Outcome definitions

Trial	Comparison	Cardiovascular death	Myocardial infarction
CAD-Man (15)	CCTA vs. ICA	Cased definitions of the American Heart Association, World Heart Federation Council on Epidemiology and Prevention, and the European Society of Cardiology Working Group on Epidemiology and Prevention (58).	Cased definitions of the American Heart Association, World Heart Federation Council on Epidemiology and Prevention, and the European Society of Cardiology Working Group on Epidemiology and Prevention (58).
CONSERVE (16)	CCTA vs. ICA	NA	Defined as 1) abnormal biomarker level > institutional URL (either troponin or CK-MB), and either ischemic discomfort lasting > 10 minutes or ECG changes indicative of ischemia or infarction, or 2) new abnormal Q waves consistent with infarction. Peri-procedural myocardial infarctions are defined as >3x upper limit of normal for serum CK-MB for percutaneous coronary intervention and >5x URL for coronary artery bypass surgery.
DISCHARGE (17)	CCTA vs. ICA	Death resulting due to acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, or other cardiovascular causes.	Defined by the Third Universal Definition (59).
Reis et al (18)	CCTA vs. ICA	NA	NA
CAPP (19)	CCTA vs. Exercise ECG	Death due to heart failure related to CAD, sudden cardiac arrest, fatal myocardial infarction, or end-stage CAD.	Both STEMI and NSTEMI were defined as troponin T levels >0.1 mmol/L with corresponding electrocardiogram changes in the setting of chest pain.
SCOT-HEART (9,20)	CCTA plus standard of care vs. standard of care	Death from coronary heart disease	Defined by the Third Universal Definition (59).
CARE-CCTA (21)	CCTA vs. SPECT-MPI	NA	NA
IAEA-SPECT/CTA (22)	CCTA vs. SPECT-MPI	NA	A typical rise and fall in concentrations of CK-MB with at least one of the following: ischemic symptoms, development of pathological Q waves, or ischemic electrocardiographic changes. One value of elevated cardiac troponin was considered sufficient evidence of nonfatal myocardial infarction if accompanied by any of the above symptoms or ECG changes.
Min et al (23)	CCTA vs. SPECT-MPI	NA	NA
PROMISE (10)	CCTA vs. Functional testing	NA	Defined as either 1) an abnormal cardiac biomarker level > institutional URL (either troponin or CK-

			MB), and either ischemic discomfort lasting > 10 minutes or ECG changes indicative of ischemia or infarction, or 2) new abnormal Q waves consistent with infarction. Additionally peri-procedural infarctions are defined as >3x upper limit of normal for serum CK-MB for PCI and >5x upper limit of normal for CABG.
RESCUE (24)	CCTA vs. SPECT-MPI	Any sudden cardiac death, death due to acute myocardial infarction, and death to heart failure/ cardiogenic shock. Death without a clear non-cardiovascular cause or death without known cause were presumed cardiovascular death.	Myocardial necrosis/loss of viable myocardium in a clinical setting consistent with myocardial infarction.
Sabharwal et al (25)	SPECT-MPI vs. Exercise ECG	NA	NA
WOMEN (26)	SPECT-MPI vs. Exercise ECG	Confirmed enzymatic evidence of acute myocardial infarction with death ensuing within 24 hours; sudden cardiac death defined as a witnessed or unwitnessed sudden death of suspected cardiac etiology defined as the primary cause of death on the death certificate; or death related to an ischemic cardiomyopathy defined as end-stage CAD in a patient with a prior diagnosis of heart failure or defined as primary cause of death on death certificate review.	Defined by hospitalization records noting biomarker elevations concordant with myocardial necrosis. For a nonfatal myocardial infarction, the discharge summary diagnosis of acute myocardial infarction was needed for defining this event.
CE-MARC 2 (27)	SPECT-MPI vs. CMR	NA	Defined by the Third Universal Definition (59). Periprocedural myocardial infarction—type 4a (related to PCI) and type 5 (related to CABG)—and planned revascularization (PCI or CABG) based on the index fractional flow reserve results were censored.
Gurunathan et al (28)	Stress Echocardiography vs. Exercise ECG	NA	Ischemic chest pain associated with an elevation of cardiac enzymes with or without electrocardiographic changes.

Abbreviations: CABG=coronary artery bypass grafting; CAD=coronary artery disease; CK-MB=creatine kinase-muscle/brain; PCI=percutaneous coronary intervention; URL=upper normal limit.

Supplement Table 5. Key features of included trials

Trial	Comparison	Multicenter	Recruitment period	Inclusion criteria	Exclusion criteria	Significant CAD at CCTA	Significant ischemia at functional tests	FFR-Guided revascula-rization
CAD-Man (15)	• CCTA • ICA	No	February 2009 – August 2015	Patients presenting during working days from 7.30 am until 4 pm with suspected coronary artery disease and a clinical indication for coronary angiography on the basis of atypical presentation for study participation. Atypical presentation was defined as the presence of a maximum of two of the three criteria for typical angina pectoris (retrosternal chest discomfort, precipitation by exertion, and prompt relief within 30 seconds to 10 minutes by rest or nitroglycerine) using a clinically relevant classification of chest discomfort.	Patients with two positive test results for ischemia; patients not in sinus rhythm; signs of myocardial infarction (persistent ST segment elevation, creatine phosphokinase- MB >24 U/L, or pulmonary oedema due to ischemia); inability to hold the breath for five seconds; age below 30 years; renal insufficiency with dialysis. had a history of or were receiving dialysis.	Obstructive coronary artery disease was defined as at least one 50% diameter stenosis in the left main coronary artery or at least one 70% diameter stenosis in other coronary arteries	-	No
CONSERVE (16)	• CCTA • ICA	Yes	December 2012 – July 2015	Patients with suspected but without known CAD referred for nonemergent ICA based upon the ACC/AHA guidelines for coronary angiography, and included indications based on abnormal stress testing or suspected CAD symptoms.	Known history of CAD; ACC/AHA Class I or III indication for ICA; known complex congenital heart disease; planned ICA for reasons other than CAD evaluation; other reasons that precluded randomization to either group for reasons of safety.	The presence or absence of angiographic stenoses ≥50% using a Society of Cardiovascular Computed Tomography coronary tree model was recorded by local site physicians, and the maximum on per-patient basis was	-	No

						used to define obstructive CAD.		
DISCHARGE (17)	• CCTA • ICA	Yes	October 2015 – April 2019	Age ≥ 30 years old; stable chest pain; suspected CAD; patients referred for ICA with intermediate (10-60%) pretest probability of obstructive CAD	Hemodialysis; no sinus rhythm; pregnancy; any medical condition giving rise to concern that participation might not be in the best interest of health	A coronary diameter stenosis >50% in a major epicardial artery >2 mm was considered significant.	-	Could be conducted when deemed clinically indicated by the operator and according to local routine practice.
Reis et al (18)	• CCTA • ICA	No	January 2015 – December 2018	Age ≥18 years old; patients referred for ICA based on clinical suspicion of de novo CAD and an abnormal non-invasive ischemia tests: exercise treadmill stress tests and SPECT-MPI using technetium-99m.	Uncontrolled severe angina; acute coronary syndromes; previously known CAD; atrial fibrillation; inability to obtain a steady sinus rhythm; chronic kidney disease or previous kidney transplantation; contrast allergy; other CCTA-specific contraindications; abnormal non-invasive ischemia tests classified as severe or reported as inconclusive.	CCTA results were classified as "positive" in the presence of obstructive CAD defined as at least one segment with stenosis ≥70%, left main stenosis ≥50%, high calcium score precluding CT angiogram as determined by the attending imager or by the presence of any uninterpretable segment.	-	No
CAPP (19)	• CCTA • Exercise ECG: Standard Bruce protocol.	No	September 2010 – November 2011	Patients over 40 years old referred for suspicion of angina; ability to hold breath	Significant renal dysfunction with an eGFR<35 ml/min; recent history of alcohol, drug abuse, or other medical conditions that might compromise safety, successful completion of,	A coronary diameter stenosis >50% in a major epicardial artery >2 mm was considered significant. Such results could involve either	*Exercise ECG*: results were classified as negative, positive, or inconclusive as defined by previous criteria (60).	No

					or drug compliance during the study; patients with a history of chronic inflammatory conditions (such as severe arthritis, lupus, or inflammatory bowel disease); patients taking immunosuppressant agents (such as cyclosporine, tacrolimus, azathioprine, or chronic oral glucocorticoids); unstable angina pectoris; uncontrolled fast atrial fibrillation or other arrhythmias that may interfere with ECG-gated triggering of CT; patients with extreme tachycardia, greater than 110 bpm, despite rate controlling agents; pregnancy; morbid obesity (BMI >35); known contrast medium allergy; known ischemic heart disease with previous intervention in the form of CABG or PCI; inability to lie flat; severe aortic stenosis; acute myocarditis/pericarditis; uncontrolled hypertension >220/100; severe peripheral vascular disease or impaired immobility; significant chronic obstructive pulmonary	calcified or non-calcified disease.		

					disease that would impair exercise or B blocker use; left bundle branch.			
SCOT-HEART (9,20)	• CCTA plus standard of care: Calcium scoring prior to CCTA. Physicians caring for patients in this group were prompted to consider the results of the CCTA in their management decisions. • Standard of care: Evaluation of clinical history of angina pectoris, cardiovascular risk assessment (according to ASSIGN score) and demonstrate objective evidence of exercise-induced myocardial ischemia through exercise stress testing (standard Bruce protocol). High-risk patients will be treated for coronary heart disease and undergo invasive coronary angiography, intermediate-risk patients will be treated and further investigated at the	Yes	November 2010 – September 2014	Age >18 and ≤75 years; attendance at the out-patient cardiology clinic with chest pain (Rapid Access Chest Pain Clinic).	Inability or unwilling to undergo computed tomography scanning; known severe renal failure (serum creatinine >2.26 mg/dL or eGFR <30 mL/min/1.73 m2); major allergy to iodinated contrast agent; known pregnancy; acute coronary syndrome within 3 months.	Obstructive coronary artery disease was defined as a luminal stenosis more than 70% in one or more major epicardial vessel or more than 50% in the left main stem	NA	No

	discretion of the clinician, and low-risk patients will be reassured and discharged.							
CARE-CCTA (21)	• CCTA • SPECT-MPI: performed with pharmacologic stress using adenosine.	Yes	September 2011 – January 2014	Age 30-80 years old with newly developed stable chest pain; 10-90% risk of significant CAD by Diamond-Forrester risk score.	Previous known history of significant CAD (≥ 50% stenosis in any epicardial coronary artery) or PCI or CABG or myocardial infarction; acute coronary syndrome; ≥90% risk or <10% of significant coronary artery disease by Diamond-Forrester risk score; significant renal impairment (serum creatinine ≥1.4 mg/dL); allergic reaction to the radiocontrast dye; female with a potential to be pregnant during the study enrollment; any comorbidity with life expectancy less than 1 year.	CCTA results were classified as severe (≥70% or completely occluded), moderate, mild (1-49%), none (0%) or indeterminate (image interpretation not possible because of severe calcification or poor image acquisition) based on the severity of stenosis in any of the major epicardial artery and its major branches	*SPECT-MPI*: Any SPECT image with ≥1 segment perfusion deficit at stress image was defined as a positive SPECT result.	No
IAEA-SPECT/CTA (22)	• CCTA • SPECT-MPI: Exercise protocol or pharmacologic stressor agent was left to physician discretion.	Yes	June 2011 – June 2014	Age ≥ 21 years old; mildly symptomatic patients with an intermediate likelihood of having CAD, or asymptomatic patients who were determined to be at intermediate or high risk of coronary events by the Framingham (ATP III) criteria.	Known CAD (documented either by invasive or non-invasive imaging, a history of myocardial infarction or coronary revascularization); severely symptomatic patients (class III or IV NYHA); chronic renal impairment precluding contrast injection; severe medical disease with	Studies were reported as being normal, if there were no coronary stenoses or any luminal narrowing was less than 30% of the reference vessel diameter. Stenoses were categorized as being mild (30%-49%), moderate	NA	No

					limited life-expectancy; known contraindication or allergy to pharmacologic stress agents or contrast agents; abnormal cardiac rhythm (including persistent atrial fibrillation) which precluded ECG gating; very obese patients; pregnancy; breastfeeder.	(50%-69%), or severe (≥70%).		
Min et al (23)	• CCTA • SPECT-MPI: performed with exercise stress or pharmacologic stress using adenosine.	Yes	December 2008 – June 2009	≥40 years of age; no known history of CAD (as defined by prior myocardial infarction, coronary revascularization, or at least mildly abnormal CAD test), stable chest pain syndrome; suspected CAD; a determination by the referring physician that CAD evaluation with noninvasive imaging was warranted	Suspected acute coronary syndrome; noncardiac illness with life expectancy <2 years; pregnant state or possible pregnant state; allergy to iodinated contrast agent; serum creatinine ≥1.7 mg/dL, irregular heart rhythm; heart rate ≥100 beat/min, systolic blood pressure ≤90 mm Hg, contraindication to β-blocker or nitroglycerin; class I ACC/AHA indication for urgent or emergent ICA.	A stenosis ≥50% was considered abnormal	*SPECT-MPI*: abnormal scans were defined as myocardium abnormal ≥5%	No
PROMISE (10)	• CCTA • Functional testing (Exercise ECG, Stress Echocardiography, or SPECT-MPI)	Yes	July 2010 – September 2013	Age >54 years (in men) or >64 years (in women) or between 45-54 years (in men) or between 50-64 years (in women) with at least one cardiac risk factor (diabetes, peripheral arterial disease, cerebrovascular disease, current or past tobacco use, hypertension, or dyslipidemia); symptomatic outpatients without diagnosed	Unstable hemodynamic status or arrhythmias that required urgent evaluation for suspected acute coronary syndrome; a history of CAD or evaluation for CAD within the previous 12 months; clinically significant congenital, valvular, or	CCTA will be considered positive if there is a ≥70% stenosis in either the left anterior descending, left circumflex, or right coronary artery, or a ≥50% stenosis in the left main coronary artery.	Considered positive if there is a reversible perfusion defect (inducible ischemia) or mixed defect (infarct and ischemia) during stress in at least one territory.	No

				CAD whose physicians believed that nonurgent, noninvasive cardiovascular testing was necessary for the evaluation of suspected CAD.	cardiomyopathic heart disease			
RESCUE (24)	• CCTA • SPECT-MPI	Yes	May 2011 – June 2013	Age ≥40 years old; presentation with symptoms of stable angina (Canadian Cardiovascular Society class I to III) or angina equivalent with or without known CAD; planned non-invasive imaging for CAD diagnosis; able to tolerate CCTA or SPECT-MPI per randomization as required by protocol.	Prior revascularization; not suitable to undergo CT with an iodinated contrast agent because of a known allergy; renal failure or insufficiency as determined by eGFR <30 mL/min per 1.73 m2; atrial fibrillation or significant arrhythmia judged to potentially limit quality of CCTA; acute ischemia or acute myocardial infarction; severe myocardial ischemia defined by markedly positive exercise treadmill stress test (significant ST segment depressions or hypotensive response during stage I of the Bruce protocol); unable to suspend respiration for 15 seconds or to follow instructions to do so; unstable angina and symptoms refractory to maximal oral and intravenous medical therapy (persistent Canadian Cardiovascular Society class IV); history of known left ventricular ejection fraction <45%; pulmonary edema or	NA	*SPECT-MPI*: patients with ≥10% reversible defect.	No

					heart failure unresponsive to standard medical therapy; pacemaker, due to potential beam-hardening artifacts; valvular heart disease likely to require surgery in the next 18 months; congenital heart disease or cardiomyopathy likely to affect prognosis during follow up; significant systemic hypertension (blood pressure >200/100 mm Hg) unresponsive to medical therapy; severe non-cardiovascular comorbidity limiting survival (e.g., cancer or other life threatening illness for which the patient is expected to live less than 12 months); prior imaging evaluation for this episode of symptoms (eg, SPECT-MPI or CCTA within the previous 72 hours); BMI >40 kg/m2 because of likely limited examination quality; pregnancy or intent to become pregnant.			
Sabharwal et al (25)	• SPECT-MPI: performed with exercise stress or pharmacologic stress using dipyridamole infusion (or	No	February 2001 – July 2002	Age over 25 years and chest pain suspicious of CAD.	Acute coronary syndromes; known CAD; pregnant; lactating women.	-	*SPECT-MPI*: NA *Exercise ECG*: symptoms or standard ECG criteria (1 mm of	No

	dobutamine if contraindication). • Exercise ECG: Standard Bruce or modified Bruce protocol						horizontal or downsloping ST-segment depression during exercise or persisting into recovery in 1 lead or exertional hypotension [>20 mmHg]).	
WOMEN (26)	• SPECT-MPI • Exercise ECG: Standard or modified Bruce protocols.	Yes	NA	Women with typical/atypical chest pain or ischemic equivalents (e.g., dyspnea); interpretable baseline ECG (i.e., no significant resting ST-segment changes ≥0.5 mm); age ≥40 years or postmenopausal; capable of performing ≥5 metabolic equivalents (METs) on the Duke Activity Status Index questionnaire; were at intermediate pretest CAD likelihood	Women with known CAD defined as a history of myocardial infarction or catheterization results revealing a >50% lesion in one or more coronary arteries; nursing or pregnant females; women having a nuclear medicine study within the preceding 10 days; electrocardiographic abnormalities excluded: left bundle branch block, electronic ventricular pacemaker, left ventricular hypertrophy, and resting ST-T wave changes; significant valvular heart disease (i.e., severe aortic stenosis or regurgitation, or severe mitral insufficiency); uncontrolled hypertension (blood pressure [>210/110 mmHg); hypotension (<90/ 60 mm/Hg), history of heart failure; left ventricular ejection	-	*SPECT-MPI*: each segment was scored with a 5-point scoring system (0=normal perfusion to 4=no uptake). A normal, mildly abnormal, and moderate to severely abnormal MPI was defined as a summed stress score of <4, 4 to 8, and >8, respectively. *Exercise ECG:* abnormal if there is ≥1 mm of horizontal (occurring 60 ms past the J-point) or downsloping ST-segment depression, or if there is a change of ≥1 mm in a segment with a baseline abnormality of <0.5 mm deviation from	No

					fraction <50%; women receiving digoxin therapy.		the isoelectric line. A threshold of 1.5 mm ST segment depression will also be considered when upsloping ST-segment depression is noted.	
CE-MARC 2 (27)	• SPECT-MPI: performed with exercise stress, pharmacologic vasodilator stress (with adenosine or regadenoson), or a combination • CMR: Stress perfusion imaging performed with adenosine	Yes	November 2012 – March 2015	Age ≥30 years; suspected stable angina that requires further investigation; a defined pre-test risk of 10-90% (according to NICE guidelines); suitable for revascularization if required.	Non-anginal chest pain; normal SPECT/CCTA within the last 2 years; clinically unstable; previous MI or biomarker positive ACS; previous revascularization with CABG or PCI; contraindication to CMR imaging (pacemaker, intra-orbital debris, intra-auricular implants, intracranial clips, severe claustrophobia); contrain dication to adenosine infusion (regular adenosine antagonist medication, significant reversible airways disease, second or third degree atrio-ventricular heart block, sino-atrial disease); known adverse reaction to adenosine or gadolinium/iodinated contrast agents; obesity (where body girth exceeds scanner diameter); pregnancy and breast feeding; known chronic	-	*SPECT-MPI*: Each segment was scored as 0 = normal, 1 = mild hypokinesia, 2 = severe hypokinesia, 3 = akinesia, or 4 = dyskinesia. A positive result was considered as a summed stress score ≥ 4. *CMR*: ≥2 adjacent segments [or 60° arc- equivalent if the defect crosses segmental boundaries] with ≥50% transmural extent of ischemia, scar, or ischemia-scar combination.	Yes

					renal failure (eGFR <30ml/min/1.73m2)			
Gurunathan et al (28)	• Stress Echocardiography: performed with exercise stress • Exercise ECG: Standard Bruce protocol.	No	February 2013 – March 2014	Patients referred for evaluation of possible CAD; normal resting ECG; pre-test probability of CAD > 10% (according to NICE guidelines); moderate physical functioning; no known history of CAD.	Unstable angina; prior history of CAD; patients with pre-test probability of CAD < 10%	-	*Exercise ECG*: patients, who developed significant chest pain, hypotension, an arrhythmia, or ≥1 mm planar or downsloping ST depression in two or more leads of the same territory, during exercise or in recovery, were considered to have a positive test. *Stress echocardiography*: patients with evidence of wall motion abnormalities at rest or who developed regional wall motion abnormalities at peak stress were deemed to have a positive stress echocardiogram.	No

Abbreviations: ACC/AHA=American College of Cardiology/American Heart Association; BMI=body mass index; CABG=coronary artery bypass grafting; CAD=coronary artery disease; CCTA=coronary computed tomographic angiography; CMR=cardiovascular magnetic resonance; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FFR=fractional flow reserve; ICA=invasive coronary angiography; NICE=National Institute for Health and Care Excellence; NYHA=New York Heart Association; PCI=percutaneous coronary intervention; SPECT-MPI=single photon emission computed tomography-myocardial perfusion imaging.

Supplement Table 6. Diagnostic protocols of included trials

Trial	Comparison	CCTA Protocol	Functional Test Protocol
CAD-Man (15)	CCTA vs. ICA	Images were evaluated by two independent readers, of whom at least one was a board certified radiologist and, as in routine clinical practice, decisions were made by consensus. In patients with heart rates up to 65 bpm, 320 row coronary CT angiography enabled reconstruction windows of 175 msec (Aquilion ONE, Toshiba Medical Systems, 121 patients) or 137.5 msec (Aquilion ONE Vision Edition, 44 patients). In patients with heart rates of at least 65 bpm, temporal resolution was improved by two beat acquisition in 23 patients and three beat acquisition in two patients. Coronary calcium scoring was used to individually adjust the acquisition length of CT angiography, but was not used to defer CT angiography.	-
CONSERVE (16)	CCTA vs. ICA	NA	-
DISCHARGE (17)	CCTA vs. ICA	Calcium score calculation should only be done after performing CCTA in order to not obstruct workflow. Even in patients with high calcium scores, CTA will always be done. It was recommended to use double oblique views, multi-planar reformations, and cross-sections in all coronary artery segments. Each CT was evaluated by two local readers at each center of whom at least one had to be certified as a level-2 reader according to the Society of Cardiovascular Computed Tomography or similar certification. At least one CT reader per center was required to have level-3 certification for cardiac CT lab leadership.	-
Reis et al (18)	CCTA vs. ICA	From January 2015 to May 2016 a 64-detector computed tomography (CT) scanner (*VCT 64 Lightspeed, GE health- care, Wisconsin, USA*) was used. Thereafter, the exams were performed on a dual-source 128-detector CT scanner (*Somatom Definition Flash, Siemens, Erlangen, Germany).* Acquisition protocols, interpretation, and reporting were performed according to local standardized practice. In general, tube voltage is set to 80 Kv for patient body weight < 60Kg, 100 kV for weight 60–80 and 120 for weight > 120 kV. Iterative reconstruction was introduced and routinely used (kernel 39f) when the GE VCT scanner were changed for Siemens' Dual source Flash Scanner. All patients received nitroglycerin before CCTA. Acquisition protocols were	-

		performed according to local standardized practice and left at the discretion of clinical imagers. The institution practice is to target heart rate <65 bpm. When patients present with higher heart rates, oral metoprolol 50–100 mg is given and repeated 30 min after when necessary. Coronary calcium quantification and classification per the Agatston method were carried out in all cases.	
CAPP (19)	CCTA vs. Exercise ECG	Patients underwent both a calcium score and subsequent CCTA, regardless of initial calcium score. These were performed on a 64-detector platform (Philips Brilliance 64 Cleveland, Ohio, USA). As per departmental policy, both oral and intravenous beta blockers were used for heart rate control pre-scan. A heart rate of 65 bpm or below was considered optimal for imaging, although CCTA would have been performed below the level of 70 bpm. Patients with heart rates above 70 bpm despite intravenous beta blockers were rescheduled for a later date with larger doses of oral pre-procedure. A non-contrast enhanced, axial prospective triggered CS was performed at 3-mm slice thickness with milliamperes optimized per patient and a standard 120 kV. CTCA contrast medium enhancement was achieved with a biphasic injection protocol. An aliquot of 80 – 100 mL of iodinated contrast material (Ioversol, Optiray 350 mgI/mL, Covidien, Hampshire, UK) was administered through an 18-gauge intravenous antecubital fossa cannula at a flow rate of 6 mL/s followed by a saline chaser of 50 mL at 3.5 mL/s. An automated bolus tracking technique prospectively monitored contrast arrival in the descending aorta. A threshold of 110 Hounsfield units was used to initiate the scan. Image acquisition was in the cranio- caudal direction, and the scan field of view was refined using precise anatomical landmarks cross referenced from the coronary CS. Images from CTCA were reconstructed at 0.8-mm slice thickness with the standard reconstruction filter. Scan parameters (kV, mAs) were optimized by the imaging clinician and were patient specific. The choice of a retrospective gating, or an axial prospective triggering algorithm, was at the discretion of the clinician. For all retrospective examinations, ECG dose modulation was applied (DoseRight Cardiac, Philips Healthcare, Cleveland, Ohio, USA).	**Exercise ECG.** Performed using a standard Bruce protocol treadmill with continuous 12-lead ECG monitoring and registration at 1-min intervals. Manual blood pressure monitoring was performed every 2 min. Criteria for discontinuation of the test were ST changes of depression >0.3 mV or elevation >0.1 mV; blood pressure changes of systolic >230 mmHg or diastolic >130 mmHg or a >10 mmHg systolic blood pressure drop; arrhythmias such as sustained ventricular tachycardia, increasing frequency of polymorphic ventricular complexes, or altered atrioventricular or intraventricular conduction; and patient symptoms of exhaustion, extreme dyspnea, or angina.

SCOT-HEART (9,20)	CCTA plus standard of care vs. standard of care	Scans will be performed using a 64, 128 or 320-multidetector scanner. CCTA protocol optimizations will be performed at all sites throughout the study, to optimize scanning parameters, such as radiation dose and contrast administration. Before calcium scoring, patients with a heart rate of greater than 60 beats/min and systolic blood pressure >110 mmHg will receive rate-limiting medication. If a participant's heart rate is above 100 beats per minute despite rate-limiting medication, CCTA will not be performed. A small dose of oral diazepam may be prescribed for anxious patients, to improve heart rate control. Sublingual glyceryl trinitrate will be administered immediately prior to CT imaging. Coronary artery calcium score will be performed prior to coronary angiography. Investigators blind to patient characteristics will conduct off-line analyses using automated computerized software programs that employ the Agatston scoring method using a threshold of 130 Hounsfield units. The calcium score percentile based on age and sex will be calculated using coronary artery calcium score distributions from the Multi-Ethnic Study of Atherosclerosis (MESA). For patients younger than 45, 45 years will be used for the calculation of the calcium score percentile. Coronary angiography will be conducted during contrast enhancement using pre-specified protocols (as recommended by the scanner manufacturers) during a single breath hold with prospective electrocardiographic gating as appropriate.	**Exercise ECG**. Symptom-limited using the standard Bruce protocol.
CARE-CCTA (21)	CCTA vs. SPECT-MPI	All CCTA images were obtained using CT systems with 64 slices or more (SOMATOM Sensation 64 and SOMATOM Definition; Siemens Medical Solutions, Forchheim, Germany, or Brilliance 64; Philips Medical Systems, Best, the Netherlands). Before CCTA, patients were given sublingual nitroglycerin, and patients with average heart rate >65 beats/min received 50- to 100-mg oral metoprolol in the absence of contraindications. Helical scan data were obtained with retrospective electrocardiography (ECG)-gating protocol. All results were transferred to an external 3-dimensional workstation (Brilliance; Philips Medical Systems) and analyzed by 2 or more experienced radiologists.	**SPECT-MPI.** Rest ^{201}thallium or stress ^{99m}technetium methoxyisobutylisonitrile ECG-gated SPECT was performed with pharmacologic stress using adenosine. No patient underwent exercise SPECT because all medical centers in Korea have a uniform format of using adenosine for stress in taking the SPECT test. All images were taken using a dual-head camera equipped with a low-energy, high-resolution collimator (Vertex EPIC; ADAC Laboratories, Milpitas, CA). Two separate experienced nuclear cardiologists interpreted the images based on semiquantitative polar maps of perfusion.
IAEA-SPECT/CTA (22)	CCTA vs. SPECT-MPI	Performed using a multidetector scanner (64-slice or greater), and reported in accordance with current practice guidelines (61). Calcium scoring was performed prior to contrast injection.	**SPECT-MPI.** Choice of exercise protocol or pharmacologic stressor agent was left to physician discretion. Perfusion data were recorded using a 17-segment model and perfusion

			abnormalities were quantitated using summed scores. Physicians adhered to standard procedures and guideline recommendations while performing stress testing, image acquisition, interpretation, and reporting (62).
Min et al (23)	CCTA vs. SPECT-MPI	Performed with a 64-detector row CT scanner (Lightspeed VCT; GE Healthcare, Milwaukee, WI) with the use of 100 mL of iodinated contrast (Isovue-370; Bracco Diagnostics, Princeton, NJ; or Visipaque; GE Healthcare, Princeton, NJ) followed by a 50-mL saline flush with contrast timing to optimize uniform enhancement of the coronary arteries. The scan parameters were 64 x 0.625 mm of collimation, tube voltage of 120 mV, and effective tube current of 400–650 mA. Axial scanning with prospective ECG gating was performed for heart rate <65 beat/min and absence of sinus arrhythmia. Otherwise, helical scan data were obtained with retrospective ECG gating. Images were reconstructed immediately after completion of the scan to identify motion-free coronary artery images. Optimal phase reconstruction was assessed by comparison of different phases, if available, and the phase with the least amount of coronary artery motion was chosen for analysis. All scans were analyzed by a level III-certified cardiologist with experience interpreting several thousand CCTA scans.	**SPECT-MPI.** Patients undergoing dual-isotope imaging received 3–4.5 mCi thallium-201 at rest, and patients undergoing single-isotope imaging received 9–10 mCi of technetium-99m sestamibi at rest. Stress exercise or adenosine protocols with or without low-level treadmill exercise were performed with stress injection of 25–40 mCi of technetium-99m sestamibi. Twelve-lead ECG was performed during stress tests. All MPI scans were analyzed by a board-certified cardiologist with experience interpreting several thousand MPI scans.
PROMISE (10)	CCTA vs. Functional testing	Sites used standard equipment for functional testing as defined in current practice guidelines and ≥64-slice multidetector CCTA. Although sample protocols were provided for all modalities, sites were allowed to use their own acquisition protocols as long as they fell within national standard-of-care guidelines. (63-65) All diagnostic tests were interpreted by qualified diagnosticians at the sites in real time according to current clinical guidelines to ensure timely availability of results for patient management.	
RESCUE (24)	CCTA vs. SPECT-MPI	ECG-gated coronary CTA was performed on 64-slice or greater CT scanners and gated SPECT-MPI to fall within literature-based guidelines. CCTA guidelines for RESCUE Sites were as follows: All image acquisitions were performed using a breath hold in inspiration during intravenous administration of 80 mL of iodinated contrast, on average, injected as a bolus at a rate of 5 mL/s to attenuate the lumen of the coronary arteries, the aorta, and the left ventricle. Appropriate timing of the contrast bolus was ensured by either the determination of the transit time or the bolus trigger technique. Using ECG gating, the tube current was reduced during systole according to each manufacturer's specific protocol	**SPECT-MPI**. All site protocols were reviewed and approved by the ACRIN core lab prior to the enrollment period in order to ensure optimal imaging techniques. At minimum, SPECT-MPI data sets were to consist of the following: non attenuated-corrected AND attenuated corrected raw rest and stress projection data; reconstructed files (short axis, vertical long axis, and horizontal short axis); screen capture of quantitative analysis results page displaying "% of LV ischemia or "% LV reversibility" from a commercial quantitative software program (ie, Emory Cardiac Toolbox, 4D-MSPECT, QPS (Cedars Sinai); gated SPECT MPI data with Beat Length Histogram (if available).

		to minimize radiation exposure. Sites were permitted to perform this with either prospective or retrospective ECG-gating. If retrospective gating was performed, the scan was required to be performed with radiation dose modulation or a minimum radiation dose protocol to reduce the tube current during systole. With the exception of sites with a dual-source CT (DSCT) scanner, all participants with a heart rate >65 beats per minute received a heart-rate lowering drug (usually a β-blocker), intravenously or orally, to optimize image quality and sublingual nitroglycerin to maximally dilate the coronary arteries unless their systolic blood pressure was <100 mm Hg or other contraindications were present. At sites with a DSCT scanner, due to the improved temporal resolution, heart-rate lowering drugs were not required, with participants receiving only sublingual nitroglycerin if there were no contraindications. At least one data set that showed the least cardiac motion was reconstructed a minimum 0.8 mm thick axial images, with 50% overlap from the contrast-enhanced CCTA scan for the detection of coronary plaque and stenosis (pixel matrix: 512 x 512, FOV: 25 cm).	SPECT MPI image quality was evaluated to determine whether the entire left ventricle was in the Field of View; raw data projection images were of minimal motion and low levels of hepatic and bowel uptake; gated nuclear images were assessed to ensure optimal gating was achieved.
Sabharwal et al (25)	SPECT-MPI vs. Exercise ECG	-	**SPECT-MPI.** Patients underwent stress testing with exercise, dipyridamole infusion (Boehringer Ingelheim, Barcelona, Spain), or both. If there was a contraindication to dipyridamole, dobutamine was used. Pharmacologic stress was allowed in order to retain the maximum benefit from the SPECT technique. Pharmacologic stress was only used if, after detailed questioning, the patient or physician did not believe that an adequate workload might be reached with treadmill stress, the default stressor with MPI. Pharmacologic stress was achieved by use of 0.56 mg/kg of dipyridamole over a period of 4 minutes before low-level treadmill exercise. At peak stress, 400 to 600 MBq of Tc-99m sestamibi (Cardiolite; Bristol-Myers Squibb Medical Imaging, Fleurus, Belgium) was injected, and treadmill exercise was continued at the same level for a further minute after injection of the isotope. Imaging was carried out approximately 60 to 90 minutes later. A dual-head gamma camera with a large field of view (Sopha DS7; Sopha Medical Vision, Buc, France) equipped with high-resolution collimators was used. We acquired 32 projections (20 seconds per projection) over a 180° arc, from

			45° right anterior oblique to 45° left posterior oblique. Strict quality-control and motion artifact correction was used when required. Rest scans were carried out 24 to 48 hours later if the stress scan was abnormal or ambiguous. Therefore rest imaging was not performed if the stress image was entirely normal. Images were acquired and analyzed by use of a Vision computer (Sopha Medical Vision). Routine gamma camera quality control was maintained throughout the study. Each study was initially analyzed without knowledge regarding the pretest likelihood; however, the referring physician then reviewed the SPECT results with the expert to provide clinical correlation for the report. Perfusion images were scored semiquantitatively by use of a 20-segment model. Gated acquisition was used to clarify ambiguous attenuation artifacts. **Exercise ECG**. Symptom limited Bruce or modified Bruce protocol exercise treadmill test by use of a Marquette CASE 8000 system (Marquette, Milwaukee, Wis). Standard criteria were used for termination of the stress test: significant chest pain, ventricular tachycardia, greater than 3 mm of ST-segment depression, or decrease in systolic blood pressure of more than 20 mm Hg. Continuous blood pressure measurements and electrocardiograms were obtained during exercise and recovery. Two or more physicians read the findings, and consensus was attained if there was any disagreement.
WOMEN (26)	SPECT-MPI vs. Exercise ECG	-	**SPECT-MPI.** MPI procedures were standardized across centers and consistent with published guidelines (66). Before trial initiation, sites were required to send representative MPI scans to the quality control laboratory for approval. Data on rest/stress myocardial perfusion and poststress left ventricular ejection fraction were recorded. Tc-99m tetrofosmin or Tl-201 was used. **Exercise ECG**. Performed with the use of the standard or modified Bruce protocol. The ETT was continued until the occurrence of marked ST-segment changes, worsening chest pain, sustained ventricular arrhythmias, or excessive fatigue. Throughout testing, ST-segment changes, heart rate, and

			blood pressure measurements were recorded. Exertional chest pain or excessive dyspnea was also documented.
CE-MARC 2 (27)	SPECT-MPI vs. CMR	-	**CMR**. Performed on a clinical 3.0-T scanner using protocols that conform to international standards. A cardiac imaging receiver coil configuration will be used, and ECG gating will be performed. The scan will comprise the following: 1. Survey and reference scans prior to defining the short, vertical long, and horizontal long axes acquired with a balanced steady-state free precession (bSSFP), single-slice breath-hold sequence. bSSFP pulse sequence parameters dependent on scanner manufacturer and site. Typical parameters are as follows: echo time 1.3 milliseconds, repetition time 2.6 milliseconds, flip angle 40°, field of view 320-420 mm according to patient size, SENSE or GRAPPA acceleration, slice thickness 10 mm, and 30 phases per cardiac cycle. 2. Stress perfusion imaging performed with adenosine administered initially at 140 μg kg^{-1} min^{-1}. Adequate hemodynamic response is assessed by either ≥10% heart rate increase or ≥10 mm Hg decrease in systolic blood pressure. If there is inadequate hemodynamic response, then the dose will be increased incrementally to 170 μg kg^{-1} min^{-1} and then 210 μg kg^{-1} min^{-1} for a further 2 minutes until hemodynamic response is achieved. Perfusion image acquisition will use a 2-dimensional, T1-weighted saturation recovery–prepared gradient echo-pulse sequence in 3 short-axis slices, planned using the 3/5 technique, using either parallel imaging acceleration (SENSE or GRAPPA) or spatiotemporal undersampling (5X kt-BLAST). First-pass contrast-enhanced study will be performed using a dual-bolus technique (0.075 mmol/kg gadobutrol [Gadovist; Bayer Schering Pharma, Berlin, Germany]) for the main bolus preceded by the same volume of a 10% dilute contrast agent dose for the prebolus, both administered at a rate of 4.0mL/s followed by a 20-mL saline flush. 3. Resting wall motion and left ventricular function will be assessed with a contiguous stack of multiphase ventricular short-axis bSSFP cines (10-12 slices, 30 phases, 10-mm slice thickness, 0-mm gap, same cine pulse sequence as above).

			4. The rest myocardial perfusion study will use identical pulse sequence, slice positioning, and injection characteristics to the stress perfusion scan. If the stress perfusion scan was not of adequate quality (eg, ectopics and failure to trigger), a repeat stress may be performed as alternative to the rest study. 5. Late gadolinium enhancement (LGE) performed in 10 to 12 short-axis slices 10 to 15 minutes after step 4 with an inversion recovery–prepared T1-weighted gradient echo-pulse sequence. Typical parameters are as follows: echo time 2.0 milliseconds, repetition time 3.7 milliseconds, flip angle 25°, acquired spatial resolution 0.70 x 0.70 x 10 mm^3, and inversion time individually adjusted according to inversion time scout. LGE will be acquired with alternate heart beat acquisition (with single-shot or navigated LGE, an option for poor breath holders) and long-axis and modified views acquired if clinically indicated. **SPECT-MPI**. Radionuclide imaging will be performed according to local standard departmental practice conforming to both national and international guidelines. Patients will undergo either a 1- or 2-day scanning protocol with a radioisotope tracer 99mTc-tetrofosmin or 99mTc-sestamibi (Myoview, GE Healthcare and CARDIOLITE, Lantheus Medical Imaging). A weight-adjusted dose up to a maximum of 1000 MBq per examination will be used for stress and rest imaging, which will be performed within 5 days of each other. Stress examination will be performed with either treadmill or bicycle exercise, pharmacologic vasodilator stress (with adenosine or regadenoson), or a combination. Treadmill will involve exercise using the BRUCE or modified BRUCE protocol or bicycle ergometer typically commencing at 25 W increasing workload by 25 W every 2 minutes. Radioisotope tracer will be injected at peak stress. If pharmacologic stress with adenosine is used, the administration regimen will be comparable with the CMR protocol. If regadenoson is used, 0.4 mg will be delivered by rapid intravenous injection. Radioisotope tracer will be injected after at least 4 minutes of adequate hemodynamic/symptom response. Vasodilator stress may be

			combined with submaximal exercise. Images will be acquired on either a dual headed gamma camera or solid-state cadmium zinc telluride camera. Stress and rest images will be gated to the ECG, and attenuation correction will be used where routinely available.
Gurunathan et al (28)	Stress Echocardiography vs. Exercise ECG	-	**Exercise ECG.** The standard Bruce protocol was used according to standard clinical practice. **Stress Echocardiography**. A resting two-dimensional echocardiogram was performed in the lateral decubitus position. Digital images, with tissue harmonic imaging, of the Left Ventricle (LV) were obtained in the parasternal long-axis, short- axis, and apical, four-, two-, and three-chamber views using an IE33 echocardiography system with an S5 probe (Philips, Best, the Netherlands). Stress images were acquired immediately (within 90 s) after peak exercise. Immediate post-exercise images with the best endocardial definition were selected and displayed alongside the corresponding baseline images. In technically difficult patients (when two or more segments were not adequately visualized at rest or during deep breathing), intravenous contrast (Sonovue, Bracco, Milan, Italy) was used to enhance endocardial border definition. Bolus injections of 0.3 – 0.5 mL were administered through a peripheral cannula followed by a flush with 0.9% NaCl solution.

Supplement Table 7. Baseline characteristics of patients in the included trials

Trial	Group	Age (mean)	Female, n (%)	Symptoms at presentation				Hyper-tension, n (%)	Dyslipi-demia, n (%)	Diabetes, n (%)	Current smoking, n (%)	Family history of CAD, n (%)	Statin, n (%)	Antiplatelet therapy, n (%)	Pretest likelihood of CAD (%)
				Typical angina	*Atypical angina*	*Non-anginal chest pain*	*Other CAD symptoms*								
CAD-Man (15)	CCTA	60.4	88 (52.7)	0 (0)	65 (38.9)	97 (58.1)	5 (3.0)	111 (66.5)	95 (56.9)	15 (9.0)	41 (24.5)	24 (14.4)	42 (25.1)	47 (28.1)	34.6*
	ICA	60.4	78 (48.1)	0 (0)	79 (48.8)	80 (49.4)	3 (1.8)	112 (69.1)	81 (51.0)	30 (18.5)	34 (21.0)	16 (9.9)	41 (25.3)	41 (25.3)	
CONSERVE (16)	CCTA	59.9	378 (48.3)	243 (31.0)	315 (40.2)	18 (2.3)	117 (14.9)	446 (56.9)	259 (33.0)	203 (25.9)	108 (13.8)	67 (8.5)	NA	NA	51°
	ICA	60.8	316 (43.9)	216 (30.1)	278 (38.7)	10 (1.4)	138 (19.2)	424 (59.0)	249 (34.6)	212 (29.5)	98 (13.6)	57 (7.9)	NA	NA	52°
DISCHARGE (17)	CCTA	61.3	1019 (56.4)	232 (12.8)	843 (46.6)	677 (37.4)	56 (3.1)	1102 (61.3)	874 (48.6)	263 (14.6)	343 (19.6)	515 (28.5)	808 (45.0)	857 (47.7)	36.6¶
	ICA	60.6	983 (56.1)	275 (15.7)	805 (45.9)	634 (36.2)	39 (2.2)	1020 (58.5)	832 (47.8)	294 (16.9)	300 (17.7)	548 (31.3)	787 (45.2)	884 (50.7)	37.9¶
Reis et al (18)	CCTA	69.3	52 (45.2)	36 (31.3)	NA	NA	NA	89 (77.4)	94 (81.7)	28 (24.3)	NA	21 (18.3)	NA	NA	34.4*
	ICA	68.2	37 (35.2)	34 (32.3)	NA	NA	NA	87 (82.9)	86 (81.9)	39 (37.1)	NA	29 (27.6)	NA	NA	33.2*
CAPP (19)	CCTA	57.8	105 (43.2)	84 (34.6)	16 (6.6)	143 (58.8)	NA	77 (31.7)	NA	14 (5.8)	46 (18.9)	NA	NA	NA	47.8§
	Exercise ECG	58.9	114 (46.5)	68 (27.8)	20 (8.2)	156 (63.7)	NA	73 (29.8)	NA	12 (4.9)	47 (19.2)	NA	NA	NA	44.9§
SCOT-HEART (whole population) (9,20)	CCTA	57.1	911 (44)	737 (36)	502 (24)	833 (40)	0 (0)	712 (34)	1099 (54)	223 (11)	NA	887 (43)	902 (44)	1009 (49)	NA
	Standard of care	57.0	910 (44)	725 (35)	486 (24)	859 (41)	0 (0)	683 (33)	1077 (52)	221 (11)	NA	829 (40)	884 (43)	984 (48)	NA
CARE-CCTA (21)	CCTA	63.5	278 (60.4)	NA	NA	NA	NA	312 (67.8)	319 (69.3)	215 (46.7)	32 (7.0)	30 (6.5)	220 (47.8)	204 (44.4)	43.5§

	SPECT-MPI	63.2	249 (56.2)	NA	NA	NA	NA	275 (62.1)	320 (72.2)	252 (54.8)	36 (8.1)	31 (7.0)	222 (48.3)	207 (45.0)	45.3§
IAEA-SPECT/CTA (22)	CCTA	58.9	77 (50.7)	122 (80.3)		NA	15 (9.9)	97 (63.8)	89 (58.6)	43 (28.3)	36 (23.7)	48 (31.6)	72 (47.4)	72 (47.4)	NA
	SPECT-MPI	60.2	81 (53.6)	121 (80.1)		NA	13 (8.6)	97 (64.2)	83 (55.0)	43 (28.5)	25 (16.6)	45 (29.8)	76 (50.3)	76 (50.3)	NA
Min et al (23)	CCTA	55.9	38 (42)	29 (31.9)	21 (23.1)	25 (27.5)	NA	61 (59)	54 (61)	19 (21)	NA	43 (48)	31 (34.4)	40 (44.4)	NA
	SPECT-MPI	58.9	51 (57)	20 (22.5)	22 (24.7)	22 (24.7)	NA	56 (62)	48 (53)	21 (23)	NA	37 (41)	35 (39.8)	32 (36.4)	NA
PROMISE (whole population) (10)	CCTA	60.7	2595 (51.9)	590 (11.8)	3873 (77.5)	533 (10.7)	1319 (26.5)	3247 (65.0)	3365 (67.4)	1065 (21.3)	NA	1624 (32.6)	2215 (46.3)	2164 (45.2)	53.4&
	SPECT-MPI	60.9	2675 (53.4)	576 (11.5)	3900 (77.9)	531 (10.6)	1405 (28.0)	3254 (65.0)	3402 (67.9)	1079 (21.5)	NA	1578 (31.6)	2174 (45.4)	2116 (44.2)	53.2&
RESCUE (24)	CCTA	57	233 (45)	NA	NA	NA	NA	318 (62)	324 (63)	105 (20)	74 (14)	NA	NA	NA	NA
	SPECT-MPI	58	244 (46)	NA	NA	NA	NA	317 (60)	313 (59)	114 (21)	87 (16)	NA	NA	NA	NA
Sabharwal et al (25)	SPECT-MPI	59.7	111 (44.6)	NA	NA	NA	NA	133 (53.2)	NA	48 (19.2)	32 (12.8)	108 (43.2)	NA	NA	NA
	Exercise ECG	58.9	88 (42.5)	NA	NA	NA	NA	96 (46.3)	NA	30 (14.5)	34 (16.4)	96 (46.3)	NA	NA	NA
WOMEN (26)	SPECT-MPI	62	384 (100)	230 (59.8)	36 (9.3)	107 (27.8)	186 (48.3)	200 (52.0)	206 (53.7)	55 (14.2)	NA	176 (45.8)	127 (33.1)	143 (37.1)	NA
	Exercise ECG	63	388 (100)	238 (61.2)	43 (9.1)	105 (27.0)	208 (53.5)	214 (55.2)	194 (50.0)	49 (12.6)	NA	184 (47.3)	123 (31.7)	129 (33.2)	NA
CE-MARC 2 (27)	SPECT-MPI	55.9	225 (46.8)	156 (32.4)	325 (67.6)	0 (0)	NA	182 (37.8)	198 (41.2)	73 (15.2)	271 (56.3)	259 (53.8)	201 (41.8)	268 (55.7)	48.6°
	CMR	56.5	227 (47.2)	163 (33.9)	318 (66.1)	0 (0)	NA	177 (36.8)	186 (38.7)	53 (11.0)	284 (59.0)	252 (52.4)	191 (39.7)	271 (56.3)	49.9°
Gurunathan et al (28)	Stress Echo	55	57 (30)	NA	NA	NA	NA	76 (40)	67 (35)	27 (14)	27 (14)	46 (24)	NA	NA	35*
	Exercise ECG	54	66 (34)	NA	NA	NA	NA	60 (31)	72 (37)	33 (17)	35 (18)	52 (27)	NA	NA	34*

*Duke score (29). §Diamond-Forrester score (30). ¶Diamond and Forrester updated score (31). &Combined Diamond and Forrester and Coronary Artery Surgery Study risk score (32). °Not reported.
Abbreviations: CAD=coronary artery disease; CCTA=coronary computed tomographic angiography; CMR=cardiovascular magnetic resonance; ECG=electrocardiogram; echo=echocardiography; ICA=invasive coronary angiography; SPECT-MPI=single photon emission computed tomography-myocardial perfusion imaging.

Supplement Table 8. GRADE assessment for all comparisons

*Study limitations (↓1 level for studies with "high risk" of bias or "some concerns" contributed >50% of the effect estimate). **Study limitations (↓2 level for all studies were "high risk" of bias or "some concerns")

†Indirectness (↓1 level for substantial differences exist between interventions, populations, outcomes, or time-points of measurement across studies).

‡Imprecision (↓1 level for sample size <2000). §Imprecision (↓1 level for sample size >2000 but CI of the overall estimate crosses 1.0 and includes an important benefit or harm [RR reduction or increase >30%]). §§Imprecision (↓2 level for CI of the overall estimate including both important benefit or harm [RR reduction and increase >30%]).

#Inconsistency (↓1 level for I^2>70%, CIs of individual studies don't overlap and few [<30%] are in complete opposite directions). ##Inconsistency (↓2 level for I^2>70%, CIs of individual studies don't overlap and many [>30%] are in complete opposite directions).

¶Publication bias (↓1 level for the evidence consists of a single study or a number of small studies or funnel plots indicates asymmetry).

Cardiovascular death and myocardial infarction

Comparison	Number of studies	RR (95% CI)	Certainty of evidence
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	1	0.83 (0.26-2.71)	Very low§§¶
Stress Echocardiography vs. Exercise ECG	0	-	-

All-cause death

Comparison	Number of studies	RR (95% CI)	Certainty of evidence
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	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

Comparison	Number of studies	RR (95% CI)	Certainty of evidence
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	1	3.00 (0.31-28.74)	Very low§§¶
Stress Echocardiography vs. Exercise ECG	0	-	-

Myocardial infarction

Comparison	Number of studies	RR (95% CI)	Certainty of evidence
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	1	0.40 (0.08-2.05)	Very low§§¶
Stress Echocardiography vs. Exercise ECG	1	1.02 (0.06-16.12)	Very low**§§¶

Index ICA

Comparison	Number of studies	RR (95% CI)	Certainty of evidence
CCTA vs. ICA	4	0.23 (0.22-0.25)	High
CCTA vs. Exercise ECG	2	1.09 (0.86-1.38)	Low§†
CCTA vs. SPECT-MPI	4	1.07 (0.77-1.50)	Very low*§##
SPECT-MPI vs. Exercise ECG	2	0.61 (0.20-1.89)	Very low*§§
SPECT-MPI vs. CMR	1	0.92 (0.69-1.21)	Low§¶
Stress Echocardiography vs. Exercise ECG	1	0.48 (0.22-1.04)	Very low**§¶

Index Revascularization

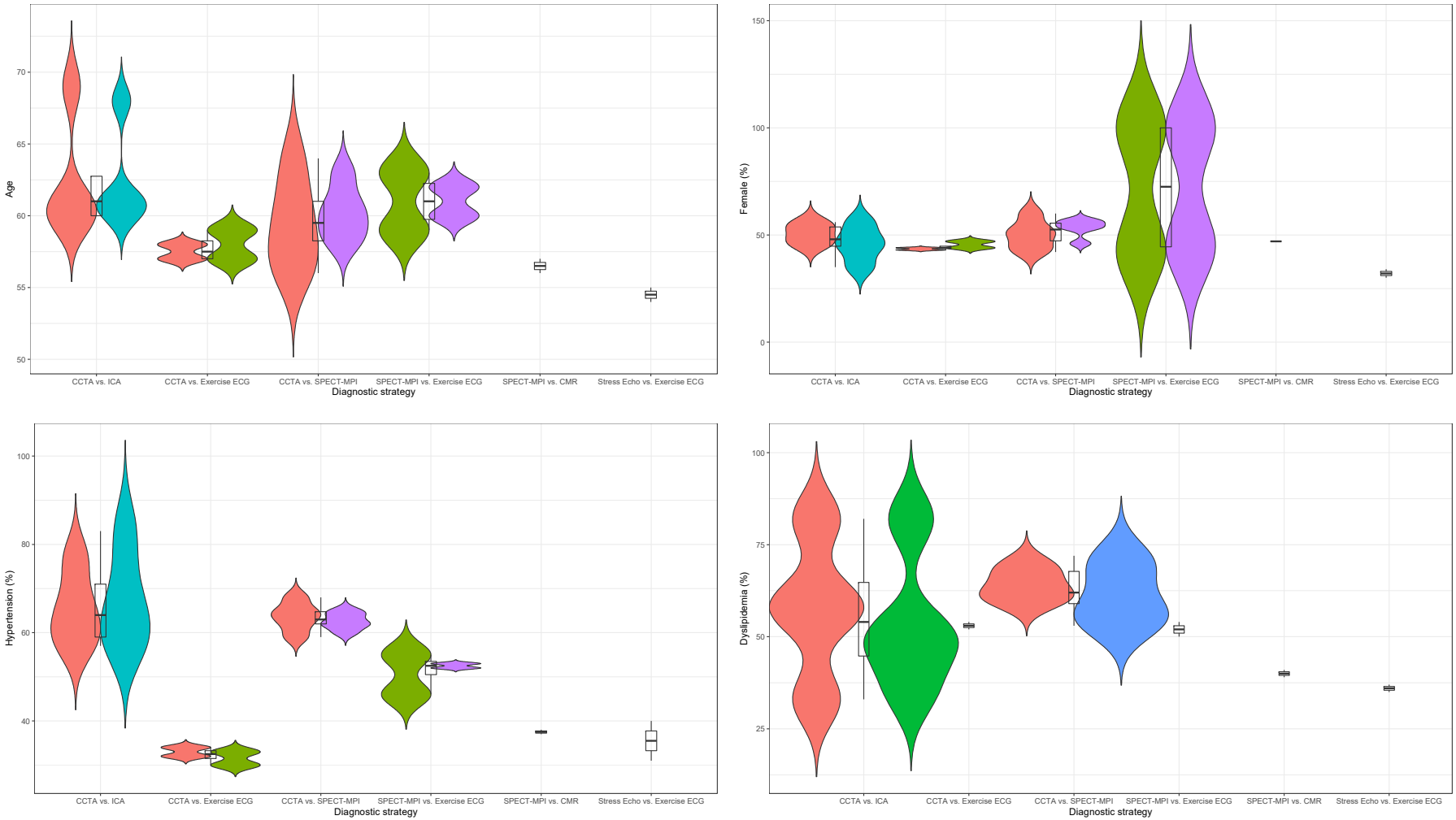
Comparison	Number of studies	RR (95% CI)	Certainty of evidence
CCTA vs. ICA	4	0.71 (0.63-0.80)	Moderate*
CCTA vs. Exercise ECG	2	1.78 (1.33-2.38)	Moderate†
CCTA vs. SPECT-MPI	4	1.38 (0.95-2.01)	Moderate§
SPECT-MPI vs. Exercise ECG	2	1.03 (0.29-3.64)	Very low*§§
SPECT-MPI vs. CMR	1	0.77 (0.52-1.14)	Low§¶
Stress Echocardiography vs. Exercise ECG	1	0.93 (0.42-2.06)	Very low**§§¶

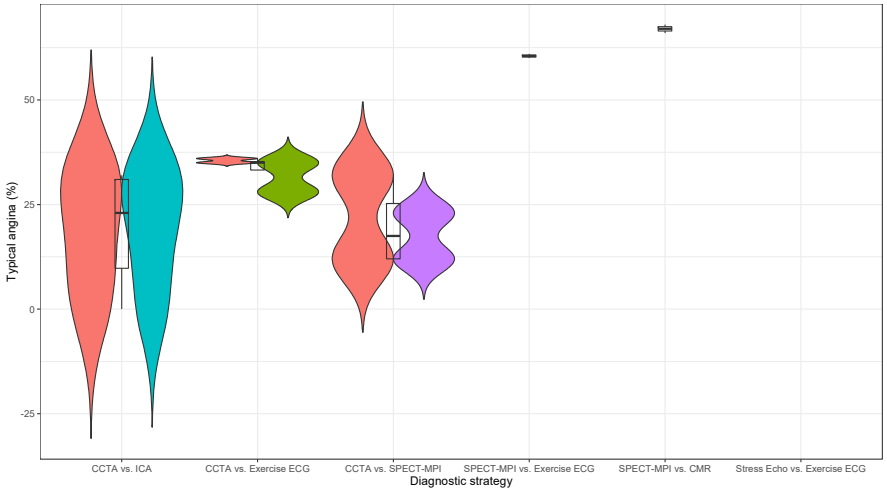
Downstream testing

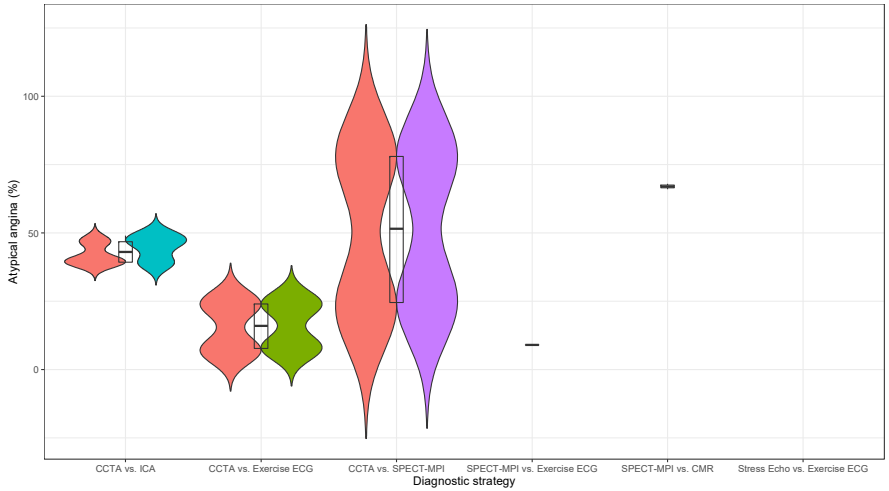
Comparison	Number of studies	RR (95% CI)	Certainty of evidence
CCTA vs. Exercise ECG	1	0.56 (0.45-0.71)	Very low**¶
CCTA vs. SPECT-MPI	4	1.07 (0.71-1.64)	Very low§##
SPECT-MPI vs. Exercise ECG	1	0.23 (0.17-0.31)	Very low**¶
SPECT-MPI vs. CMR	1	0.63 (0.41-0.96)	Low‡¶
Stress Echocardiography vs. Exercise ECG	1	0.62 (0.35-1.09)	Very low**§¶

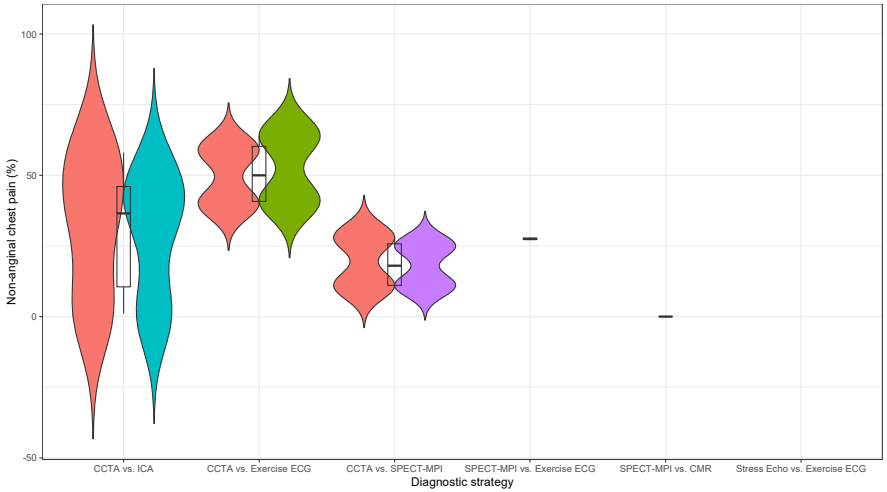
Supplement Figure 1. Violin and box-whisker plots for baseline characteristics of patients

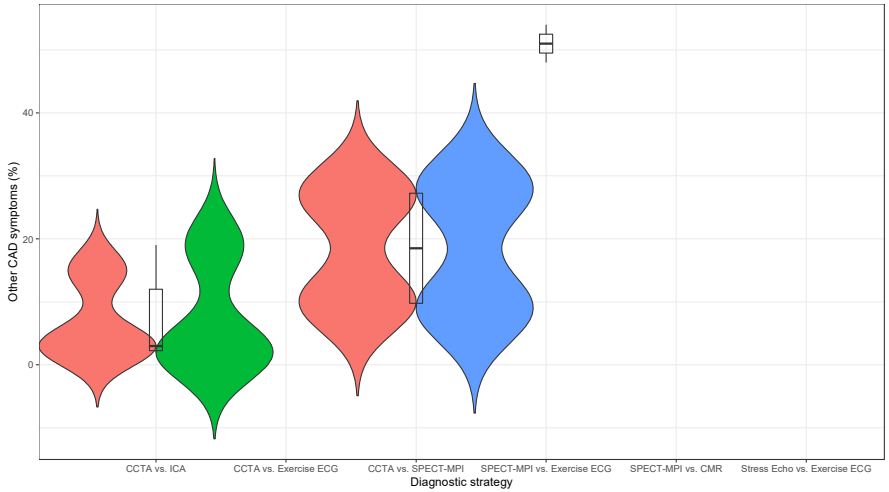
Similar distribution of the considered characteristic is represented by overlaps in the y-axis dimension.

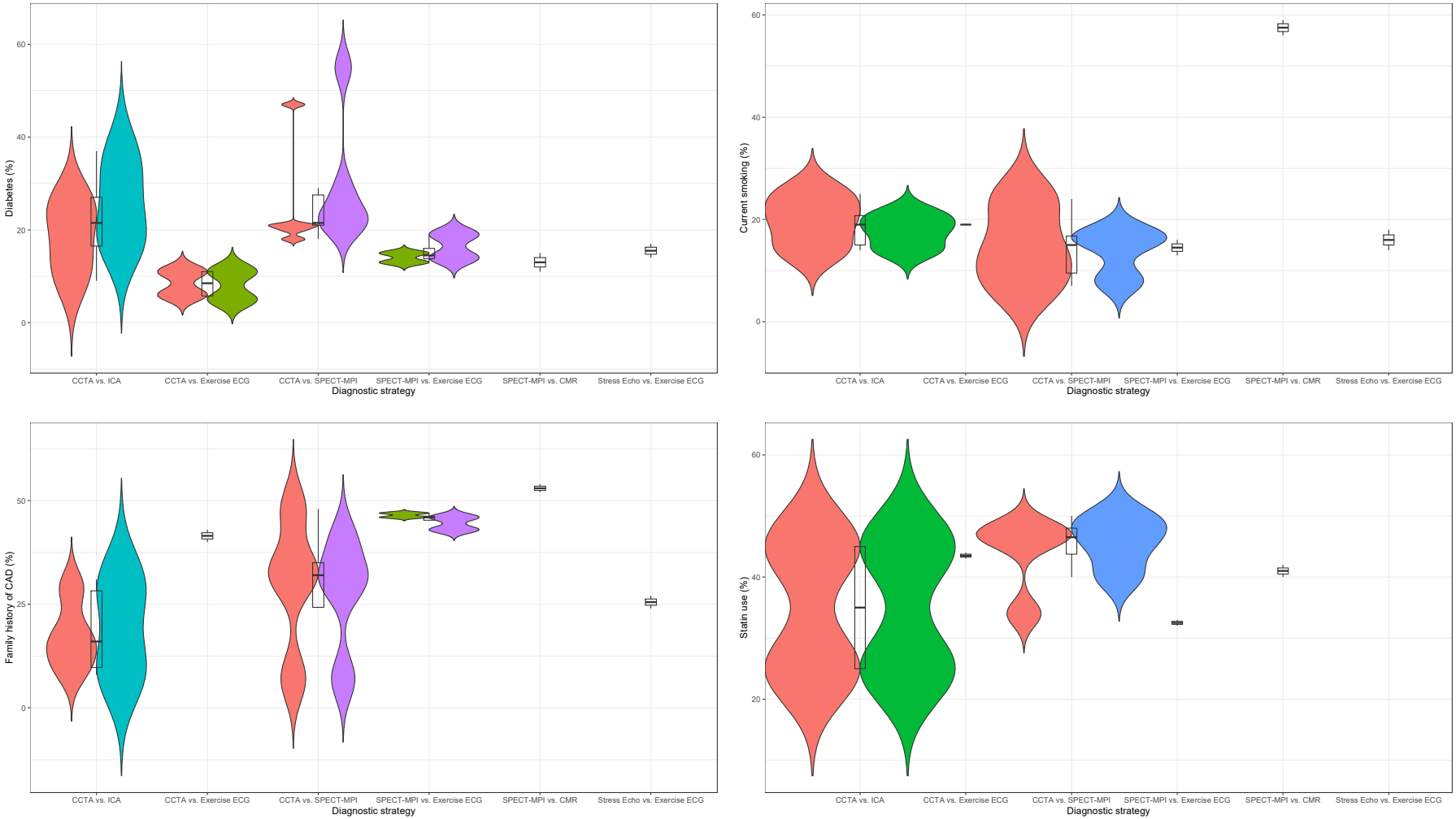


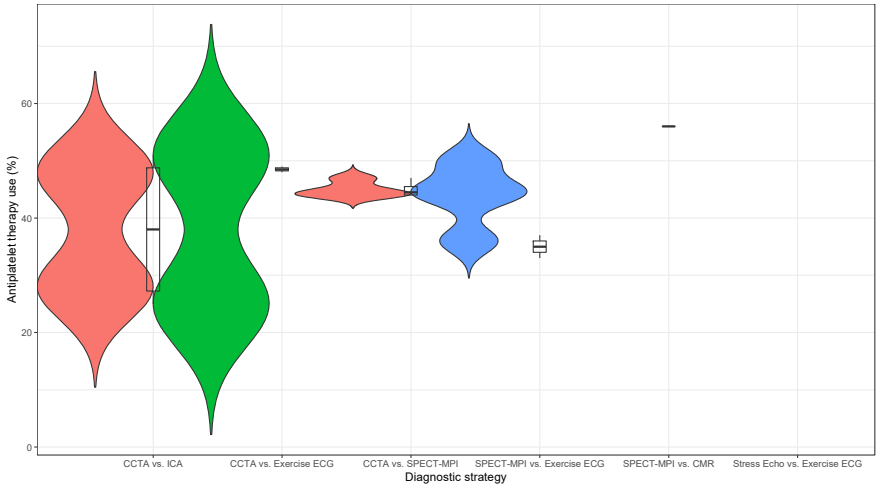

Typical angina (%)
50
25
0
-25
CCTA vs. ICA
CCTA vs. Exercise ECG
CCTA vs. SPECT-MPI
SPECT-MPI vs. Exercise ECG
SPECT-MPI vs. CMR
Stress Echo vs. Exercise ECG
Diagnostic strategy

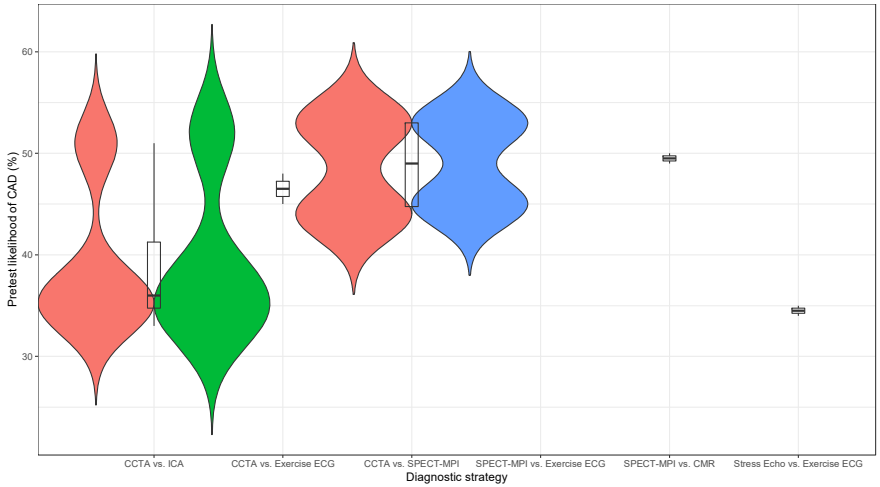

Atypical angina (%)
100
50
0
CCTA vs. ICA
CCTA vs. Exercise ECG
CCTA vs. SPECT-MPI
SPECT-MPI vs. Exercise ECG
SPECT-MPI vs. CMR
Stress Echo vs. Exercise ECG
Diagnostic strategy


Non-anginal chest pain (%)
100
50
0
-50
CCTA vs. ICA
CCTA vs. Exercise ECG
CCTA vs. SPECT-MPI
SPECT-MPI vs. Exercise ECG
SPECT-MPI vs. CMR
Stress Echo vs. Exercise ECG
Diagnostic strategy

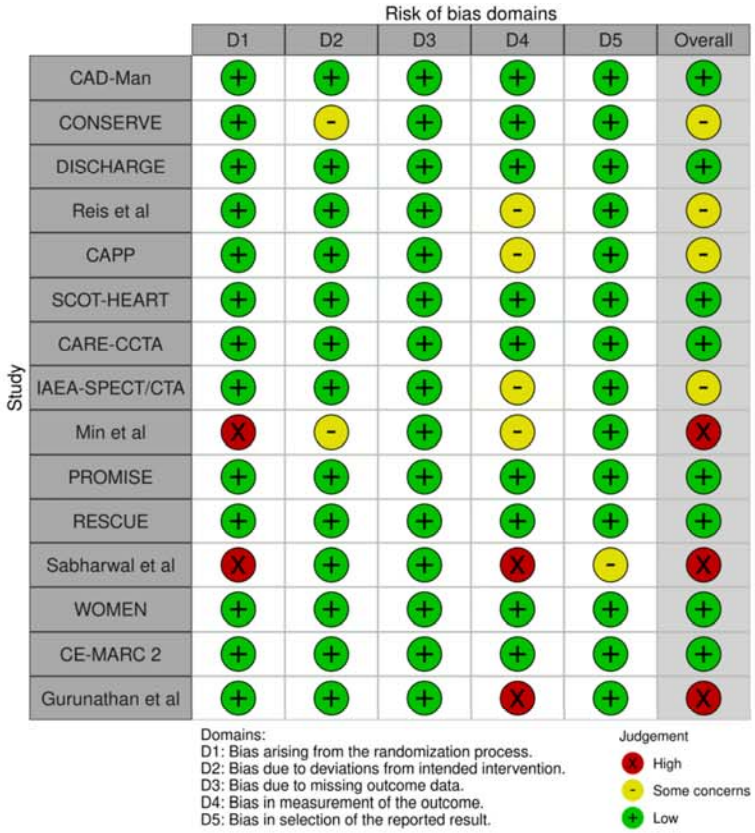

Other CAD symptoms (%)
40
20
0
CCTA vs. ICA
CCTA vs. Exercise ECG
CCTA vs. SPECT-MPI
SPECT-MPI vs. Exercise ECG
SPECT-MPI vs. CMR
Stress Echo vs. Exercise ECG
Diagnostic strategy

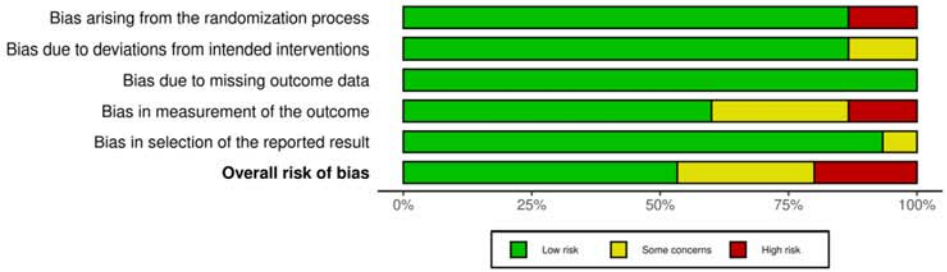

Diabetes (%)
Current smoking (%)
Family history of CAD (%)
Statin use (%)
CCTA vs. ICA
CCTA vs. Exercise ECG
CCTA vs. SPECT-MPI
SPECT-MPI vs. Exercise ECG
SPECT-MPI vs. CMR
Stress Echo vs. Exercise ECG
Diagnostic strategy


Antiplatelet therapy use (%)
0
20
40
60
CCTA vs. ICA
CCTA vs. Exercise ECG
CCTA vs. SPECT-MPI
SPECT-MPI vs. Exercise ECG
SPECT-MPI vs. CMR
Stress Echo vs. Exercise ECG
Diagnostic strategy

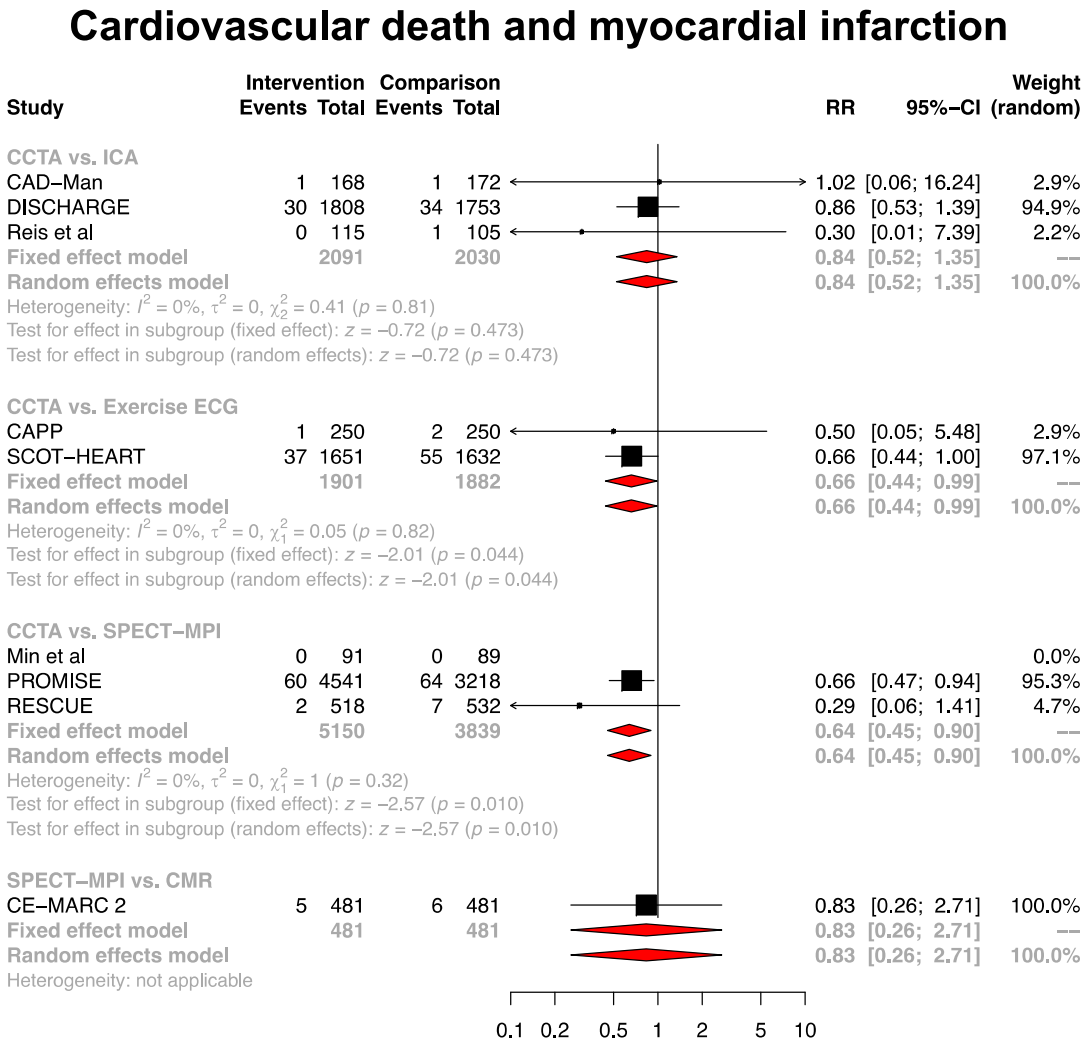

Pretest likelihood of CAD (%)
30
40
50
60
CCTA vs. ICA
CCTA vs. Exercise ECG
CCTA vs. SPECT-MPI
SPECT-MPI vs. Exercise ECG
SPECT-MPI vs. CMR
Stress Echo vs. Exercise ECG
Diagnostic strategy

Supplement Figure 2. Risk of bias assessment

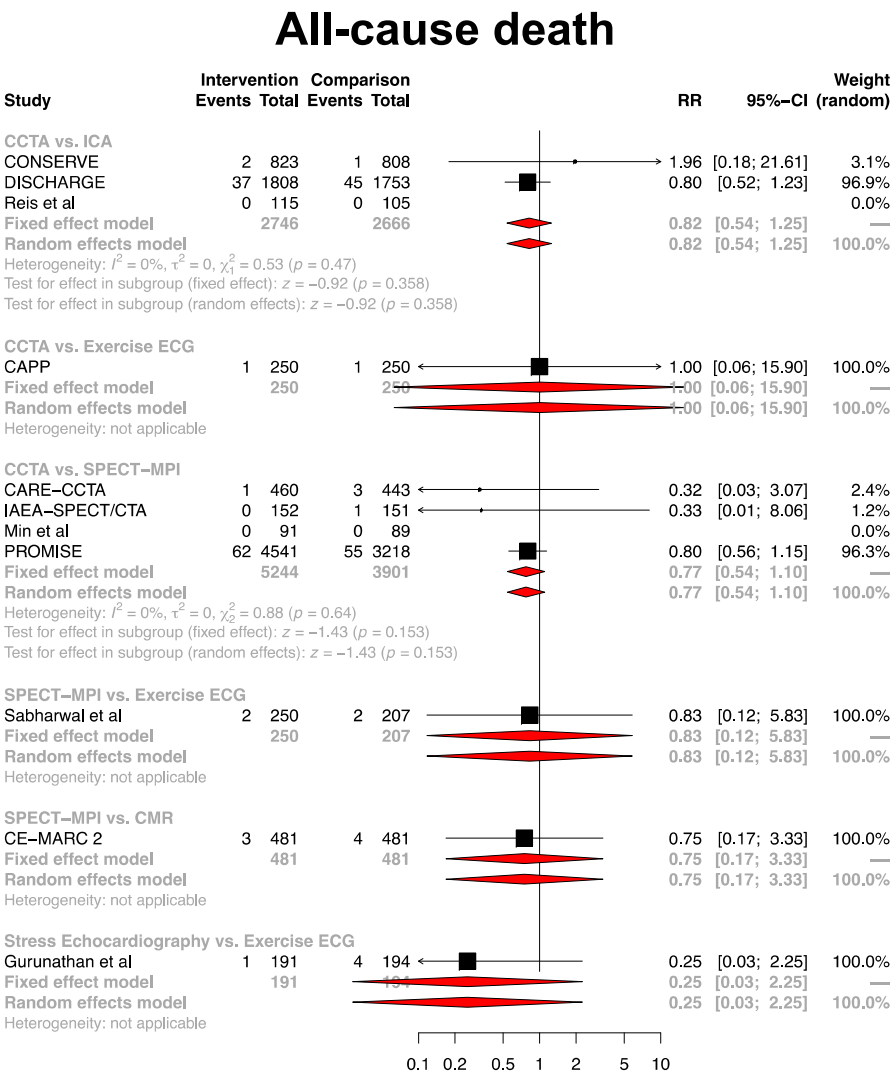




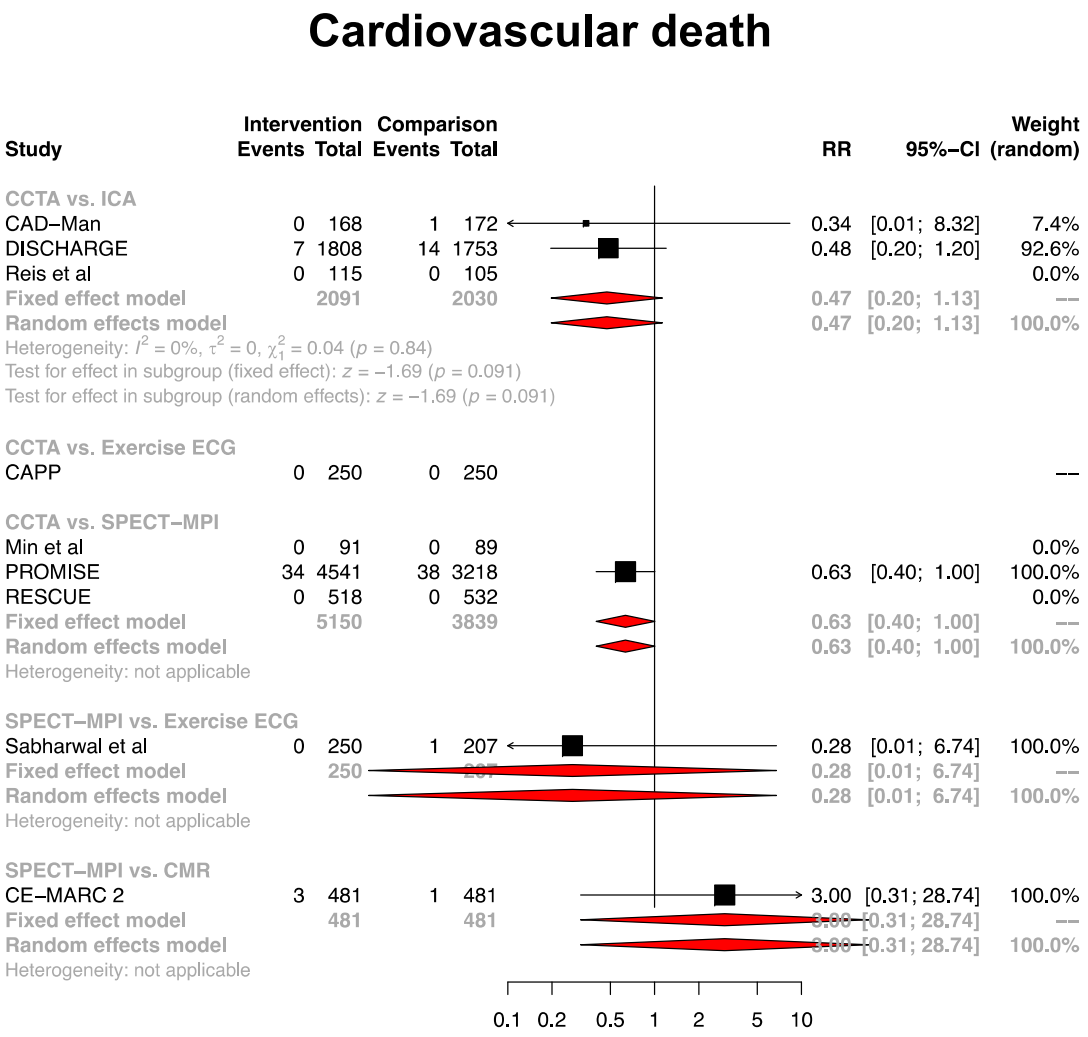
Supplement Figure 3. Forest plot for cardiovascular death and myocardial infarction



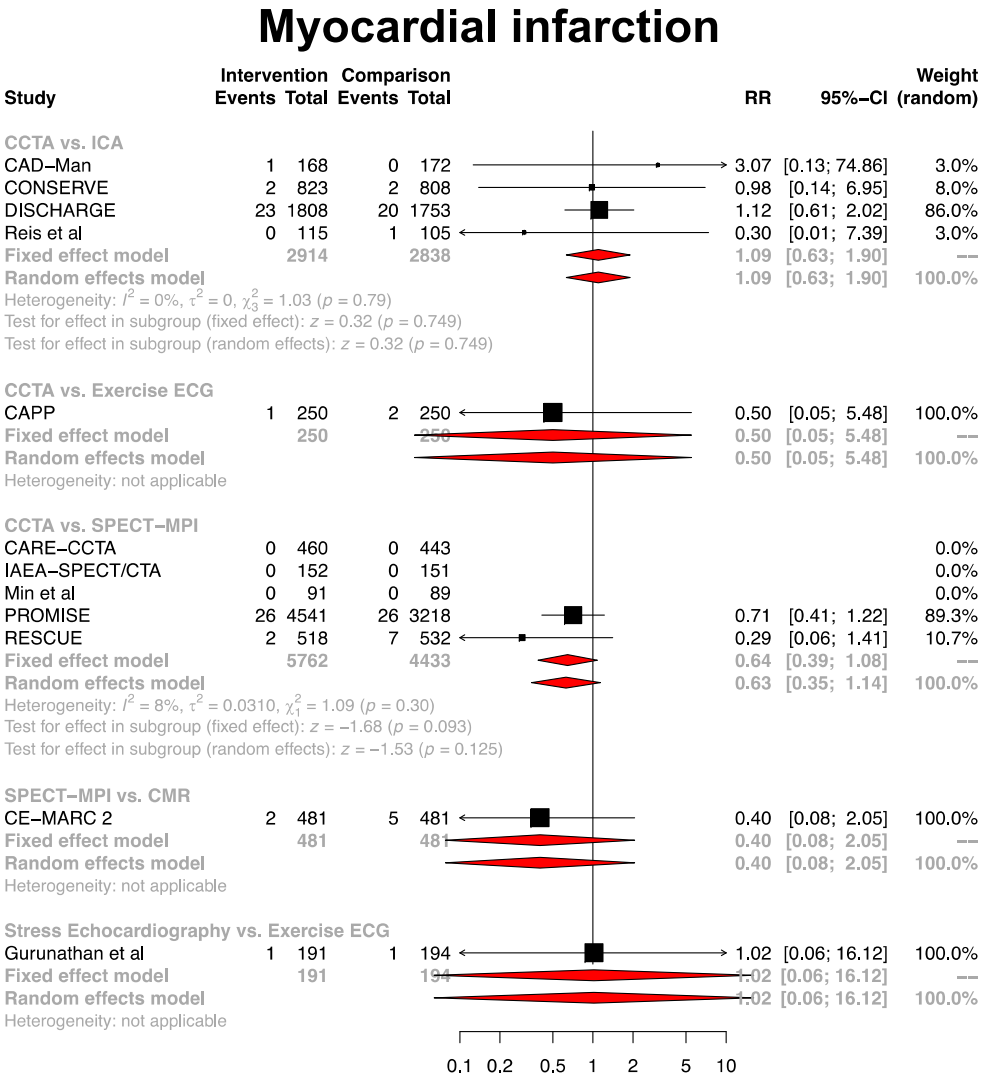
Supplement Figure 4. Forest plot for all-cause death



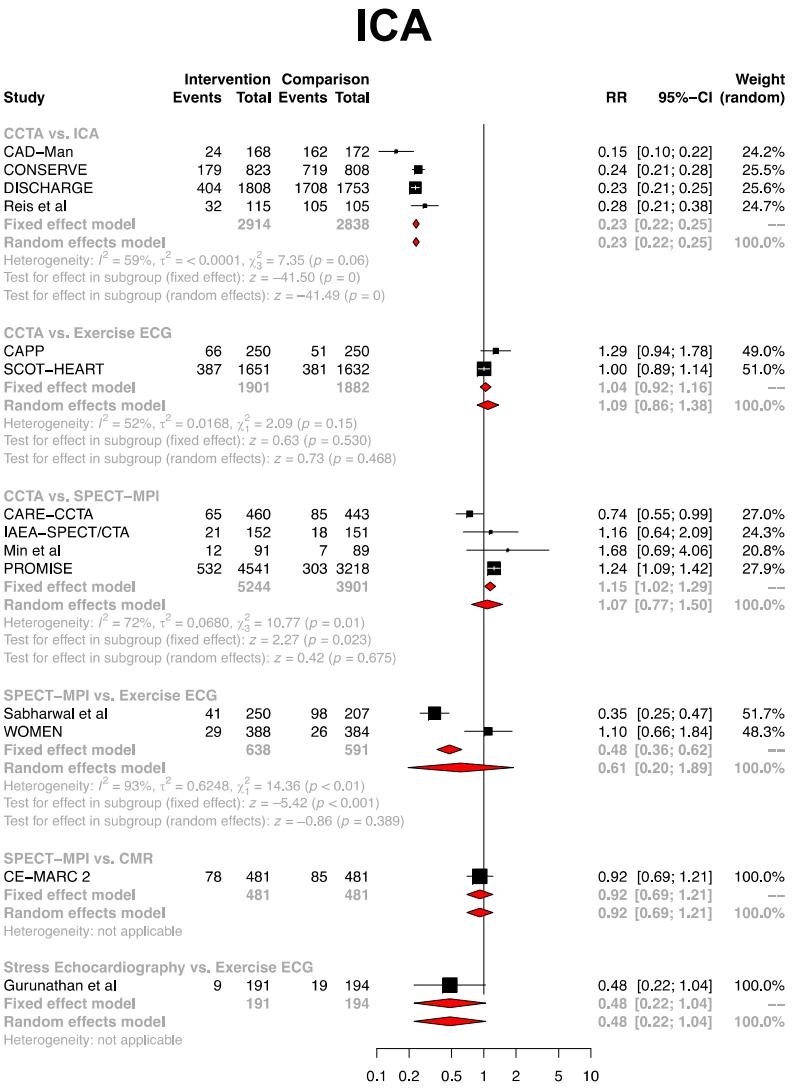
Supplement Figure 5. Forest plot for cardiovascular death



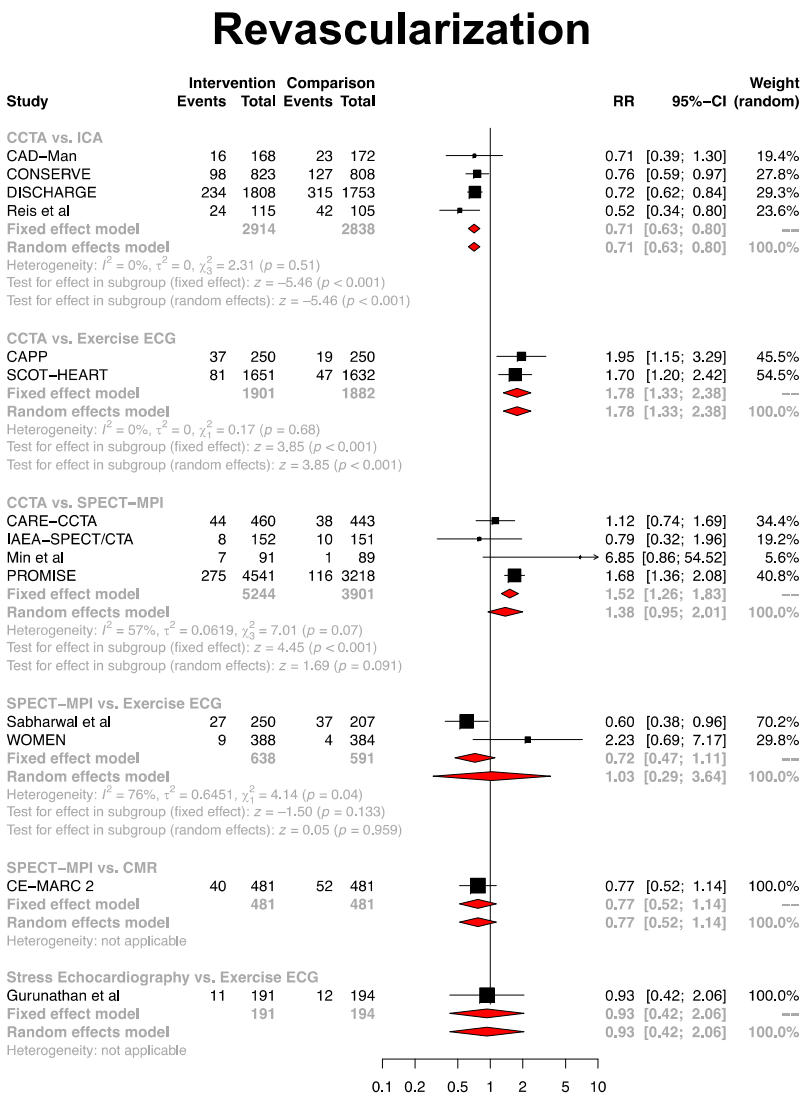
Supplement Figure 6. Forest plot for myocardial infarction



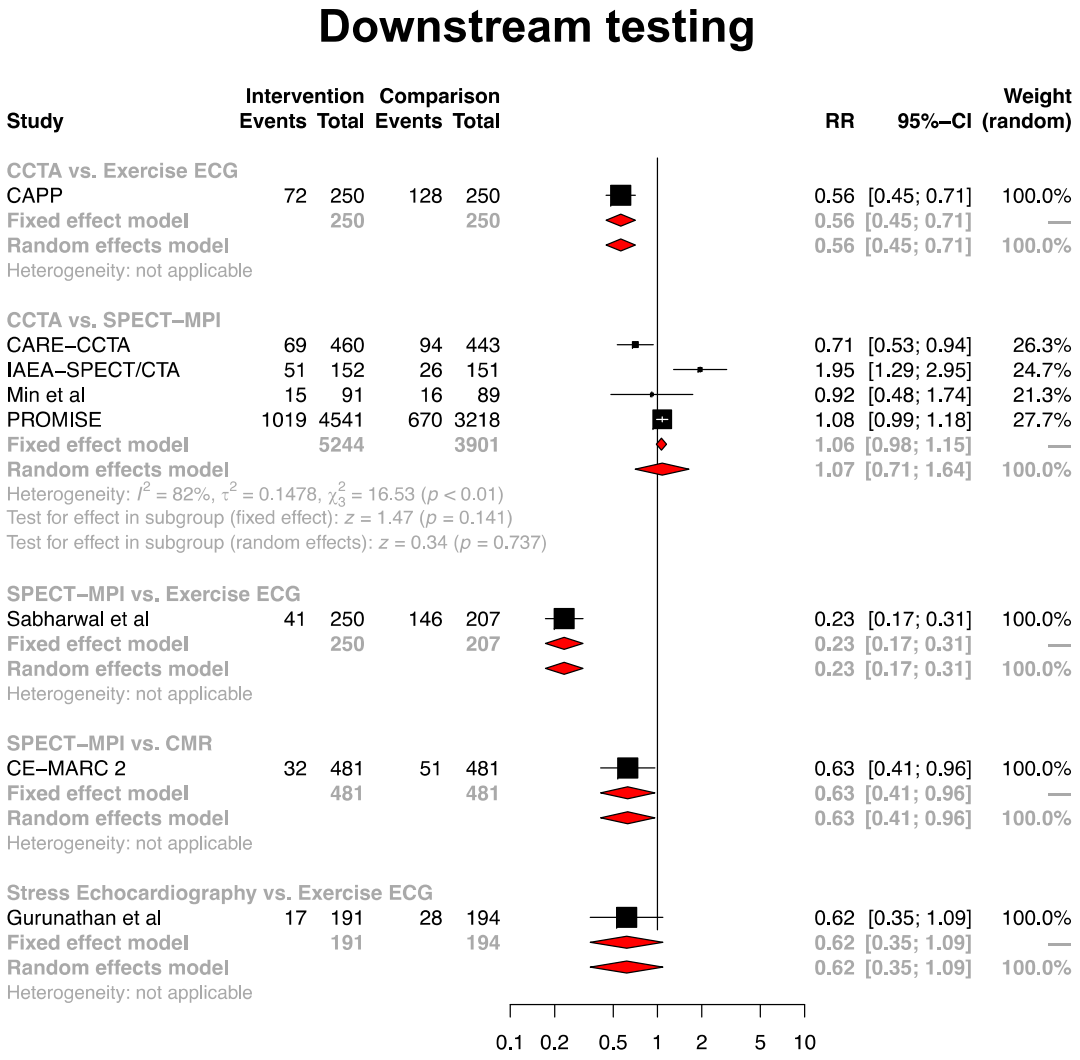
Supplement Figure 7. Forest plot for index ICA



Supplement Figure 8. Forest plot for index revascularization

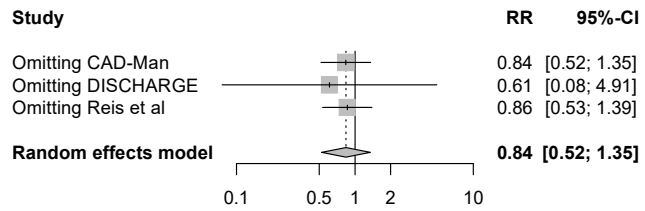


Supplement Figure 9. Forest plot for downstream testing

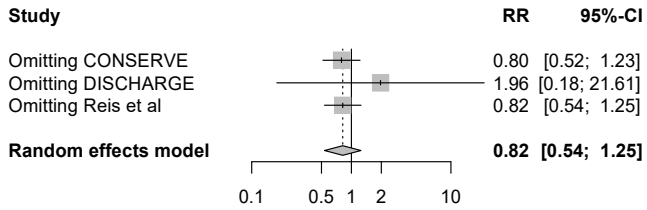


Supplement Figure 10. Leave-one-out sensitivity analyses for CCTA vs. ICA

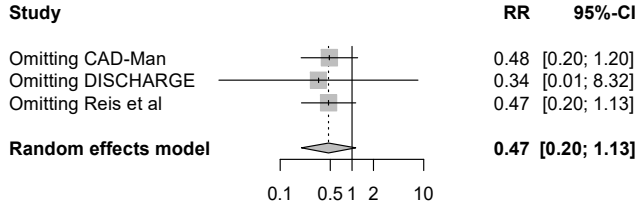
Cardiovascular death and myocardial infarction



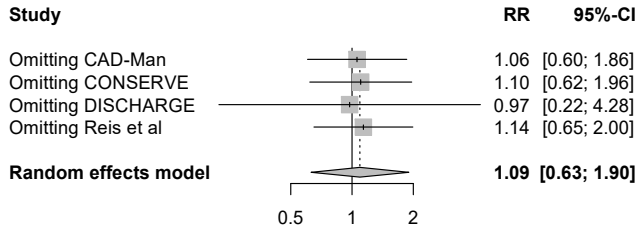
All-cause death



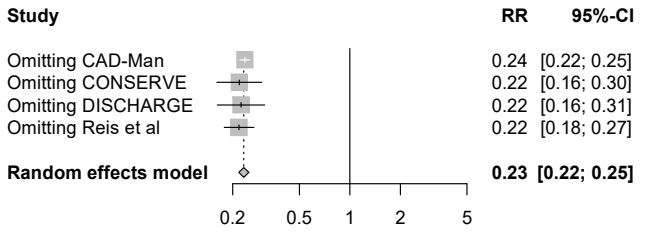
Cardiovascular death



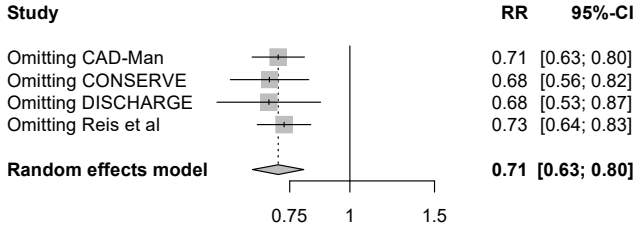
Myocardial infarction



ICA

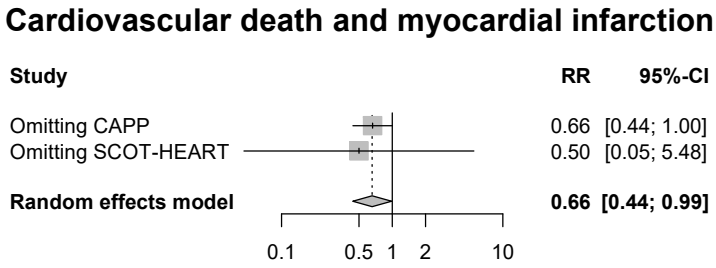


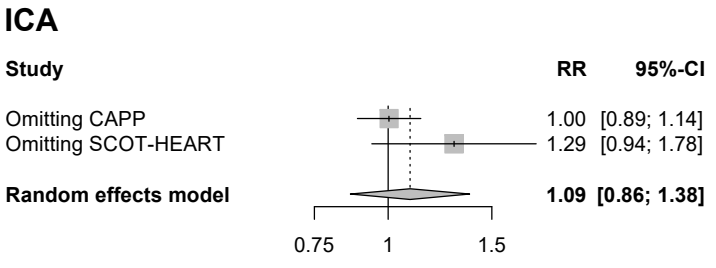
Revascularization

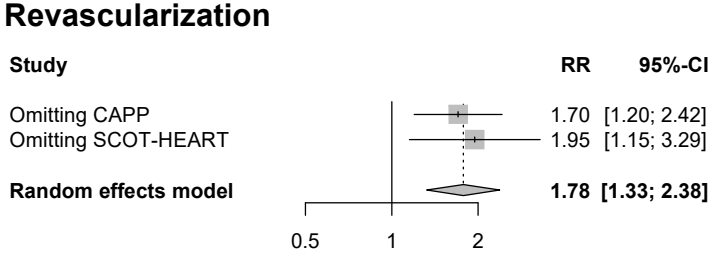


Supplement Figure 11. Leave-one-out sensitivity analyses for CCTA vs. Exercise ECG

Only outcomes pooling at least two studies were reported.

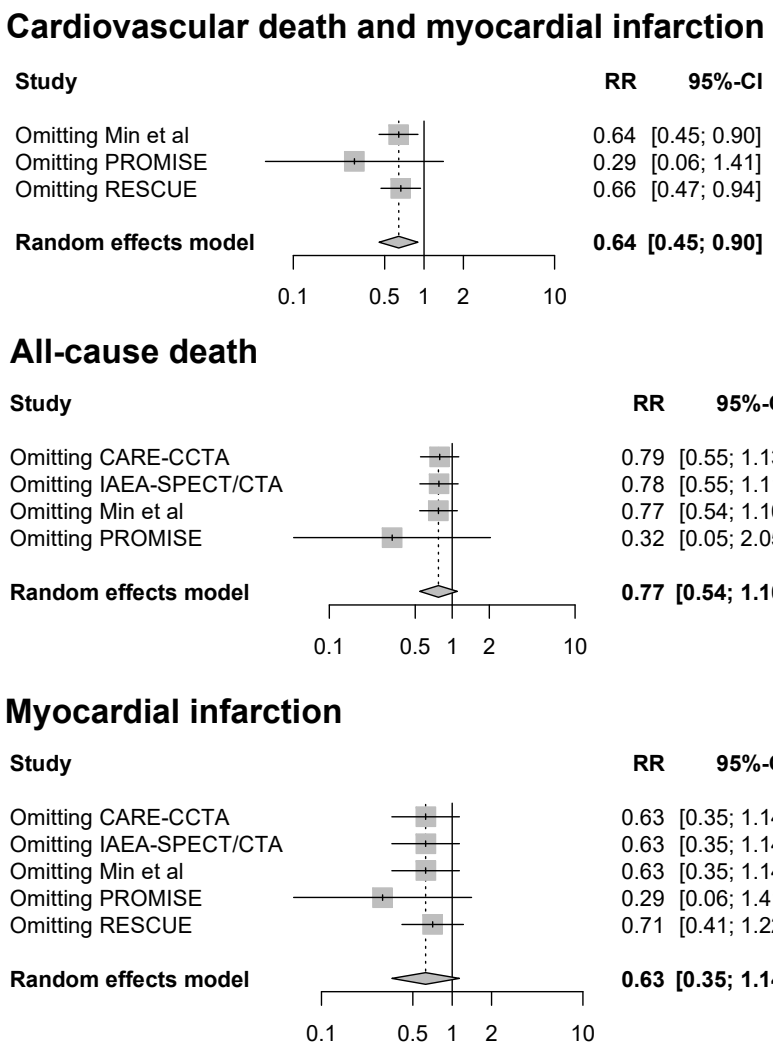






Supplement Figure 12. Leave-one-out sensitivity analyses for CCTA vs. SPECT-MPI

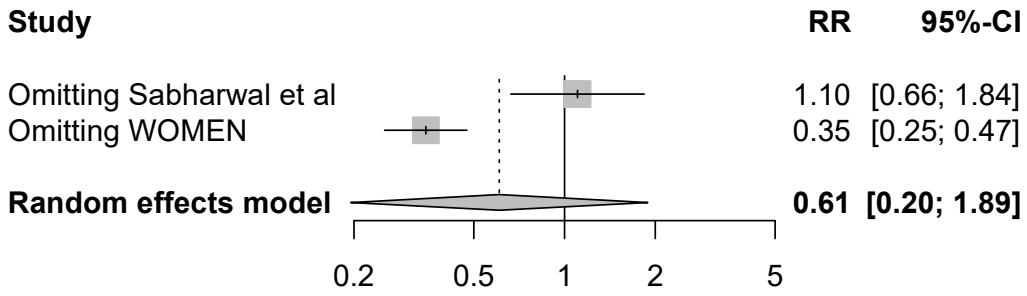
Only outcomes pooling at least two studies were reported.



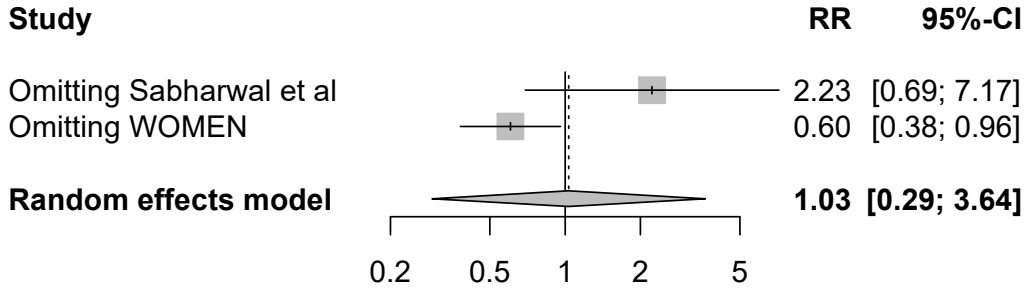
Supplement Figure 13. Leave-one-out sensitivity analyses for SPECT-MPI vs. Exercise ECG

Only outcomes pooling at least two studies were reported.

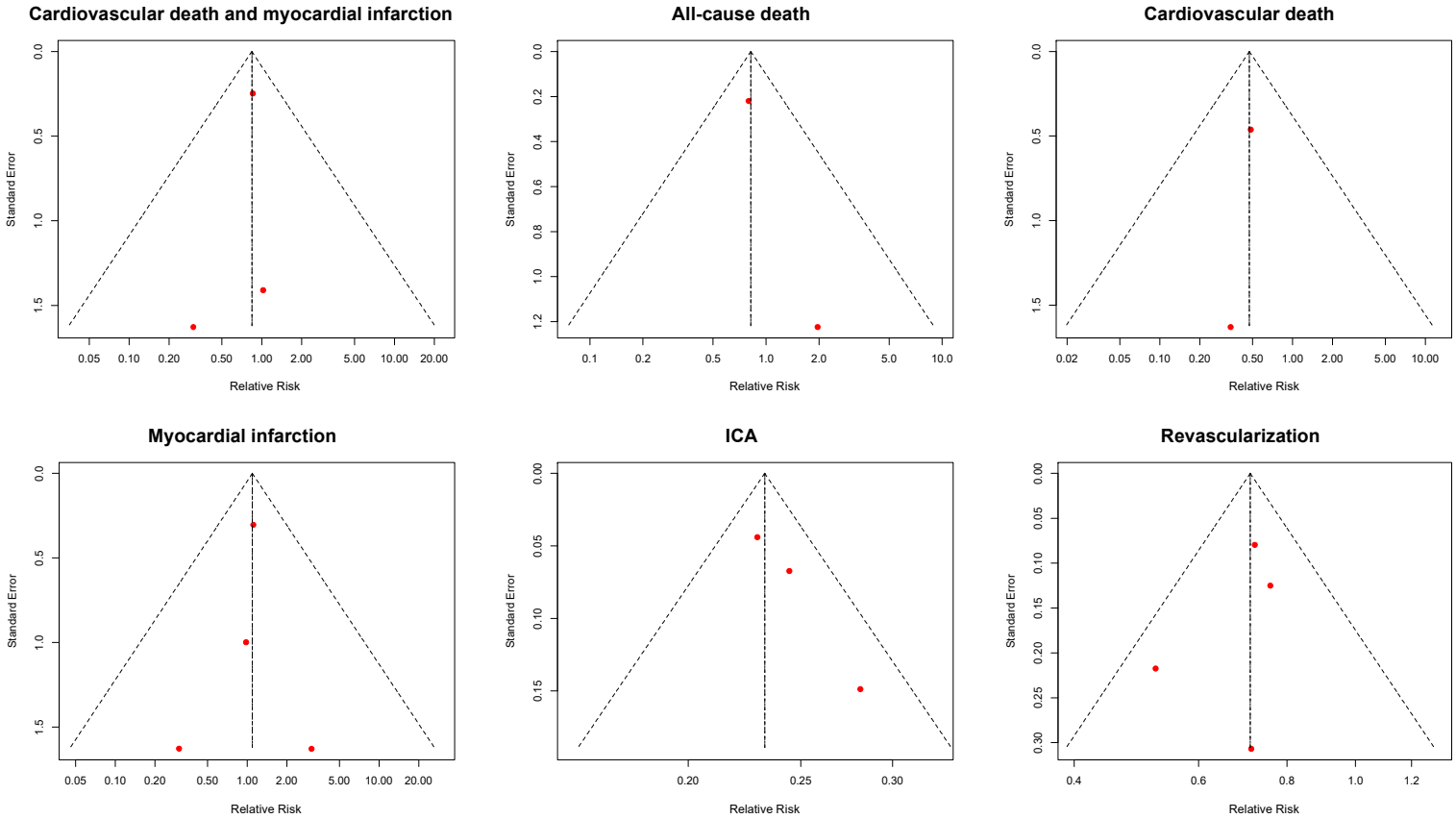
ICA



Revascularization

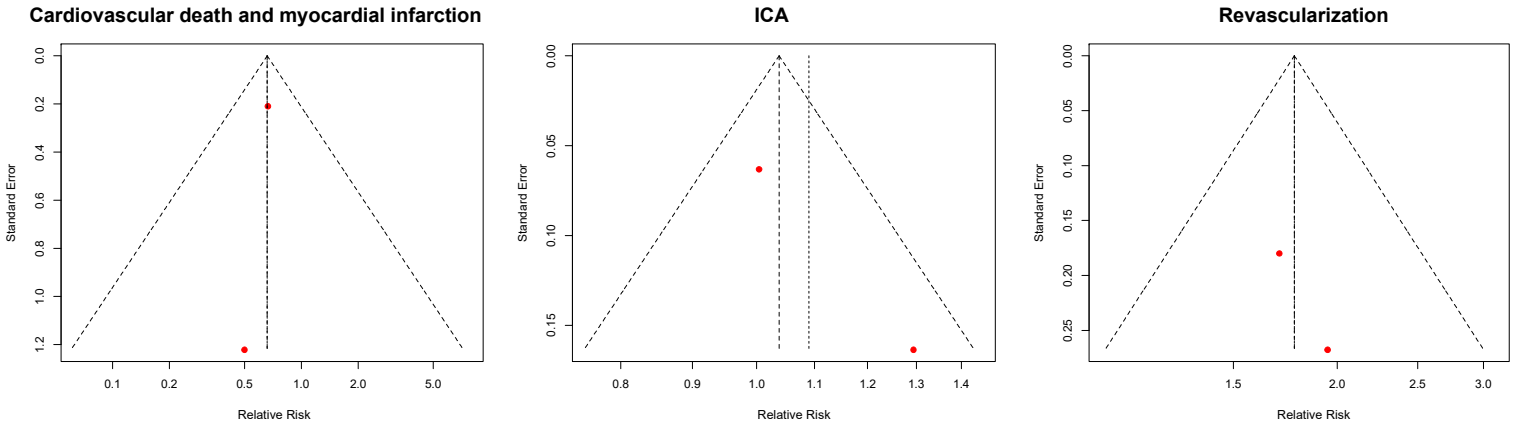


Supplement Figure 14. Funnel plots for CCTA vs. ICA



Supplement Figure 15. Funnel plots for CCTA vs. Exercise ECG

Only outcomes pooling at least two studies were reported.



Supplement Figure 16. Funnel plots for CCTA vs. SPECT-MPI

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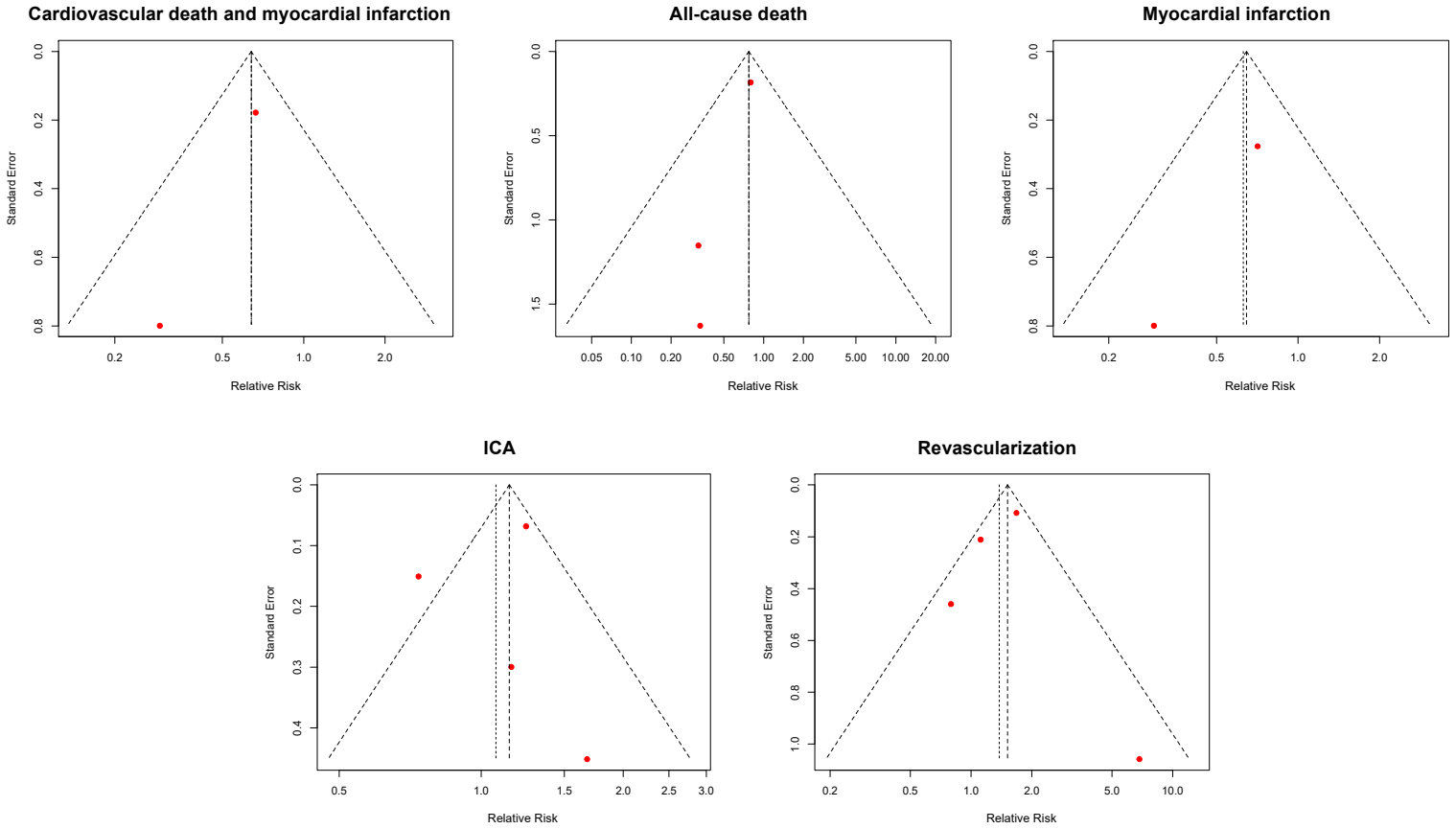
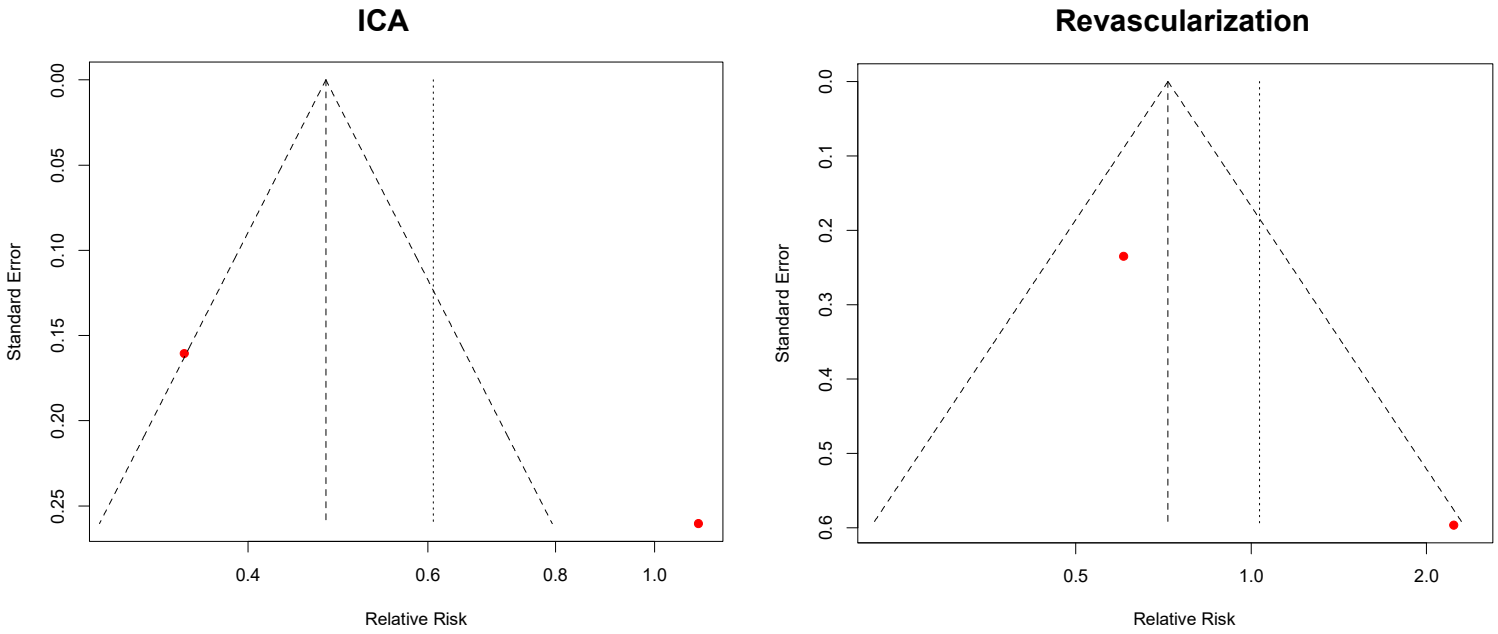


Supplement Figure 17. Funnel plots for SPECT-MPI vs. Exercise ECG

Only outcomes pooling at least two studies were reported.



Supplementary References

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