Washington State Health Care Authority

Noninvasive Cardiac Imaging for Coronary Artery Disease – Rereview

Appendices

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Noninvasive Cardiac Imaging for Coronary Artery Disease – Rereview

Aggregate Analytics, Inc.

Appendices

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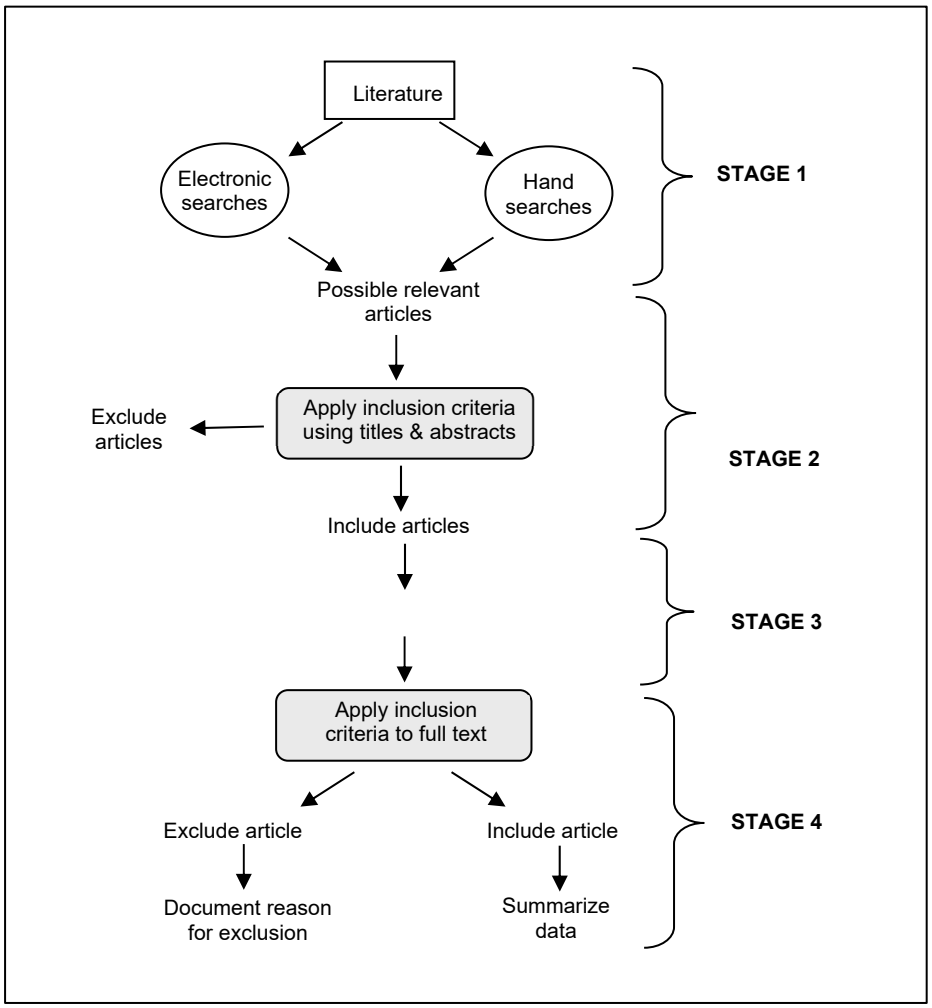
Appendix Tables and Figures

APPENDIX A. Algorithm for Article Selection



APPENDIX B. Search Strategies

Below are the search strategies for PubMed and Embase. Keyword searches were conducted in the other listed resources. In addition, hand-searching of included studies was performed.

Appendix Table B1: PubMed Search Strategy for CCTA and Nuclear Imaging (PET, SPECT)
Searched on: 03-23-21
Filters applied: English, from 2000/1/1 - 2020/12/13

1	“Myocardial Ischemia"[Mesh] OR "Coronary Disease"[Mesh] OR "Coronary Artery Disease"[Mesh] OR "Coronary Stenosis"[Mesh] OR "Myocardial Infarction"[Mesh]	222,901
2	"Cardiac Imaging Techniques"[Mesh] OR "Myocardial Perfusion Imaging"[Mesh] OR "Tomography, X-Ray Computed"[Mesh] OR "Computed Tomography Angiography"[Mesh] OR “Coronary Computed Tomography Angiography” OR “Cardiac Computed Tomography Angiography” OR CCTA OR CTA OR "Multimodal Imaging"[Mesh] OR "Positron-Emission Tomography"[Mesh] OR PET OR "Tomography, Emission-Computed, Single-Photon"[Mesh] OR SPECT OR "Coronary Circulation"[Mesh] OR "Fractional Flow Reserve, Myocardial"[Mesh]	545,165
3	“Chest pain”[Mesh] OR “symptom*”	887,162
4	"Asymptomatic Diseases"[Mesh] OR “asymptomatic” OR “no symptoms” OR “symptomless”	119,697
5	#1 AND #2	57,344
6	#5 AND #3	8,895
7	**#6 NOT #4**	**8,317**

Appendix Table B2: PubMed Search Strategy for Stress Echo
Searched on: 03-23-21
Filters applied: English

1	“Myocardial Ischemia"[Mesh] OR "Coronary Disease"[Mesh] OR "Coronary Artery Disease"[Mesh] OR "Coronary Stenosis"[Mesh] OR "Myocardial Infarction"[Mesh]	355,582
2	"Echocardiography, Stress"[Mesh] OR "Dobutamine"[Mesh]	7,721
3	“Chest pain”[Mesh] OR “symptom*”	1,125,183
4	"Asymptomatic Diseases"[Mesh] OR “asymptomatic” OR “no symptoms” OR “symptomless”	158,869
5	#1 AND #2	3,322
6	#5 AND #3	558
7	**#6 NOT #4**	**514**

Total from PubMed: 8,831

Appendix Table B3: Embase Search Strategy for CCTA, Nuclear Imaging (PET, SPECT), and Stress Echo
Searched on: 03-23-21

1	'heart muscle ischemia'/exp OR 'cardiac ischaemia' OR 'cardiac ischemia' OR 'cardiac muscle ischaemia' OR 'cardiac muscle ischemia' OR 'coronary artery ischaemia' OR 'coronary artery ischemia' OR 'coronary ischaemia' OR 'coronary ischemia' OR 'coronary syndrome' OR 'heart ischaemia' OR 'heart ischaemic arrest' OR 'heart ischaemic attack' OR 'heart ischemia' OR 'heart ischemic arrest' OR 'heart ischemic attack' OR 'heart muscle ischaemia' OR 'heart muscle ischemia' OR 'heart transient ischaemic attack' OR 'heart transient ischemic attack' OR 'hypoxia, heart' OR 'hypoxic heart' OR 'ischaemic heart' OR 'ischaemic heart arrest' OR 'ischaemic myocardium' OR 'ischemic heart' OR 'ischemic heart arrest' OR 'ischemic myocardium' OR 'myocardial anoxia' OR 'myocardial hypoxia' OR 'myocardial ischaemia' OR 'myocardial ischemia' OR 'myocardium hypoxia' OR 'myocardium ischaemia' OR 'myocardium ischemia' OR 'transient ischaemic attack, heart' OR 'transient ischemic attack, heart' OR 'coronary artery disease'/exp OR 'coronary artery disease' OR 'coronary disease' OR 'multivessel coronary artery disease' OR 'coronary artery obstruction'/exp OR 'arteria coronaria ostium stenosis' OR 'arterial obstruction, coronary' OR 'arterial obstruction, coronary artery' OR 'artery obstruction, coronary' OR 'coronary arterial obstruction' OR 'coronary artery obstruction' OR 'coronary artery stenosis' OR 'coronary obstruction' OR 'coronary ostial stenosis' OR 'coronary ostium obstruction' OR 'coronary stenosis' OR 'heart infarction'/exp	865,017
2	'cardiac imaging'/exp OR 'cardiac imaging' OR 'cardiac imaging technique' OR 'cardiac imaging techniques' OR 'myocardial perfusion imaging'/exp OR 'myocardial perfusion imaging' OR 'myocardial scintigraphy' OR 'x-ray computed tomography'/exp OR 'ct scan' OR 'ct scanning' OR 'tomography, x-ray computed' OR 'x-ray computed tomography' OR 'coronary computed tomographic angiography'/exp OR 'cardiac computed tomography'/exp OR 'cardiac computed tomographic angiography'/exp OR 'positron emission tomography'/exp OR 'pet scan' OR 'pet scanning' OR 'p.e.t.' OR 'positron emission tomographic scan' OR 'positron emission tomographic scanning' OR 'positron emission tomography' OR 'positron tomography' OR 'positron-emission tomography' OR 'tomography, positron' OR 'single photon emission computed tomography'/exp OR 'spect' OR 'computer assisted tomography, single photon emission' OR 'emission computer tomography, single photon' OR 'single photon emission computed tomography' OR 'single photon emission computer tomography' OR 'single-photon emission-computed tomography' OR 'tomography, emission-computed, single-photon' OR 'coronary artery blood flow'/exp OR 'arterial flow, cardiac muscle' OR 'blood flow, coronary artery' OR 'cardiac blood supply' OR 'cardiac muscle arterial flow' OR 'cardiac muscle artery flow' OR 'cardial muscle arterial flow' OR 'cardial muscle blood flow' OR 'circulation, coronary' OR 'coronary arterial flow' OR 'coronary artery blood flow' OR 'coronary artery circulation' OR 'coronary artery circulation time' OR 'coronary artery flow' OR 'coronary artery perfusion' OR 'coronary blood flow' OR 'coronary circulation' OR 'coronary circulation time' OR 'coronary flow' OR 'coronary perfusion' OR 'coronary perfusion pressure' OR 'heart blood flow' OR 'heart blood supply' OR 'heart muscle arterial flow' OR 'heart muscle artery flow' OR 'intracardiac blood flow' OR 'myocardial arterial flow' OR 'myocardial artery	494,312

	flow' OR 'myocardial flow' OR 'fractional flow reserve'/exp OR 'fractional flow reserve' OR 'fractional flow reserve, myocardial' OR 'myocardial fractional flow reserve'	
3	'thorax pain'/exp OR 'symptom*'	2,018,438
4	'nuclear magnetic resonance'/exp OR 'nmr' OR 'magnetic resonance' OR 'mr' OR 'nuclear magnetic relaxation dispersion' OR 'nuclear magnetic resonance' OR 'resonance, magnetic' OR 'asymptomatic disease'/exp OR 'asymptomatic condition' OR 'asymptomatic conditions' OR 'asymptomatic disease' OR 'asymptomatic diseases' OR 'asymptomatic disorder' OR 'asymptomatic disorders' OR 'asymptomatic'	1,764,908
5	#1 AND #2	63,795
6	#3 AND #5	9,703
7	#6 NOT #4	7,345
8	**#6 NOT #4 AND [english]/lim AND [2000-2021]/py**	**6,067**
9	'stress echocardiography'/exp OR 'echo stress test' OR 'echocardiographic stress test' OR 'echocardiography, stress' OR 'stress mce' OR 'stress contrast echocardiography' OR 'stress echo test' OR 'stress echocardiogram' OR 'stress echocardiography' OR 'stress myocardial contrast echocardiography'	
10	#1 AND #9	7,299
11	#3 AND #10	1,779
12	**#11 NOT #4 AND [english]/lim AND [2000-2021]/py**	**1,320**

Total from Embase: 7,387

Electronic Database Searches
EMBASE
PubMed
ClinicalTrials.gov

Additional Economics, Clinical Guideline and Gray Literature Databases
ECRI Guidelines Trust
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google

APPENDIX C. Excluded Articles

Articles excluded as primary studies after full text review, with reason for exclusion.

Appendix Table C1. List of Excluded Articles

	Citation	Reason for exclusion after full-text review
1	Adamson PD, Williams MC, Dweck MR, et al. Guiding Therapy by Coronary CT Angiography Improves Outcomes in Patients With Stable Chest Pain. Journal of the American College of Cardiology 2019;74:2058-70.	Ineligible study design.
2	Al Badarin FJ, Spertus JA, Bateman TM, Patel KK, Burgett EV, Kennedy KF, Thompson RC. Drivers of radiation dose reduction with myocardial perfusion imaging: A large health system experience. J Nucl Cardiol. 2020 Jun;27(3):785-794. doi: 10.1007/s12350-018-01576-w. Epub 2019 Jan 31. PMID: 30706351; PMCID: PMC6669103.	Safety specific; ineligible outcomes.
3	AlJaroudi WA, Alraies MC, Cerquiera MD, Jaber WA. Safety and tolerability of regadenoson in 514 SPECT MPI patients with and without coronary artery disease and submaximal exercise heart rate response. European journal of nuclear medicine and molecular imaging 2013;40:341-8.	Safety specific; ineligible intervention and comparator.
4	Amer H. Side effects of adenosine as a pharmacologic stress agent for myocardial perfusion scan in a local setup. European journal of nuclear medicine and molecular imaging 2015;42:S507.	Abstract only.
5	Andell P, Berntorp K, Christiansen EH, et al. Reclassification of Treatment Strategy With Instantaneous Wave-Free Ratio and Fractional Flow Reserve: a Substudy From the iFR-SWEDEHEART Trial. JACC Cardiovascular interventions 2018;11:2084-94.	Ineligible study design.
6	Andrikopoulou E, Hage FG. Adverse effects associated with regadenoson myocardial perfusion imaging. Journal of Nuclear Cardiology 2018;25:1724-31.	Safety specific; ineligible study design.
7	Aquilante CL, Humma LM, Yarandi HN, et al. Influence of gender and race on hemodynamic response to dobutamine during dobutamine stress echocardiography. American Journal of Cardiology 2004;94:535-8.	Safety specific; ineligible population.
8	Baggiano A, Guglielmo M, Muscogiuri G, et al. Additional role of CT-derived fractional flow reserve and stress computed tomography perfusion in the management of patients with stable chest pain compared to coronary computed tomography angiography alone. Giornale Italiano di Cardiologia 2019;20:94S.	Abstract only.
9	Baggiano A, Guglielmo M, Muscogiuri G, et al. Additional role of FFRct and stress CT perfusion in the management of patients with stable chest pain compared to cCTA alone. European heart journal cardiovascular Imaging 2020;21:i710.	Abstract only.
10	Baggiano A, Guglielmo M, Muscogiuri G, et al. Additional role of FFRct and stress CT perfusion in the management of patients with stable chest pain compared to cCTA. International Journal of Cardiovascular Imaging 2019;35:2290-1.	Abstract only.

	Citation	Reason for exclusion after full-text review
11	Bamberg F, Mayrhofer T, Ferencik M, et al. Age- and sex-based resource utilisation and costs in patients with acute chest pain undergoing cardiac CT angiography: pooled evidence from ROMICAT II and ACRIN-PA trials. Eur Radiol. 2018 Feb;28(2):851-60. PMID: 28875364.	Costing only.
12	Bamberg F, Mayrhofer T, Ferencik M, et al. Age- and sex-based resource utilisation and costs in patients with acute chest pain undergoing cardiac CT angiography: pooled evidence from ROMICAT II and ACRIN-PA trials. European radiology 2018;28:851-6	Ineligible study design.
13	Baptista SB, Raposo L, Santos L, et al. Impact of routine fractional flow reserve evaluation during coronary angiography on management strategy and clinical outcome. Circulation: Cardiovascular Interventions 2016;9.	Ineligible intervention.
14	Baskaran L, Danad I, Gransar H, et al. A Comparison of the Updated Diamond-Forrester, CAD Consortium, and CONFIRM History-Based Risk Scores for Predicting Obstructive Coronary Artery Disease in Patients With Stable Chest Pain: The SCOT-HEART Coronary CTA Cohort. JACC Cardiovascular imaging 2019;12:1392-400.	Ineligible study design.
15	Bateman TM, McGhie IA, Heller G, Courter S, Burgett E, Case J. Relative performance of SPECT and PET myocardial perfusion imaging in a prospectively randomized population of symptomatic patients with known coronary artery disease. Journal of the American College of Cardiology 2016;67:1586.	Abstract only.
16	Bech GJ, De Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation 2001;103:2928-34.	Ineligible intervention.
17	Berry C, Layland J, Sood A, et al. FFR versus angiography in guiding management to optimise outcomes in NSTEMI clinical trial: Study design and participant characteristics at baseline. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2014.	Abstract only.
18	Bhakta M, Sweeney J, Lee R, Fortuin FD. Fractional flow reserve provides additional risk assessment to the prognostic information provided by noninvasive stress imaging. Catheterization and Cardiovascular Interventions 2011;77:S70-S1.	Abstract only.
19	Bilbey N, Blanke P, Naoum C, Arepalli CD, Norgaard BL, Leipsic J. Potential impact of clinical use of noninvasive FFRCT on radiation dose exposure and downstream clinical event rate. Clinical imaging 2016;40:1055-60.	Ineligible study design.
20	Bittner DO, Ferencik M, Douglas PS, Hoffmann U. Coronary CT Angiography as a Diagnostic and Prognostic Tool: Perspective from a Multicenter Randomized Controlled Trial: PROMISE. Current cardiology reports 2016;18:40.	Abstract only.
21	Bittner DO, Mayrhofer T, Bamberg F, et al. Impact of Coronary Calcification on Clinical Management in Patients With Acute Chest Pain. Circulation Cardiovascular imaging 2017;10.	Ineligible study design.

	Citation	Reason for exclusion after full-text review
22	Blankstein R, Ahmed W, Bamberg F, et al. Comparison of exercise treadmill testing with cardiac computed tomography angiography among patients presenting to the emergency room with chest pain: the Rule Out Myocardial Infarction Using Computer-Assisted Tomography (ROMICAT) study. Circulation Cardiovascular imaging 2012;5:233-42.	Ineligible study design; RCT data available.
23	Budoff MJ, Mayrhofer T, Ferencik M, et al. Prognostic Value of Coronary Artery Calcium in the PROMISE Study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation 2017;136:1993-2005.	Ineligible study design.
24	Burger AJ, Notarianni MP, Aronson D. Safety and efficacy of an accelerated dobutamine stress echocardiography protocol in the evaluation of coronary artery disease. The American journal of cardiology 2000;86:825-9.	Safety specific; ineligible intervention and comparator.
25	Candell-Riera J, Oller-Martínez G, Pereztol-Valdés O, et al. Early myocardial perfusion gated-SPECT in patients with chest pain and non-diagnostic ECG in the emergency department. Revista espanola de cardiologia 2004;57:225-33.	Ineligible intervention.
26	Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. The New England journal of medicine 2001;344:1879-87.	Ineligible intervention.
27	Cannon CP, Weintraub WS, Demopoulos LA, Robertson DH, Gormley GJ, Braunwald E. Invasive versus conservative strategies in unstable angina and non-Q-wave myocardial infarction following treatment with tirofiban: rationale and study design of the international TACTICS-TIMI 18 Trial. Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy. Thrombolysis In Myocardial Infarction. American journal of cardiology 1998;82:731-6	Ineligible intervention.
28	Centonze M, Steidler S, Casagranda G, Alfonsi U, Spagnolli F, Rozzanigo U, Palumbo D, Faletti R, De Cobelli F. Cardiac-CT and cardiac-MR cost-effectiveness: a literature review. La radiologia medica. 2020 Sep 24:1-8.	Narrative review.
29	Chadika S, Kokkirala AR, Giedd KN, Johnson LL, Giardina EGV, Bokhari S. Focal uptake of radioactive tracer in the mediastinum during SPECT myocardial perfusion imaging. Journal of Nuclear Cardiology 2005;12:359-61.	Abstract only.
30	Chinnaiyan KM, Safian RD, Gallagher ML, et al. Clinical Use of CT-Derived Fractional Flow Reserve in the Emergency Department. JACC Cardiovascular imaging 2020;13:452-61.	Ineligible comparator.
31	Cury RC, Budoff M, Taylor AJ. Coronary CT angiography versus standard of care for assessment of chest pain in the emergency department. Journal of cardiovascular computed tomography 2013;7:79-82.	Ineligible study design.
32	Curzen NP, Nolan J, Zaman AG, Nørgaard BL, Rajani R. Does the Routine Availability of CT–Derived FFR Influence Management of Patients With Stable Chest Pain Compared to CT Angiography Alone?: The FFRCT RIPCORD Study. JACC: Cardiovascular Imaging 2016;9:1188-94.	Ineligible comparator.

	Citation	Reason for exclusion after full-text review
33	Daly C, Norrie J, Murdoch DL, Ford I, Dargie HJ, Fox K. The value of routine non-invasive tests to predict clinical outcome in stable angina. European heart journal 2003;24:532-40.	Ineligible study design.
34	Damman P, Hirsch A, Windhausen F, Tijssen JG, de Winter RJ. 5-year clinical outcomes in the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial a randomized comparison of an early invasive versus selective invasive management in patients with non-ST-segment elevation acute coronary syndrome. Journal of the American College of Cardiology 2010;55:858-64.	Ineligible intervention.
35	Davies JE, Sen S, Dehbi HM, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. New England journal of medicine 2017;376:1824-34.	Ineligible intervention.
36	De Abreu JS, Pinheiro Diogenes TC, Liberato Ponte Farias AG, Bonfim De Morais JM, Nogueira Paes Jr J. Safety and feasibility of dobutamine-atropine stress echocardiography in octogenarian patients. Arquivos brasileiros de cardiologia 2005;85:198-204.	Abstract only.
37	de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. The New England journal of medicine 2005;353:1095-104.	Ineligible intervention.
38	deFilippi CR, Rosanio S, Tocchi M, et al. Randomized comparison of a strategy of predischarge coronary angiography versus exercise testing in low-risk patients in a chest pain unit: in-hospital and long-term outcomes. Journal of the American College of Cardiology 2001;37:2042-9.	Ineligible intervention.
39	Desideri A, Suzzi GL, Terlizzi R, Canel F, Cernetti C, Celegon L. Dipyridamole stress echocardiography and exercise testing for risk stratification after uncomplicated myocardial infarction. Giornale Italiano di Cardiologia 1998;28:754-9.	Ineligible population.
40	Dey S, Taraphder A, Chakraborty R. Non invasive diagnosis of coronary artery disease in a cohort of chronic kidney disease diagnosis of coronary artery disease in a cohort of chronic kidney disease. Nephrology Dialysis Transplantation 2017;32:iii542.	Cannot locate full text, likely not in English.
41	Di Serafino L, Turturo M, Lanzone S, et al. Comparison of the Effect of Dual-Axis Rotational Coronary Angiography Versus Conventional Coronary Angiography on Frequency of Acute Kidney Injury, X-Ray Exposure Time, and Quantity of Contrast Medium Injected. The American journal of cardiology 2018;121:1046-50.	Ineligible intervention and comparator.
42	Diderholm E, Andrén B, Frostfeldt G, et al. Effects of an early invasive strategy on ischemia and exercise tolerance among patients with unstable coronary artery disease. The American journal of medicine 2003;115:606-12.	Ineligible intervention.
43	Dolly S, Moteea S, Preston C, Watson V, Bulugahapitiya S. CT coronary angiography (CTCA) vs myocardial perfusion imaging (MPI) in cardiac chest pain evaluation in patients with diabetes and an intermediate probability of coronary artery disease (CAD). European heart journal cardiovascular Imaging 2019;20:iii44.	Abstract only.

	Citation	Reason for exclusion after full-text review
44	Doris M, Newby DE. Coronary CT Angiography as a Diagnostic and Prognostic Tool: Perspectives from the SCOT-HEART Trial. Current cardiology reports 2016;18:1-8.	Narrative review.
45	Douglas PS, De Bruyne B, Pontone G, et al. Long-term outcomes of an FFRCT diagnostic strategy versus usual care in suspected coronary artery disease: Results from the platform (prospective longitudinal trial of FFRCT: Outcome and resource impacts) study. Journal of the American College of Cardiology 2016;67:1589.	Abstract only.
46	El Bez I, Tulbah R, Munir I, Alghamlas F, Alharbi M. Incidental findings on myocardial perfusion spect/CT images. European journal of nuclear medicine and molecular imaging 2019;46:S473.	Abstract only.
47	Elhendy A, Schinkel AF, van Domburg RT, Bax JJ, Valkema R, Poldermans D. Risk stratification of patients after myocardial revascularization by stress Tc-99m tetrofosmin myocardial perfusion tomography. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2003;10:615-22.	Ineligible study design.
48	Escaned J, Ryan N, Mejía-Rentería H, et al. Safety of the Deferral of Coronary Revascularization on the Basis of Instantaneous Wave-Free Ratio and Fractional Flow Reserve Measurements in Stable Coronary Artery Disease and Acute Coronary Syndromes. JACC Cardiovascular interventions 2018;11:1437-49.	Ineligible intervention. Ineligible study design.
49	Estrada JN, Rolandi F, Bansilal S, et al. Stress testing and troponin in unstable coronary syndromes: the status trial-clinical outcomes and resource use. The American heart hospital journal 2006;4:252-8; quiz 9-60.	Ineligible comparator.
50	Farkouh ME, Smars PA, Reeder GS, et al. A clinical trial of a chest-pain observation unit for patients with unstable angina. New England Journal of Medicine 1998;339:1882-8.	Ineligible intervention.
51	Ferencik M, Liu T, Mayrhofer T, et al. hs-Troponin I Followed by CT Angiography Improves Acute Coronary Syndrome Risk Stratification Accuracy and Work-Up in Acute Chest Pain Patients: Results From ROMICAT II Trial. JACC Cardiovascular imaging 2015;8:1272-81.	Ineligible study design.
52	Ferencik M, Mayrhofer T, Bittner DO, et al. Use of High-Risk Coronary Atherosclerotic Plaque Detection for Risk Stratification of Patients With Stable Chest Pain: A Secondary Analysis of the PROMISE Randomized Clinical Trial. JAMA cardiology 2018;3:144-52.	Ineligible study design.
53	Ferencik M, Mayrhofer T, Puchner SB, et al. Computed tomography-based high-risk coronary plaque score to predict acute coronary syndrome among patients with acute chest pain--Results from the ROMICAT II trial. Journal of cardiovascular computed tomography 2015;9:538-45.	Ineligible study design.
54	Fox KA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomized trial. Lancet (London, England) 2005;366:914-20.	Ineligible intervention.
55	Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomized trial. Randomized Intervention Trial of unstable Angina. Lancet (London, England) 2002;360:743-51.	Ineligible intervention.

	Citation	Reason for exclusion after full-text review
56	Galassi AR, Grasso C, Azzarelli S, Ussia G, Moshiri S, Tamburino C. Usefulness of exercise myocardial scintigraphy in multivessel coronary disease after incomplete revascularization with coronary stenting. American Journal of Cardiology 2006;97:207-15.	Ineligible study design. Ineligible intervention.
57	Genders TSS, Coles A, Hoffmann U, et al. The External Validity of Prediction Models for the Diagnosis of Obstructive Coronary Artery Disease in Patients With Stable Chest Pain: Insights From the PROMISE Trial. JACC Cardiovascular imaging 2018;11:437-46.	Ineligible study design.
58	Gibbons RJ, Carryer D, Hodge D, Miller TD, Roger VL, Askew JW. Stress Testing in the Evaluation of Stable Chest Pain in a Community Population. Mayo Clinic proceedings 2020;95:319-27.	Ineligible study design; RCT data available.
59	Glaser R, Herrmann HC, Murphy SA, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes. Jama 2002;288:3124-9.	Ineligible intervention.
60	Goehler A, McMahon PM, Lumish HS, et al. Cost-effectiveness of follow-up of pulmonary nodules incidentally detected on cardiac computed tomographic angiography in patients with suspected coronary artery disease. Circulation 2014;130:668-75.	Safety specific; ineligible outcomes.
61	Goncalves S, Bosch X, Sanchis L, et al. Stress echocardiography and multidetector computed tomography in the evaluation of acute chest pain: A randomized pilot study. European heart journal 2011;32:169.	Abstract only.
62	Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. New England journal of medicine 2017;376:1813-23.	Ineligible study design.
63	Gray AJ, Roobottom C, Smith JE, et al. The RAPID-CTCA trial (Rapid Assessment of Potential Ischaemic Heart Disease with CTCA) - a multicentre parallel-group randomized trial to compare early computerised tomography coronary angiography versus standard care in patients presenting with suspected or confirmed acute coronary syndrome: study protocol for a randomized controlled trial. Trials 2016;17:579.	Protocol only, no published results identified (only an abstract).
64	Hamilton-Craig C, Bhuiyan K, Branch K, et al. CT fractional flow reserve improves the accuracy of CT coronary angiography in the emergency department - A substudy of ctcompare. Heart Lung and Circulation 2016;25:S224.	Abstract only.
65	Hendel RR, Shaw L, Mieres J, Heller G. The women study (what is the optimal method for ischaemia evaluation in women?): Preliminary results. European Heart Journal, Supplement 2009;11:S92.	Abstract only.
66	Hirsch A, Windhausen F, Tijssen JG, Verheugt FW, Cornel JH, de Winter RJ. Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): a follow-up study. Lancet (London, England) 2007;369:827-35.	Ineligible intervention.

	Citation	Reason for exclusion after full-text review
67	Hlatky MA, De Bruyne B, Pontone G, Patel MR, Norgaard BL, Byrne RA, Curzen N, Purcell I, Gutberlet M, Rioufol G, Hink U. Quality-of-life and economic outcomes of assessing fractional flow reserve with computed tomography angiography: PLATFORM. Journal of the American College of Cardiology. 2015 Dec 1;66(21):2315-23.	Costing only.
68	Hochman JS, Reynolds HR, Bangalore S, et al. Baseline Characteristics and Risk Profiles of Participants in the ISCHEMIA Randomized Clinical Trial. JAMA cardiology 2019;4:273-86.	Ineligible intervention.
69	Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. The New England journal of medicine 2012;367:299-308.	Ineligible study design.
70	Irfan A, Kanbour M, Acosta G, Studeny M. Additional cost of two-day myocardial perfusion scan: Rationale for study comparing CCTA vs stress only SPECT-MPI for the diagnosis of coronary artery disease among obese inpatients. European heart journal cardiovascular Imaging 2019;20:iii28.	Abstract only.
71	Jang EJ, Lee HJ, Kim YJ, et al. The clinical usefulness of ct coronary angiography for the diagnosis of ischemic heart disease in patients with chest pain. Value in Health 2012;15:A63.	Abstract only.
72	Januzzi JL, Jr., Suchindran S, Coles A, et al. High-Sensitivity Troponin I and Coronary Computed Tomography in Symptomatic Outpatients With Suspected CAD: Insights From the PROMISE Trial. JACC Cardiovascular imaging 2019;12:1047-55.	Ineligible study design.
73	Juselius WE, Salame G, Bendelow T, Burden M, Long C, Beaty B, Dickinson M, Krantz M. Stress echocardiography and myocardial perfusion imaging in the evaluation of chest pain: A comparative effectiveness study. Journal of the American College of Cardiology. 2014 Apr 1;63(12S):A1242-.	Abstract only.
74	Kapetanopoulos A, Heller GV, Selker HP, et al. Acute resting myocardial perfusion imaging in patients with diabetes mellitus: results from the Emergency Room Assessment of Sestamibi for Evaluation of Chest Pain (ERASE Chest Pain) trial. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2004;11:570-7.	Ineligible intervention.
75	Kim J, Lee H, Song S, et al. Efficacy and safety of the computed tomography coronary angiography based approach for patients with acute chest pain at an emergency department: one month clinical follow-up study. Journal of Korean medical science 2010;25:466-71.	Safety specific; ineligible outcomes.
76	Kishi S, Magalhães TA, Cerci RJ, et al. Comparative effectiveness of coronary artery stenosis and atherosclerotic plaque burden assessment for predicting 30-day revascularization and 2-year major adverse cardiac events. International Journal of Cardiovascular Imaging 2020;36:2365-75.	Ineligible study design. Ineligible population.
77	Klein AJ, Garcia JA, Hudson PA, et al. Safety and efficacy of dual-axis rotational coronary angiography vs. standard coronary angiography. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2011;77:820-7.	Safety specific; ineligible intervention and comparator.

	Citation	Reason for exclusion after full-text review
78	Ladeiras-Lopes R, Bettencourt N, Almeida J, Dias T, Fonseca P, Gama V. Diagnostic yield of invasive coronary angiography in the workup of patients suspected of coronary artery disease: Referral strategies in a tertiary care hospital. European heart journal 2014;35:1056.	Abstract only.
79	Lange RA, Hillis LD. Dobutamine stress echocardiography in patients with low-gradient aortic stenosis. Circulation 2006;113:1718-20.	Editorial.
80	Lee SP, Seo JK, Hwang IC, et al. Coronary computed tomography angiography vs. myocardial single photon emission computed tomography in patients with intermediate risk chest pain: a randomized clinical trial for cost-effectiveness comparison based on real-world cost. European heart journal cardiovascular Imaging 2019;20:417-25.	Ineligible study design. Ineligible population.
81	Leesar MA, Abdul-Baki T, Akkus NI, Sharma A, Kannan T, Bolli R. Use of fractional flow reserve versus stress perfusion scintigraphy after unstable angina. Effect on duration of hospitalization, cost, procedural characteristics, and clinical outcome. Journal of the American College of Cardiology 2003;41:1115-21.	Ineligible intervention and comparator.
82	Lehman SJ, Abbara S, Cury RC, et al. Significance of cardiac computed tomography incidental findings in acute chest pain. The American journal of medicine 2009;122:543-9.	Safety specific; summarized in an included systematic review.
83	Lin F, Koduru S, Cole JH, et al. Near-term post-test treatment, functional status and resource utilization in intermediate risk individuals with stable chest pain syndrome undergoing 64-detector row coronary computed tomographic angiography versus myocardial perfusion spect: A prospective multicenter randomized trial. Journal of the American College of Cardiology 2010;55:A73.E686.	Abstract only.
84	Linde JJ, Hove JD, Kuhl JT, et al. Clinical feasibility of myocardial computed tomographic perfusion imaging in patients with recent acute-onset chest pain. International journal of cardiology 2014;174:195-7.	Ineligible study design; RCT data available.
85	Litt H, Greco E, Sengupta S, Rogers C, Hamilton-Craig C, Hollander J. Non-invasive calculation of fractional flow reserve for reclassification of potentially hemodynamically-significant coronary artery disease by coronary computed tomography angiography in emergency department chest pain patients. Journal of the American College of Cardiology 2016;67:1676.	Abstract only.
86	Litwin S, Coles A, Pagidipati NJ, et al. Effects of obesity on noninvasive testing and angiography results in patients with suspected cardiac ischemia: Insights from the promise trial. Circulation 2016;134.	Abstract only.
87	Liu HL, Jin ZG, Yang SL, et al. Randomized study on the safety and efficacy of dual-axis rotational versus standard coronary angiography in. Chinese medical journal 2012;125:1016-22.	Ineligible intervention.
88	Liu T, Maurovich-Horvat P, Mayrhofer T, Puchner SB, Lu MT, Ghemigian K, Kitslaar PH, Broersen A, Pursnani A, Hoffmann U, Ferencik M. Quantitative coronary plaque analysis predicts high-risk plaque morphology on coronary computed tomography angiography: results from the ROMICAT II trial. The international journal of cardiovascular imaging. 2018 Feb;34(2):311-9.	Ineligible study design (single arm data only).

	Citation	Reason for exclusion after full-text review
89	Lorenzoni V, Neglia D, Bellelli S, et al. Comparative cost-effectiveness of computed tomography coronary angiography alone or in combination with stress imaging for the diagnosis of coronary artery disease in patients with stable angina. results from the evinci study. Circulation. 2016;134.	More recent update available.
90	Lu MT, Ferencik M, Roberts RS, et al. Noninvasive FFR derived from coronary CT angiography: management and outcomes in the PROMISE trial. JACC: Cardiovascular Imaging 2017;10:1350-8.	Ineligible study design.
91	Lu MT, Park J, Ghemigian K, et al. Epicardial and paracardial adipose tissue volume and attenuation–Association with high-risk coronary plaque on computed tomographic angiography in the ROMICAT II trial. Atherosclerosis 2016;251:47-54.	Ineligible outcome. Ineligible study design.
92	Lubbers M, Coenen A, Bruning T, et al. Sex Differences in the Performance of Cardiac Computed Tomography Compared With Functional Testing in Evaluating Stable Chest Pain: Subanalysis of the Multicenter, Randomized CRESCENT Trial (Calcium Imaging and Selective CT Angiography in Comparison to Functional Testing for Suspected Coronary Artery Disease). Circulation Cardiovascular imaging 2017;10.	Ineligible intervention.
93	Lubbers M, Dedic A, Coenen A, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. European heart journal 2016;37:1232-43.	Ineligible intervention.
94	Lubbers MM, Dedic A, Kurata A, et al. Round-the-clock performance of coronary CT angiography for suspected acute coronary syndrome: Results from the BEACON trial. European radiology 2018;28:2169-75.	Ineligible intervention.
95	Maaniitty T, Jaakkola S, Saraste A, Knuuti J. Hybrid coronary computed tomography angiography and positron emission tomography myocardial perfusion imaging in evaluation of recurrent symptoms after coronary artery bypass grafting. European heart journal cardiovascular Imaging 2019;20:1298-304.	Ineligible study design.
96	MacHaalany J, Yam Y, Ruddy TD, Abraham A, Chen L, Beanlands RS, Chow BJ. Potential clinical and economic consequences of noncardiac incidental findings on cardiac computed tomography. Journal of the American College of Cardiology. 2009 Oct 13;54(16):1533-41.	Safety specific; summarized in an included systematic review.
97	Mahler SA, Miller CD, Snyder B, Gatsonis C, Litt HI, Hollander JE. Performance of the 2-hour accelerated diagnostic protocol within the american college of radiology imaging network PA 4005 cohort. Academic Emergency Medicine 2014;21:S91-S2.	Abstract only.
98	Mahmarian JJ, Cerqueira M, Burton T, Seare J, Kristy R, Kitt T, Spalding J. Stress myocardial perfusion imaging versus exercise treadmill testing: Comparison of clinical and economic outcomes in real-world emergency department settings. Journal of the American College of Cardiology. 2017 Mar 21;69(11S):1398-.	Abstract only.
99	Mahmarian JJ. Optimizing evaluation of patients with low to intermediate risk acute chest pain: What is the relative values of stress myocardial perfusion imaging when incorporating stress-only imaging versus cardiac computed tomography. Cardiology (Switzerland) 2016;134:25.	Abstract only.

	Citation	Reason for exclusion after full-text review
100	Mahmoudi M, Nicholas Z, Nuttall J, et al. Fractional Flow Reserve Derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain: Rationale and Design of the FORECAST Trial. Cardiovascular Revascularization Medicine 2020;21:890-6.	Protocol, no results posted.
101	Mahmoudi M, Nicholas Z, Nuttall J, et al. Fractional Flow Reserve Derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain: Rationale and Design of the FORECAST Trial. Cardiovascular Revascularization Medicine 2020;21:890-6.	Safety specific; ineligible outcomes
102	Malahfji M, Al-Mallah MH. Incidental findings on cardiac computed tomography: No new emergencies to declare! Journal of Nuclear Cardiology 2020;27:2316-9.	Editorial.
103	Mark DB, Federspiel JJ, Cowper PA, Anstrom KJ, Hoffmann U, Patel MR, Davidson-Ray L, Daniels MR, Cooper LS, Knight JD, Lee KL. Economic outcomes with anatomical versus functional diagnostic testing for coronary artery disease. Annals of internal medicine. 2016 Jul 19;165(2):94-102.	Costing only.
104	Maron DJ, Hochman JS, O'Brien SM, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: Rationale and design. American heart journal 2018;201:124-35.	Ineligible intervention.
105	Maron DJ, Hochman JS, Reynolds HR, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. New England journal of medicine 2020;382:1395-407.	Ineligible intervention.
106	Mathias Jr W, Beneti LP, Dos Santos FC, et al. Safety and feasibility of dobutamine-atropine stress echocardiography. Arquivos brasileiros de cardiologia 1997;69:31-4.	Not in English.
107	McLenachan S, Camilleri F, Smith M, Newby D, Williams M. Breast arterial calcification on mammography and risk of coronary artery disease: a SCOT-HEART sub-study. Clinical radiology 2019;74:421-8.	Ineligible intervention.
108	Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. The New England journal of medicine 2009;360:2165-75.	Ineligible intervention.
109	Mercuri M, Einstein AJ. Good drivers: Achieving dose reduction across a health care system through implementation of multiple radiation-sparing practices.	Editorial.
110	Mironov V. The role of fractional flow reserve measurements in intermediate coronary lesions treatment in patients with multi-vessel and diffuse coronary artery disease. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2015.	Not in English.

	Citation	Reason for exclusion after full-text review
111	Modas Daniel P, Ramos R, Morais LA, et al. CCTA-guided invasive coronary angiography in symptomatic patients with positive ischemia test. European heart journal 2017;38:1245.	Abstract only.
112	Mols RE, Jensen JM, Sand NP, et al. Visualization of Coronary Artery Calcification: Influence on Risk Modification. The American journal of medicine 2015;128:1023.e23-31.	Ineligible intervention.
113	Montisci R, Ruscazio M, Zedda N, et al. Feasibility, symptoms, adverse effects and complications associated with non invasive assessment of coronary flow velocity in women with suspected or known coronary artery disease. Experience in 1455. European heart journal 2012;33:729.	Abstract only.
114	Morrow DA, Cannon CP, Rifai N, et al. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. Jama 2001;286:2405-12.	Ineligible intervention.
115	Moscariello A, Vliegenthart R, Schoepf UJ, et al. Coronary CT angiography versus conventional cardiac angiography for therapeutic decision making in patients with high likelihood of coronary artery disease. Radiology 2012;265:385-92.	Ineligible study design; RCT data available.
116	Moschetti K, Petersen SE, Pilz G, Kwong RY, Wasserfallen JB, Lombardi M, Korosoglou G, Van Rossum AC, Bruder O, Mahrholdt H, Schwitter J. Cost-minimization analysis of three decision strategies for cardiac revascularization: results of the "suspected CAD" cohort of the european cardiovascular magnetic resonance registry. Journal of Cardiovascular Magnetic Resonance. 2015 Dec;18(1):1-0.	Ineligible intervention.
117	Moss AJ, Newby DE. CT coronary angiographic evaluation of suspected anginal chest pain. Heart (British Cardiac Society) 2016;102:263-8.	Narrative review.
118	Mukundan S, Levsky J, Spevack D, Travin M. Myocardial Perfusion Imaging Has a Higher Rate of False Positivity Compared to CT Angiography in Intermediate Risk Chest Pain Patients Undergoing Catheterization. Circulation 2015;132:A19284-A.	Not in English.
119	Nakhle A, Hammond C, Giles C, et al. Inconclusive cardiac stress echocardiography and the utility of the double product in predicting outcomes: Early results. Journal of the American Society of Echocardiography 2018;31:B127.	Abstract only.
120	Nasis A, Meredith I, Sinha P, Cameron J, Seneviratne S. Long-term safety of a coronary computed tomography angiography-guided strategy for assessment of chest pain in the emergency department. Journal of the American College of Cardiology 2012;59:E1361.	Abstract only.
121	Nasis A, Meredith I, Sinha P, et al. Safety of a coronary computed tomography angiography-guided strategy for assessment of chest pain in the Emergency Department. Heart Lung and Circulation 2011;20:S191.	Abstract only.

	Citation	Reason for exclusion after full-text review
122	Nasis A, Meredith IT, Sud PS, Cameron JD, Troupis JM, Seneviratne SK. Long-term outcome after CT angiography in patients with possible acute coronary syndrome. Radiology 2014;272:674-82.	Safety specific; ineligible outcomes.
123	Nazir MS, Nicol E. The SCOT-HEART trial: cardiac CT to guide patient management and improve outcomes. Cardiovascular research. 2019 Aug 1;115(10):e88-90.	Clinical commentary.
124	Nedeljkovic I, Ostojic M, Beleslin B, et al. Comparison of exercise, dobutamine-atropine and dipyridamole-atropine stress echocardiography in detecting coronary artery disease. Cardiovascular ultrasound 2006;4.	Ineligible study design.
125	Nissen L, Winther S, Isaksen C, et al. Danish study of Non-Invasive testing in Coronary Artery Disease (Dan-NICAD): study protocol for a randomised controlled trial. Trials 2016;17:262.	Ineligible intervention.
126	Nissen L, Winther S, Westra J, et al. Diagnosing coronary artery disease after a positive coronary computed tomography angiography: the Dan-NICAD open label, parallel, head to head, randomized controlled diagnostic accuracy trial of cardiovascular magnetic resonance and myocardial perfusion scintigraphy. European heart journal cardiovascular Imaging 2018;19:369-77.	Ineligible intervention.
127	Nissen L, Winther S, Westra J, et al. Influence of Cardiac CT based disease severity and clinical symptoms on the diagnostic performance of myocardial perfusion. The international journal of cardiovascular imaging 2019;35:1709-20.	Ineligible intervention.
128	Ntoskas T, Ahmad F, Woodmansey P. Safety and efficacy of physiologist-led dobutamine stress echocardiography: Experience from a tertiary cardiac centre. Echo Research and Practice 2018;5:105-12.	Safety specific; ineligible intervention and comparator.
129	Pálinkás A, Tóth E, Amyot R, Rigo F, Venneria L, Picano E. The value of ECG and echocardiography during stress testing for identifying systemic endothelial dysfunction and epicardial artery stenosis. European heart journal 2002;23:1587-95.	Ineligible study design.
130	Patel KK, Al Badarin F, Arnold SV, et al. Quality of life outcomes in patients with known coronary artery disease presenting with suspected ischemia randomized to pharmacologic stress myocardial perfusion imaging with single photon emission computed tomography (SPECT) and positron emission tomography (PET). Circulation: Cardiovascular Quality and Outcomes 2018;11.	Abstract only.
131	Paul R, Babcock C, Bascom E. In very low risk chest pain patients, is discharge from emergency department without stress testing cost effective? Academic Emergency Medicine. 2016;23:S131.	Abstract only.
132	Petersen JR, Bhardwaj P, Joergensen TS, Nepper ML, Thygesen JP, Fornitz GG. Coronary microvascular disease in women: A diagnostic challenge. myocardial contrast perfusion stress-echocardiography as a diagnostic tool. European heart journal cardiovascular Imaging 2019;20:i10.	Abstract only.

	Citation	Reason for exclusion after full-text review
133	Pfisterer M, Buser P, Osswald S, et al. Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy: one-year results of the randomized TIME trial. Jama 2003;289:1117-23.	Ineligible intervention.
134	Picano E, Severi S, Lattanzi F, et al. The diagnostic and prognostic value of echo-dipyridamole in patients with suspected coronary disease: a comparison with the stress test. Giornale italiano di cardiologia 1991;21:621-32.	Not in English.
135	Pontone G, De Cecco C, Baggiano A, et al. Design of CTP-PRO study (impact of stress Cardiac computed Tomography myocardial Perfusion on downstream resources and PROgnosis in patients with suspected or known coronary artery disease: A multicenter international study). International journal of cardiology 2019;292:253-7.	Protocol only, no published results identified.
136	Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. Journal of the American College of Cardiology 2014;64:684-92.	Ineligible study design; data provided for CCTA arm only.
137	Pursnani A, Celeng C, Schlett CL, et al. Use of Coronary Computed Tomographic Angiography Findings to Modify Statin and Aspirin Prescription in Patients With Acute Chest Pain. American journal of cardiology 2016;117:319-24.	Ineligible study design; single arm data from RCT only.
138	Pursnani A, Chou ET, Zakroysky P, et al. Use of coronary artery calcium scanning beyond coronary computed tomographic angiography in the emergency department evaluation for acute chest pain: the ROMICAT II trial. Circulation Cardiovascular imaging 2015;8.	Ineligible comparator.
139	Quintella EF, Ferreira E, Azevedo VMP, et al. Clinical Outcomes and Cost-Effectiveness Analysis of FFR Compared with Angiography in Multivessel Disease Patient. Arquivos brasileiros de cardiologia 2019;112:40-7.	Ineligible intervention.
140	Rabbat M, Pontone G, Nørgaard B, Kauh B, Mathew V, Lopez J. Fractional flow reserve derived from coronary computed tomography improves the diagnostic yield of elective invasive coronary angiography in patients with equivocal non-invasive cardiac stress tests. Journal of cardiovascular computed tomography 2017;11:S29.	Abstract only.
141	Raff GL, Chinnaiyan KM, Berman D, et al. Coronary computed tomography for systematic triage of acute chest pain patients to treatment - (the CT-STAT trial). Circulation 2010;120:2160.	Abstract only.
142	Raggi P, Callister TQ, Cooil B, Russo DJ, Lippolis NJ, Patterson RE. Evaluation of chest pain in patients with low to intermediate pretest probability of coronary artery disease by electron beam computed tomography. The American journal of cardiology 2000;85:283-8.	Ineligible intervention.

	Citation	Reason for exclusion after full-text review
143	Ramakrishna G, Milavetz JJ, Zinsmeister AR, et al. Effect of exercise treadmill testing and stress imaging on the triage of patients with chest pain: CHEER substudy. Mayo Clinic proceedings 2005;80:322-9.	Ineligible intervention.
144	Rasmussen L, Nissen L, Westra J, et al. Combining minimal risk stratification and prediction of obstructive CAD-clinical utility of a dual pre-test probability model. European heart journal 2020;41:1376.	Abstract only.
145	Rasmussen LD, Winther S, Westra J, et al. Danish study of Non-Invasive testing in Coronary Artery Disease 2 (Dan-NICAD 2): Study design for a controlled study of diagnostic accuracy. American heart journal 2019;215:114-28.	Ineligible intervention.
146	Reinhardt SW, Lin CJ, Novak E, Brown DL. Noninvasive Cardiac Testing vs Clinical Evaluation Alone in Acute Chest Pain: A Secondary Analysis of the ROMICAT-II Randomized Clinical Trial. JAMA internal medicine 2018;178:212-9.	Ineligible study design; broke randomization.
147	Rogers IS, Banerji D, Siegel EL, et al. Usefulness of comprehensive cardiothoracic computed tomography in the evaluation of acute undifferentiated chest discomfort in the emergency department (CAPTURE). American journal of cardiology 2011;107:643-50.	Ineligible population.
148	Russak AJ, Schwartz AM, Paivanas NA, Farrukh A, Schwarz KQ, Schwartz RG. Safety, adverse symptoms, and hemodynamic effects of pharmacologic vasodilator stress testing in patients with moderate to severe aortic stenosis. Journal of Nuclear Cardiology 2018;25:1443.	Not in English.
149	San Román JA, Vilacosta I, Castillo JA, et al. Dipyridamole and dobutamine-atropine stress echocardiography in the diagnosis of coronary artery disease. Comparison with exercise stress test, analysis of agreement, and impact of antianginal treatment. Chest 1996;110:1248-54.	Ineligible intervention and comparator.
150	Savonitto S, Cavallini C, Petronio AS, et al. Early aggressive versus initially conservative treatment in elderly patients with non-ST-segment elevation acute coronary syndrome: a randomized controlled trial. JACC Cardiovascular interventions 2012;5:906-16.	Ineligible intervention.
151	Schlett CL, Banerji D, Siegel E, et al. Prognostic value of CT angiography for major adverse cardiac events in patients with acute chest pain from the emergency department: 2-year outcomes of the ROMICAT trial. JACC Cardiovascular imaging 2011;4:481-91.	Ineligible study design.

	Citation	Reason for exclusion after full-text review
152	Sels JW, Tonino PA, Siebert U, et al. Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. JACC Cardiovascular interventions 2011;4:1183-9.	Ineligible intervention.
153	Seneviratne SK, Truong QA, Bamberg F, et al. Incremental diagnostic value of regional left ventricular function over coronary assessment by cardiac computed tomography for the detection of acute coronary syndrome in patients with acute chest pain: from the ROMICAT trial. Circulation Cardiovascular imaging 2010;3:375-83.	Ineligible study design; observational and single arm data only.
154	Shah R, Yow E, Jones WS, et al. Comparison of visual assessment of coronary stenosis with independent quantitative coronary angiography: Findings from the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial. American heart journal 2017;184:1-9.	Ineligible outcome and study design.
155	Shaw LJ, Heller GV, Casperson P, et al. Gated myocardial perfusion single photon emission computed tomography in the clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE) trial, Veterans Administration Cooperative study no. 424. Journal of Nuclear Cardiology 2006;13:685-98.	Ineligible intervention.
156	Small GR, Erthal F, Alenazy A, et al. Comparison of coronary CT angiography versus functional imaging for CABG patients: A resource utilization analysis. IJC Heart and Vasculature 2020;27.	Ineligible study design.
157	Sørgaard M, Linde JJ, Hove JD, et al. Myocardial perfusion 320-row multidetector computed tomography-guided treatment strategy for the clinical management of patients with recent acute-onset chest pain: Design of the CArdiac cT in the treatment of acute CHest pain (CATCH)-2 randomized controlled trial. American heart journal 2016;179:127-35.	Ineligible comparator.
158	Sørgaard MH, Linde JJ, Kühl JT, et al. Value of Myocardial Perfusion Assessment With Coronary Computed Tomography Angiography in Patients With Recent Acute-Onset Chest Pain. JACC Cardiovascular imaging 2018;11:1611-21.	Ineligible comparator.
159	Soukka I, Maaniitty T, Saraste A, et al. Cardiac hybrid PET-CT imaging guides downstream referral for invasive coronary angiography and revascularization. European heart journal cardiovascular Imaging 2015;16:i1.	Abstract only.

	Citation	Reason for exclusion after full-text review
160	Stochkendahl MJ, Mickley H, Vach W, et al. Clinical characteristics, myocardial perfusion deficits, and clinical outcomes of patients with non-specific chest pain hospitalized for suspected acute coronary syndrome: a 4-year prospective cohort study. International journal of cardiology 2015;182:126-31.	Prospective cohort study.
161	Stowers SA, Eisenstein EL, Th Wackers FJ, et al. An economic analysis of an aggressive diagnostic strategy with single photon emission computed tomography myocardial perfusion imaging and early exercise stress testing in emergency department patients who present with chest pain but nondiagnostic electrocardiograms: results from a randomized trial. Annals of emergency medicine 2000;35:17-25.	Ineligible intervention (rest only)
162	Suliman I, AlJizeeri A, Naseem M, Naveed M, AlZaibag M, Al-Mallah M. The yield, safety and prognostic value of myocardial perfusion imaging with positron emission tomography for risk stratification of high risk chest pain patients. European journal of nuclear medicine and molecular imaging 2014;41:S615.	Letter to the editor.
163	Terpenning, Silanath, and Arthur Stillman. “Cost-effectiveness for imaging stable ischemic disease.” The British journal of radiology vol. 93,1113 (2020): 20190764. doi:10.1259/bjr.20190764	Narrative review.
164	Time Investigators. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. The Lancet. 2001 Sep 22;358(9286):951-7.	Does not assess CCTA.
165	Toth G, De Vroey F, Pyxaras S, et al. Clinical outcome of patients treated with angio-guided vs. FFR-guided CABG surgery. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2013;9:119.	Abstract only.
166	Trattner S, Halliburton S, Thompson CM, Xu Y, Chelliah A, Jambawalikar SR, Peng B, Peters MR, Jacobs JE, Ghesani M, Jang JJ. Cardiac-specific conversion factors to estimate radiation effective dose from dose-length product in computed tomography. JACC: Cardiovascular Imaging. 2018 Jan;11(1):64-74.	Safety specific; ineligible outcomes.
167	Udelson JE, Beshansky JR, Ballin DS, et al. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. Jama 2002;288:2693-700.	Ineligible intervention (rest only)
168	Vamvakidou A, Danylenko O, Pradhan J, et al. Relative clinical value of coronary computed tomography and stress echocardiography-guided management of stable chest pain patients: a propensity-matched analysis. European heart journal cardiovascular Imaging 2020.	Propensity matched cohort, CCTA vs. Stress Echo (RCT data available; otherwise includable).

	Citation	Reason for exclusion after full-text review
169	Villines TC, Gore R, Bindeman J, et al. Coronary ct angiography versus stress imaging for initial risk stratification (CT-first): A randomized prospective trial on downstream resource utilization. Circulation 2013;128.	Abstract only.
170	Wallentin L, Lagerqvist B, Husted S, Kontny F, Ståhle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. Lancet (London, England) 2000;356:9-16.	Ineligible intervention
171	Winchester D, Jeffrey R, Wymer D, Taasan V, Wokhlu A. Simplified approach to stress-first nuclear myocardial perfusion imaging: implementation of choosing wisely recommendations. BMJ open quality. 2019 Apr 1;8(2):e000352.	Safety specific; ineligible intervention and comparator.
172	Yerramasu A, Patel D. Randomized controlled trial to evaluate the cost and clinical effectiveness of CT coronary angiography in patients with stable angina pectoris (RADICAL trial). European Heart Journal, Supplement 2011;13:A45-A6.	Abstract only.
173	Zellweger MJ, Lewin HC, Lai S, et al. When to stress patients after coronary artery bypass surgery? Risk stratification in patients early and late Post-CABG using stress myocardial perfusion SPECT: Implications of appropriate clinical strategies. Journal of the American College of Cardiology 2001;37:144-52.	Ineligible study design.

APPENDIX D. Risk of Bias, Strength of Evidence, and AMSTAR-2 and QHES Determination

Assessment of studies evaluating testing

Each included comparative study is rated against pre-set criteria that resulted in a Risk of Bias (ROB) assessment and presented in a table. Assessment of RCTs followed appropriate criteria based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[30] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[3] In keeping with the AHRQ methods and the 2016 report on non-invasive imaging for CAD[83], each study was given a final rating of "good", "fair", or "poor" quality as described below in Table D1. Discrepancies in ratings between reviewers were resolved through discussion and consensus. The final quality assessments are provided in Appendix E.

Table D2 provides an example of the format used to assess ROB for comparative studies of testing/therapy. A "No" indicates that the criterion was not met; an "Unclear" indicates that the criterion could not be determined with the information provided or was not reported by the author. Risk of bias assessments were not conducted for case series; all were considered High risk of bias.

Appendix Table D1. Definition of the risk of bias categories for individual studies of testing

Rating	Description and Criteria
Good	• Least risk of bias; study results generally considered valid • Employ valid methods for selection, inclusion, and allocation of patients to testing; report similar baseline characteristics in different test groups; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinding of patients, care providers, and outcomes assessors); and use appropriate analytic methods (e.g., intention-to-treat analysis)
Fair	• Study is susceptible to some bias but not enough to necessarily invalidate results • May not meet all criteria for good quality, but no flaw is likely to cause major bias; the study may be missing information making it difficult to assess limitations and potential problems • This category is broad; studies with this rating will vary in strengths and weaknesses; some fair-quality studies are likely to be valid, while others may be only possibly valid
Poor	• Significant flaws that imply biases of various kinds that may invalidate results; the study contains "fatal flaws" in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting or serious problems with intervention delivery • Study results are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions • Considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present

Appendix Table D2: Assessment of ROB for individual studies of testing

Methodological Principle	Author 1, 2014	Author 2, 2012	Author 3, 2010
Study design			
Randomized controlled trial	■	■	■
Prospective cohort study			
Retrospective cohort study			
Case-control			
Case-series			
Random sequence generation*			
Statement of concealed allocation*			
Analysis according to random assignment (i.e., intention to treat)*			
Independent or blinded outcome assessment			
Patients comparable at baseline on key CAD risk factors			
Prespecified threshold or definition for a positive test			
Attrition (≤ 20% overall)			
<10% difference in follow-up between groups†			
Comparable followup time or accounting for time at risk			
Controlling for possible confounding†			
Full reporting on pre-specified outcomes			
Overall quality rating			

*Applies to randomized controlled trials only.

†Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g., by restriction, matching, statistical methods)

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al. embodies the primary components relevant for critical appraisal of economic studies.[63] It also incorporates a weighted scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (e.g., with respect to age, gender, medical conditions, etc.)? To what extent are the populations for each intervention comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (e.g., complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (e.g., similar protocols, follow-up procedures, evaluation of outcomes, etc.)?
- How were the data and/or patients selected or sampled (e.g., a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?

Were the outcomes and consequences of the interventions being compared comparable for each? (e.g., were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?

Assessment of Reliability Studies for Contextual Questions

Appendix Table D3. Definitions of the different risk of bias for reliability studies

Study type	Criteria
Good quality study	• Broad spectrum of persons with the expected condition • Adequate description of methods for replication • Blinded performance of tests, measurements, or interpretation • Second test/interpretation performed independently of the first
Moderate quality	• Violation of any one of the criteria for a good quality study
Poor quality study	• Violation of any two of the criteria
Very poor quality study	• Violation of all three of the criteria

Determination of the ROB involves evaluation of the following questions:

1. Was a **broad spectrum of persons with the suspected condition** used to determine reliability?

   The study population must be comprised of those with a broad spectrum of suspected disease who are likely to have the test now or in the future. Since differences in gender, age, body habitus and other characteristics may influence measurements and the ability to reproduce the results, the range of patients used for reliability studies is important. Ideally a random sample of patients from the relevant clinical population would be used but may not be feasible, depending on the study. A broad spectrum would include patients with mild as well as more severe cases, those presenting early as well as late and those whose differential diagnosis may be commonly confused with the condition of interest. Reproducibility studies in a population with known disease may give different results compared with studies on a group of normal individuals and may not give an accurate picture of overall reproducibility. (If the goal of the study is to evaluate the potential for differential measurement error or bias, the separate analyses on "normal" and "diseased" populations should be done to evaluate the extent of such bias. If it is a test-retest design, the test administrations should be on the same population. If it is an inter- or inter-rater reliability study the object (e.g., radiographs) should be the same for each reading/interpretation, (e.g., the same patients' radiographs are read twice).

2. Are the **details of the methods sufficient to allow study replication**?

   Is the description of the methods, i.e. the protocols used to collect information, measurements taken, planes of section, diagnostic criteria used, etc. sufficient that other investigators could duplicate the conditions and reproduce the findings in a similar population? Are the methods used for each part of the replication consistent?

3. Was there **blinded/independent performance of the repeat test administrations or interpretations**?

   The second administration of the test or second interpretation of results should be done without influence of the first test/interpretation. This is necessary to avoid bias. It must be clear from the text that both tests were interpreted without knowledge of the results of the other. Examples of when the administration would not be considered blinded or independent could include:

   - Interpretation of the second test is to be done without prior knowledge of the test results or the first interpretation.

- The timing of the second test administration or reading/interpretation of the results is not done such that sufficient time has elapsed between them to avoid influence of the first test/interpretation on the results of the second. In the case of re-administration of the test, the timing should not be so far apart that the stage/period of disease is different from the first administration.

Assessment of Systematic Reviews

Appendix Table D4 shows our criteria for RoB assessment based on the AMSTAR-2 tool. AMSTAR-2 is the revised and updated version of AMSTAR published in 2007 used for critical appraisal of systematic reviews.[81] It is not intended to provide an overall score, as high scores may hide weaknesses in critical domains. In light of this, we used a modified AMSTAR tool as determined by Dettori et. al.[14] Appendix Table D5 (adapted from Dettori 2020)[14] describes how overall scores were determined taking into account critical domains. Bold items in Appendix Table D4. were considered as critical items. The original AMSTAR-2 guidance suggests grading each item as no or yes, with items 2, 4, 7, 8, and 9 allowing for a 'partial yes'. We considered a 'yes' or 'partial yes' as yes.

Appendix Table D4. Criteria for assessing studies based on AMSTAR-2.

Item	Criteria
1: Did the research questions and inclusion criteria for the review include the components of PICO?	• **Yes** if all components of PICO are described somewhere in the report. • **No** if any components of PICO are missing.
2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	• **Yes** if the protocol or review methods were established prior to review. • **No** if no protocol or discussion of methods decided prior to review.
3: Did the review authors explain their selection of the study designs for inclusion in the review?	• **Yes** if study design inclusion is justified or discussed. No penalty for restricting study designs. • **No** if no discussion of justification for inclusion.
4: Did the review authors use a comprehensive literature search strategy?	• **Yes** if 2 or more electronic databases were searched and key words are available in report or appendices. No penalty for language restrictions. • **No** if less than 2 electronic databases were searched or key words are unavailable.
5: Did the review authors perform study selection in duplicate?	• **Yes** if selection at title/abstract and full text reviews were performed by 2 authors with consensus upon disagreement or single author selecting with a second checking agreement on sample and a kappa reported of ≥0.80. • **No** if no second author involved or no kappa reported.
6: Did the review authors perform data extraction in duplicate?	• **Yes** if abstraction was performed by 2 authors with consensus upon disagreement or single author abstracting with a second checking agreement on sample and a kappa of reported of ≥0.80. • **No** if no second author involved or no kappa reported.
7: Did the review authors provide a list of excluded studies and justify the exclusions?	• **Yes** if a list of potentially relevant studies is reported in appendix or discussed in text with citations with justification for exclusion. List of references must be provided. • **No** if no list of references provided or no potentially relevant but excluded studies are discussed.
8: Did the review authors describe the included studies in adequate detail?	• **Yes** if study characteristics are reported in sufficient detail to determine whether the studies met PICO criteria and provides framework to judge heterogeneity. • **No** if study characteristics are not reported or table 1 does not include age, sex, (and #'s).
9: Did the review authors use a satisfying technique for assessing	**RCTS** • **Yes** if important domains similar to Cochrane.

the RoB in individual studies that were included in the review?	**Cohort studies** • **Yes** if it addresses all of the following: confounding, selection bias, measurement bias, and selective reporting of outcomes (Newcastle okay if all 8 questions included). **Case series** (study of incidence, no direct comparison) • **Yes** if selection bias, measurement bias, and selective reporting of outcomes met (Newcastle okay IF questions #1, 2, 3, 4, 6, 7, and 8 addressed). **For all studies** • **No** if there is obvious evidence that the authors misapplied an acceptable technique.
10: Did the review authors report on the sources of funding for the studies included in the review?	• **Yes** if authors report funding of individual studies. • **No** if authors do not report funding.
11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	• **Yes** if all the following are present o Meta-analysis justified (e.g., studies comparable, direct comparison). o Explanation of fixed or random effects (must do more than merely report without explanation). o Pooled results reported separately for RCTs and cohort studies. o Assessment of heterogeneity (must address I^2). • **No** if one or more of the above are not present.
12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	• **Yes** if results are stratified by RoB or if the review only included the lowest RoB studies in the analysis. • **No** if results are not stratified by RoB and review includes a range of RoB outcomes in the analysis. No credit if RoB method from item #9 is not acceptable.
13: Did the review authors account for RoB in individual studies when interpreting or discussing the results of the review?	• **Yes** if there is a discussion of the impact of RoB in the interpretation of results and/or accounting for differences between studies. • **No** if there is no discussion of the impact of RoB in the interpretation of results and/or accounting for differences between studies. No credit if method from #9 is not acceptable.
14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	• **Yes** if I^2 demonstrates no heterogeneity (<50%) or authors explored reasons for heterogeneity if I^2 is ≥50%. • **No** if I^2 demonstrates heterogeneity (>50%) and authors do not explore reasons for heterogeneity.
15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	• **Yes** if there is an attempt to identify publication bias. Must also show awareness of likely impact of publication bias on results. Credit given if they acknowledge publication bias could be a problem but not enough data given or if they have fewer than 10 studies and show no evidence of publication bias. • **No** if there is no attempt to identify or discuss publication bias.
16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	• **Yes** if authors report no competing interests or how they managed potential conflicts of interest. • **No** if there is no discussion or reporting of potential conflicts of interest.

PICO = population, intervention, comparison, outcome; RoB = risk of bias.

Appendix Table D5. Rating overall Confidence in the Results of the Review (Dettori 2020).

High: No or 1 noncritical weakness	The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
Moderate: More than 1 noncritical weakness*	The systematic review has more than 1 weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.
Low: One critical flaw with or without noncritical weaknesses	The review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.
Critically low: More than 1 critical flaw with or without noncritical weaknesses	The review has more than 1 critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

* Multiple noncritical weaknesses may diminish confidence in the review, and it may be appropriate to move the overall appraisal down from moderate to low confidence.

Determination of Overall Strength (Quality) of Evidence

The strength of evidence for the overall body of evidence for all *critical health outcomes* was assessed by one researcher following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare Research and Quality (AHRQ).[7,27,28] The strength of evidence was based on the highest quality evidence available for a given *primary* outcome. In determining the strength of body of evidence regarding a given *primary* outcome, the following domains were considered:

- **Risk of bias:** the extent to which the included studies have protection against bias.
- **Consistency:** the degree to which the included studies report results are similar in terms of range and variability.
- **Directness:** describes whether the evidence is directly related to patient health outcomes.
- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication bias:** is considered when there is concern of selective publishing.

All AHRQ "required" and "additional" domains (risk of bias, consistency, directness, precision, and if possible, publication bias) were assessed. Bodies of evidence consisting of RCTs were initially considered as High strength of evidence (SoE), while those that comprised nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There could also be situations where the *nonrandomized* studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, presence of a dose-response relationship, and large magnitude of effect (strength of association) *if no downgrades for domains above*. Publication and reporting bias are difficult to assess. Publication bias is particularly difficult to assess with fewer than 10 RCTs (AHRQ methods guide). When publication bias was unknown in all studies and this domain is often eliminated from the strength of evidence tables for our reports. The final strength of evidence for each **primary** outcome was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

High— Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.

Moderate— Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are probably stable but some doubt remains.

Low— Limited confidence that effect size estimates lie close to the true effect for this outcome; important or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.

Insufficient— We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable deficiencies precluding judgment.

Similar methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 4 was not assessed.

Appendix Table D6. Example methodology outline for determining overall strength of evidence (SoE):

All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table below.

Baseline strength: HIGH = RCTs. LOW = observational, cohort studies, administrative data studies.

DOWNGRADE: Risk of bias for the individual article evaluations (1 or 2); Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated *a priori* and no test for interaction (2)

UPGRADE (non-randomized studies): Large magnitude of effect (1 or 2); Dose response gradient (1) done for observational studies ***if no downgrade for domains above***

Outcome	Strength of Evidence	Conclusions & Comments	Baseline SOE	DOWNGRADE	UPGRADE
Outcome	**HIGH**	Summary of findings	**HIGH** RCTs	**NO** consistent, direct, and precise estimates	**NO**
Outcome	**MODERATE**	Summary of findings	**LOW** Cohort studies	**NO** consistent, direct, and precise estimates; high quality (moderately low ROB)	**YES** Large effect
Outcome	**LOW**	Summary of findings	**HIGH** RCTs	**YES (2)** Inconsistent Indirect	**NO**

*Required domains: risk of bias, consistency, directness, precision. Plausible confounding that would decrease observed effect is accounted for in our baseline risk of bias assessment through individual article evaluation. Additional domains: dose-response, strength of association, publication bias.

**Single study = "consistency unknown", may or may not be downgraded

APPENDIX E. Study Quality: Risk of Bias evaluation

Appendix Table E1. ROB for RCTs comparing CCTA with functional testing among patients with suspected CAD

	Karthikeyan 2017 (IAEA-SPECT/CTA)	Stillman 2020 (RESCUE)	SCOT-HEART 2015	Min 2012	Douglas 2015 (PROMISE)	McKavanagh 2014 (CAPP)
Study design						
Randomized controlled trial	✓	✓	✓	✓	✓	✓
Methodological Principle						
Random sequence generation†	Yes	Yes	Yes	Unclear	Yes	Yes
Statement of Concealed allocation†	Yes	Yes	Unclear	Unclear	Yes	No
Analysis according to random assignment†	Yes	Yes	Yes	Yes	Yes	Yes
Independent or blinded outcome assessment	No	No	Yes	No	Yes	Unclear
Patients comparable at baseline on key CAD risk factors	Yes	Yes	Yes	No	Yes	Yes
Prespecified threshold or definition for a positive test	Yes	Yes	Yes	Yes	Yes	Yes
Attrition (≤ 20% overall)	Yes	Yes (primary aim) No (secondary aim)	Yes	Yes	Yes	Yes
Attrition (≤ 10% difference between groups)	Yes	Yes (primary aim) Yes (secondary aim)	Yes	Yes	Yes	Yes
Comparable followup time or accounting for time at risk	Yes	Yes	Yes	Unclear	Yes	Yes
Controlling for possible confounding‡	Yes	Yes	Yes	Yes	Yes	Yes
Full reporting on pre-specified outcomes	Yes	Yes	Yes	Yes	Yes	Yes
Overall Quality Rating	Good	Good	Good	Poor	Good	Fair

CAD = coronary artery disease; NA = not applicable; RCTG = randomized control trial.
* Studies stratified patients by low, intermediate, and high risk but study quality was assessed for the study as a whole.
†Applies only to randomized controlled trials
‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g., by restriction, matching, statistical methods)
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Appendix Table E2. ROB for RCTs comparing CCTA with ICA among patients with suspected CAD

	Dewey 2016 (CAD-Man)	Chang 2019 (CONSERVE)
Study design		
Randomized controlled trial	✓	✓
Methodological Principle		
Random sequence generation†	Yes	Yes
Statement of Concealed allocation†	Yes	No
Analysis according to random assignment†	Yes	No
Independent or blinded outcome assessment	No	No
Patients comparable at baseline on key CAD risk factors	Yes	Yes
Prespecified threshold or definition for a positive test	Yes	Yes
Attrition (≤ 20% overall)	Yes	6 months: Yes 12 months: No
Attrition (≤ 10% difference between groups)	Yes	Yes
Comparable followup time or accounting for time at risk	Yes	Yes
Controlling for possible confounding‡	Yes	Yes
Full reporting on pre-specified outcomes	Yes	Yes
Overall Quality Rating	**Good**	**Fair**

CAD = coronary artery disease; NA = not applicable; RCT = randomized control trial.

* Studies stratified patients by low, intermediate, and high risk but study quality was assessed for the study as a whole.

†Applies only to randomized controlled trials

‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g., by restriction, matching, statistical methods)

Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Appendix Table E3. ROB for RCTs comparing CCTA with functional testing among patients with suspected ACS

	Dedic 2016 (BEACON)	Linde 2013 (CATCH)	Nabi 2016	Uretsky 2017 (PERFECT trial)	Pineiro-Portela 2021	Levsky 2018	Litt 2012 (ACRIN-PA)	Miller 2011	Hoffman 2012 (ROMICAT-II)	Chang 2008	Goldstein 2011 (CT-STAT)	Goldstein 2007	Levsky 2015 (PROSPECT)	Hamilton-Craig 2014 (CT-COMPARE)
Study design														
Randomized controlled trial	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Methodological Principle														
Random sequence generation†	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
Statement of Concealed allocation†	Yes	Yes	No	No	No	Yes	No	No	No	No	Unclear	Yes	Yes	No
Analysis according to random assignment†	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Independent or blinded outcome assessment	No	No§	No	No	No	No	Unclear	Unclear	Unclear	Unclear	Yes	No	ICA not leading to revascularization yes, otherwise no	Unclear
Patients comparable at baseline on key CAD risk factors	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes
Prespecified threshold or definition for a positive test	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Unclear	Yes	Yes	Yes	No	Yes
Attrition (≤ 20% overall)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

	Dedic 2016 (BEACON)	Linde 2013 (CATCH)	Nabi 2016	Uretsky 2017 (PERFECT trial)	Pineiro-Portela 2021	Levsky 2018	Litt 2012 (ACRIN-PA)	Miller 2011	Hoffman 2012 (ROMICAT-II)	Chang 2008	Goldstein 2011 (CT-STAT)	Goldstein 2007	Levsky 2015 (PROSPECT)	Hamilton-Craig 2014 (CT-COMPARE)
Attrition (≤ 10% difference between groups)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Comparable followup time or accounting for time at risk	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controlling for possible confounding‡	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Full reporting on pre-specified outcomes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall Quality Rating	**Good**	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Poor**	**Fair**	**Fair**	**Good**	**Poor**	**Fair**	**Fair**

ACS = Acute coronary syndrome; CAD = coronary artery disease; NA = not applicable; RCTs = randomized control trial.
* Studies stratified patients by low, intermediate, and high risk but study quality was assessed for the study as a whole.
†Applies only to randomized controlled trials
‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g., by restriction, matching, statistical methods)
§All patients underwent both CCTA and a functional test (bicycle exercise-ECG and/or MPI) in addition to a clinical evaluation by an experienced cardiologist. In this way, patients and clinical staff were blinded to group allocation until all non-invasive tests were performed. However, in the standard care group CCTA results remained blinded for patients and clinical staff, and in the CCTA-guided group clinical decision making was based on CCTA-findings overruling stress test results.
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Appendix Table E4. ROB for RCTs evaluating Echocardiography

	Stable, Outpatient			Acute, ED/Hospital		
	Suspected CAD		Suspected or Known CAD	Suspected ACS	Suspected or Known ACS	
	Sanfilippo 2005	Zacharias 2017, Gurunathan 2018	Sharples 2007/ Thom 2014 CECaT	Nucifora 2009 ASSENCE	Desideri 2005 COSTAMI-II	Jeetley 2006
Methodological Principle						
Random sequence generation†	Unclear	Yes	Yes	Unclear	Yes	Unclear
Statement of Concealed allocation†	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Analysis according to random assignment†	No	Yes	Yes	Yes	Yes	Yes
Independent or blinded outcome assessment	Yes	Yes	No	Unclear	Unclear	Unclear
Patients comparable at baseline on key CAD risk factors	No	Yes	Yes	No	Yes	No
Prespecified threshold or definition for a positive test	Yes	Yes	Yes	No	Yes	Yes
Attrition (≤ 20% overall)	Yes	Yes	Yes	No	Unclear	Yes
Attrition (≤ 10% difference between groups)	Yes	Yes	Yes	Yes: echo vs. ECG No: echo vs. UC	Unclear	Yes
Comparable followup time or accounting for time at risk	Yes	Yes	Yes	Yes	Yes	Yes
Controlling for possible confounding‡	No	Yes	Yes	Yes	Yes	No
Full reporting on pre-specified outcomes	Yes	Yes	Yes	Yes	Yes	Yes
Overall Quality Rating	**Poor**	**Good**	**Good**	**Poor**	**Fair**	**Poor**

ACS = acute coronary syndrome; ASSENCE = The Assessment of cost-effectiveness of Several Strategies of Early diagnosis in patients with ACP and Non-Conclusive Electrocardiogram; CAD = coronary artery disease; CECaT = Cost-Effectiveness of functional Cardiac Testing; COSTAMI-II = cost of strategies after myocardial infarction; NA = not applicable.

* Studies stratified patients by low, intermediate, and high risk but study quality was assessed for the study as a whole.

†Applies only to randomized controlled trials

‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g., by restriction, matching, statistical methods)

Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Appendix Table E5. ROB for RCTs evaluating SPECT

	Stable, Outpatient				Acute, ED/Hospital	
	Suspected CAD			Suspected or Known CAD	Suspected ACS	Suspected or Known ACS
	Greenwood 2016 CE-MARC	Sabharwal 2007	Shaw 2011	Sharples 2007/Thom 2014 CECaT	Lim 2013	Salame 2018
Methodological Principle						
Random sequence generation†	Yes (minimization)	Yes	Yes	Yes	Yes	Yes
Statement of Concealed allocation†	Yes	No	No	Yes	Yes	No
Analysis according to random assignment†	Yes	Yes	Yes	Yes	Yes	Yes
Independent or blinded outcome assessment	Yes	Unclear	Yes	No	Unclear	Yes
Patients comparable at baseline on key CAD risk factors	Yes	Yes	Yes	Yes	Yes	No
Prespecified threshold or definition for a positive test	Yes	Yes	Yes	Yes	Yes	Yes
Attrition (≤ 20% overall)	Yes	Yes	Yes	Yes	30 days, yes 1 year, unclear	Yes
Attrition (≤ 10% difference between groups)	Yes	Yes	Yes	Yes	30 days, yes 1 year, unclear	Yes
Comparable followup time or accounting for time at risk	Yes	Yes	Yes	Yes	Yes	Yes
Controlling for possible confounding‡	Yes	Yes	Yes	Yes	Yes	No
Full reporting on pre-specified outcomes	Yes	Yes	Yes	Yes	Yes	Yes
Overall Quality Rating	**Good**	**Fair**	**Fair**	**Good**	**Fair**	**Fair**

ACS = acute coronary syndrome; CAD = coronary artery disease; CECaT = Cost-Effectiveness of functional Cardiac Testing; CE-MARC = The Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease 2 trial; NA = not applicable.

* Studies stratified patients by low, intermediate, and high risk but study quality was assessed for the study as a whole.

†Applies only to randomized controlled trials

‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g., by restriction, matching, statistical methods)

Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Appendix Table E6. ROB for RCTs evaluating PET with SPECT

	Mullani 2000	Patel 2019
Methodological Principle		
Random sequence generation†	Unclear	Yes
Statement of Concealed allocation†	Unclear	Yes
Analysis according to random assignment†	Yes	Yes
Independent or blinded outcome assessment	No	Yes
Patients comparable at baseline on key CAD risk factors	No	Yes
Prespecified threshold or definition for a positive test	No	Yes
Attrition (≤ 20% overall)	Yes	Yes
Attrition ≤ 10% difference between groups	Yes	Yes
Comparable followup time or accounting for time at risk	Unclear	Yes
Controlling for possible confounding‡	Yes	Yes
Full reporting on pre-specified outcomes	Yes	Yes
Overall Quality Rating	**Poor**	**Good**

Appendix Table E7. ROB for the prospective observational study evaluating CCTA with FFR versus any NIT and versus ICA

	Suspected CAD
	Douglas 2015, 2016 PLATFORM
Methodological Principle	
Independent or blinded outcome assessment	Yes
Patients comparable at baseline on key CAD risk factors	No
Prespecified threshold or definition for a positive test	Yes
Attrition (≤ 20% overall)	Yes
Attrition (≤ 10% difference between groups)	Yes
Comparable followup time or accounting for time at risk	Yes
Controlling for possible confounding*	Yes
Full reporting on pre-specified outcomes	Yes
Overall Quality Rating	**Good**

CAD = coronary artery disease; CCTA = coronary computed tomography; FFR = fractional flow reserve; ICA = invasive coronary angiography; NIT = noninvasive testing.
*Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g., by restriction, matching, statistical methods)
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Appendix Table E8. ROB for reliability studies

Study (year)	Patient spectrum	Methods description	Blinded performance	Risk of Bias
Williams (2017)	Yes	Yes	Yes	Good quality
Lehman (2009)	Yes	Yes	Yes	Good quality
Rinehart (2010)	Yes	Yes	Yes	Good quality
Ghaemian (2020)	Yes	Yes	No	Moderate quality
Collet (2018)	Yes	Yes	Yes	Good quality
Ferro (2007)	Yes	Yes	Yes	Good quality
Gaibazzi (2010)	Yes	Yes	Yes	Good quality
Hernandez-Gonzalez (2015)	Yes	Yes	No	Moderate quality
Hoffman (2012)	Yes	No	No	Poor quality
Gueret (2013)	Yes	Yes	Yes	Good quality
Cury (2015)	Yes	Yes	Yes	Good quality
Gaibazzzi (2013)	Yes	Yes	Yes	Good quality
Butler (2007)	Yes	Yes	Yes	Good quality
Khan (2017)	Unclear	Yes	No	Poor quality

Appendix Table E9. ROB for economic studies

Question	Points Possible	Karady 2020	Min 2017	Powell 2012	Preist 2012	Goehler 2020	Agus 2016	Bertoldi 2016	Gurunathan 2020	Lee 2015	Lorenzoni 2019	Jarfari 2020
1. Was the study objective presented in a clear, specific, and measurable manner?	7	7	7	7	7	7	0	7	7	7	7	7
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	0	4	4	0	0	4	4	0	4	4	4
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	8	8	8	0	0	8	0	8	8	0	8	0
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	1	1	1	1	1	1	1	0	1	1	1
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis	9	9	9	0	9	9	9	9	0	9	0	0

Question	Points Possible	Karady 2020	Min 2017	Powell 2012	Preist 2012	Goehler 2020	Agus 2016	Bertoldi 2016	Gurunathan 2020	Lee 2015	Lorenzoni 2019	Jarfari 2020
to cover a range of assumptions?												
6. Was incremental analysis performed between alternatives for resources and costs?	6	6	6	6	6	6	6	6	0	6	6	6
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	5	5	5	5	5	5	5	5	5	5	5
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	7	7	0	0	7	0	7	0	0	0	0
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit	8	8	8	8	8	8	8	8	8	0	8	0

Question	Points Possible	Karady 2020	Min 2017	Powell 2012	Preist 2012	Goehler 2020	Agus 2016	Bertoldi 2016	Gurunathan 2020	Lee 2015	Lorenzoni 2019	Jarfari 2020
costs clearly described?												
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	6	6	6	0	6	6	6	0	0	6	6	0
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	7	7	7	7	7	0	7	0	7	7	7
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear,	8	8	8	8	8	8	8	8	8	8	8	8

Question	Points Possible	Karady 2020	Min 2017	Powell 2012	Preist 2012	Goehler 2020	Agus 2016	Bertoldi 2016	Gurunathan 2020	Lee 2015	Lorenzoni 2019	Jarfari 2020
transparent manner?												
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	7	7	7	7	7	0	7	0	7	7	7
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	0	0	8	0	0	6	6	6	6	6	6
15. Were the conclusions/recommendations of the study justified and based on the study results?	8	8	8	8	8	8	8	8	8	8	8	8
16. Was there a statement disclosing the source of funding for the study?	3	3	3	0	3	3	3	3	0	3	3	3
Total Points	100	90	94	69	75	90	64	94	50	77	84	62

APPENDIX F. Data Abstraction of Included Studies Evaluating CCTA

Appendix Table F1. Data abstraction for CCTA vs. any functional testing: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
Suspected CAD					
PROMISE trial Douglas, 2015 Douglas, 2014 (protocol) Ladapo, 2016 Lu, 2017 Hoffman, 2017 Mark, 2016 Pagidipati, 2016 (subgroup analysis) Pagidipati, 2019 (subgroup analysis) Litwin, 2019 (subgroup analysis) Sharma, 2017 (subgroup analysis)	Population: Suspected CAD Setting: Outpatient, non-emergent from cardiology, radiology, primary care, urgent care, and anesthesiology departments Inclusion: ● New or worsening chest pain syndrome or equivalent symptoms suspicious for clinically significant CAD. ● No prior cardiac evaluation for this episode of symptoms. ● Planned noninvasive testing for diagnosis. ● Men ≥55 years and women ≥65 years. ● If age in men 45 to 54 years or women 50 to 64 years, then must have increased probability of CAD due to ≥1 of the following risk factors: - Diabetes mellitus requiring medical treatment;	**A: CCTA (64-slice or better MDCT) (n=4996)** ● 93.80% (4686/4996) underwent CCTA as first test - 91.9% (4589/4996) underwent CCTA - 1.9% (97/4996) underwent CACS only ● 6.20% (310/4996) did not undergo CCTA as first test - 3.1% (154/4996) underwent other test as first test - 0.2% (9/4996) underwent catheterization - 2.1% (104/4996) underwent nuclear stress imaging - 0.5% (27/4996) underwent stress ECHO - 0.3% (14/4996) underwent exercise ECG - 3.1% (156/4996) did not undergo test Stressor: N/A Contrast: Iodinated contrast Protocol: - A contrast-enhanced CCTA was performed as the initial test	All patients or A vs. B Pre-test risk assessment: low risk (≤30%): 37.6% (3755/9986) intermediate risk (31-70%): 57.6% (5750/9986) high risk (>70%): 4.8% (481/9986) Pre-test probability of CAD: low risk (<10%): 2.5% (250/10,003) intermediate risk (10-90%): 92.6% (9258/10,003) high risk (>90%): 4.9% (495/10,003)	A vs. B Subgroup: None N randomized: 10,003 Mean age (SD): 60.7 (8.3) vs. 60.9 (8.3) years Female: 51.9% vs. 53.4% Race: -White: 82.8% vs. 84.5% -Black: 11.3% vs. 10.6% -Asian: 2.8% vs. 2.3% -Other/Unknown: 3.1% vs. 2.6% Ethnicity -Hispanic: 7.9% vs. 7.5% Chest pain: 73.6% vs. 71.9% -Typical angina (%): 11.8% vs. 11.5% -Atypical angina (%): 77.5% vs. 77.9% -Nonanginal pain (%): 10.7% vs. 10.6% Dyspnea on exertion: 14.3% vs. 15.5% Prior MI: 0% vs. 0% Prior revascularization: 0% vs. 0%	60 days, then at 6-month intervals after randomization for a minimum of 1 year Median follow-up: 25 months (IQR 18 to 34 months) (Follow-up at 60 days could be assessed either a telephone call or a clinic visit, after which subjects were contacted centrally by interviewers.) % followed at 12 months: 93.5% (9350/10003)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
Sharma, 2019 (subgroup analysis) Lowenstern, 2020 (subgroup analysis) RCT (Multi-center; 193 sites) US and Canada Government	- Peripheral arterial disease, defined as documented peripheral arterial stenosis ≥50%, treated medically or invasively; - Cerebrovascular disease (stroke), defined as documented carotid stenosis ≥50%, treated medically or invasively; - Ongoing tobacco use; - Hypertension. - Abnormal ankle-brachia index, defined as <0.9; and - Hyperlipidemia. ● Serum creatinine ≤1.5 mG/dL within the past 90 days. ● Negative urine/serum pregnancy test result for female subjects of childbearing potential. Exclusion: ● Diagnosed or suspected ACS requiring hospitalization or urgent or emergent testing; elevated troponin or CK-MB; outpatients who have completed a rule-out ACS protocol are eligible provided they have 2 sets of negative	- 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 - The results of all tests were provided to the care team in the usual manner for that testing laboratory and the local physician continued to direct care of the subject, making all subsequent clinical decisions (e.g., need for further evaluation or admission) based upon his or her cumulative clinical assessment of the subject, including noninvasive test findings Definition of positive test: - Positive: ≥70% stenosis in either the left anterior descending (LAD), proximal LAD, left circumflex (LCS), or right coronary artery (RCA), or a ≥50% stenosis in the left main coronary artery. - Negative (normal): no vessel is positive and 4 of 5 specific criteria are met (see PROMISE supplemental table S3 for details) - Indeterminate: no vessel is positive but criteria for negative test result not met (see PROMISE supplemental table S3 for details)	Mean (SD) combined Diamond and Forrester and Coronary Artery Surgery Study risk score/pretest likelihood of obstructive CAD: 53.4% (21.4%) vs. 53.2% (21.4%)	Known CAD: 0% vs. 0% Family history of CAD: 32.63% vs. 31.6% Chest pain frequency: NR Hypertension: 65% vs. 65% Hyperlipidemia (%): 67.4% vs. 67.9% Diabetes: 21.3% vs. 21.5% Peripheral arterial or cerebrovascular disease: 5.3% vs. 5.8% Current or past tobacco use: 50.7% vs. 51.4% Regular exercise: 51.3% vs. 51.2% BMI ≥25: 83% vs. 83% Mean BMI: 30.5 vs. 30.5 History of depression: 19.6% vs. 21.6%, p<0.05	

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	biomarkers and a nondiagnostic or normal ECG. ● Hemodynamically or clinically unstable condition (systolic blood pressure [BP]<90 mm Hg, severe atrial or ventricular arrhythmias, or persistent resting chest pain felt to be ischemic despite adequate therapy). ● Known CAD with clinical history of MI, percutaneous coronary intervention, coronary artery bypass graft, or any angiographic evidence of CAD ≥50% lesion in a major epicardia vessel. ● Any invasive coronary angiography or noninvasive anatomical or functional cardiovascular test for detection of CAD, including CCTA and ExECG, within the previous 12 month (±30 days); prior resting ECG and/or resting echo do not constitute an exclusion to participation. ● Known significant congenital, valvular (greater than or equal to moderate) or cardiomyopathic process	**B: Any functional testing (n=5007)** ● 93.71% (4692/5007) underwent functional test as first test - 63.09% (3159/5007) underwent nuclear stress imaging - 21.09% (1056/5007) underwent stress echo - 9.53% (477/5007) underwent exercise ECG ● 6.29% (315/5007) did not undergo functional test as first test - 1.3% (67/5007) underwent other test as first test - 0.4% (20/5007) underwent catheterization - 0.9% (47/5007) underwent CTA or CAC scoring - 4.9% (246/5007) did not undergo test - 0.04% (2/5007) underwent test before randomization Stressor: NR Contrast: NR Protocol: - The preselected functional test was performed as the initial test (MPI, stress echo, or ExECG) - Sample protocols were provided for all modalities; sites were allowed to use their own acquisition protocols as long as			

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	(hypertrophic cardiomyopathy or reduced systolic left ventricular [LV] function [LV ejection fraction <40%]) that could explain cardiac symptoms. ● Contraindication to a CCTA, including, but not limited to: - Allergy to iodinated contrast agent, or - Pregnancy. ● Any other contraindications that would preclud performing a CCTA per local site practice, such as ≥1 of the following: - Inability to receive ß-blockers if heart rate is >65 beats/min; - Agatson score >800; - Body mass index >40 kg/m^2; and - Cardiac arrhythmia.	they fell within national standard-of-care guidelines - The results of all tests were provided to the care team in the usual manner for that testing laboratory and the local physician continued to direct care of the subject, making all subsequent clinical decisions (e.g., need for further evaluation or admission) based upon his or her cumulative clinical assessment of the subject, including noninvasive test findings Definition of positive test: Stress nuclear imaging: -Positive: reversible perfusion defect (inducible ischemia) or mixed defect (infarct and ischemia) during stress in at least one of the following territories: septal/anterior/apical, lateral, or inferior/posterior. -Negative (normal): no area is positive and 2 of 3 specific criteria are met (see PROMISE supplemental table S3 for details) -Indeterminate: no vessel is positive but criteria for negative test result not met (see PROMISE supplemental table S3 for details) Stress ECHO			

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
		-Positive: reversible wall motion abnormality or mixed abnormality during stress in at least one of the following territories: septal/anterior/apical, lateral, or inferior/posterior. -Negative (normal): no area is positive and 1 of 6 specific criteria are met (see PROMISE supplemental table S3 for details) -Indeterminate: no vessel is positive but criteria for negative test result not met (see PROMISE supplemental table S3 for details) Exercise ECG -Positive: significant ST-segment changes consistent with ischemia. -Negative (normal): no evidence of ischemia, or borderline or indeterminate in terms of changes meeting criteria for ischemia -Indeterminate: noninterpretable			
Suspected ACS					
Chang, 2008 RCT (Single center) South Korea Funding NR	Population: Suspected ACS; Stable acute chest pain Setting: ED Inclusion:	**A. CCTA (MDCT) (n=133)†** Stressor: NA Contrast: Iomeprol (80 mL Iomeron 400; Bracco, Milan, Italy) Protocol: CT scanning (64-slice) immediately after randomization, with results available immediately; subsequent tests and treatments left to discretion of treating MD after CT results made available	A vs. B‡ Low: 37.6% (50/133) vs. 36.8% (49/133)§ Intermediate: 41.4% (55/133) vs. 42.1% (56/133)	A vs. B Subgroup: None N randomized: 268 Mean age (SD): 57 (14) vs. 58 (14) years Female: 39% vs. 38% Race: NR	1 month: 99.2% (266/268) Crossover: NR

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)

	Acute chest pain syndrome; age > 18 years.
	
	Exclusion:
	Very high or very low pre-test probability for ACS; constant arrhythmia; hemodynamic or clinical instability; history of allergy to radio-contrast dye; documented renal insufficiency; pregnancy or women of childbearing age who are not using contraception; contraindication to ß blockade; recent (<1 month) diagnostic work-up for coronary disease
		Definition of positive test: >50% stenosis ("significant stenosis")
		
		B. Any functional testing (n=133)†
		Evidence-based diagnostic workup including serial ECGs, and cardiac biomarkers. Subsequent diagnostic tests, other than MDCT, and treatments were at discretion of the treating medical doctor.
		- 50% (n=67) underwent stress testing:
		  - exercise treadmill (39%, n=52)
		  - MPI (8%, n=11)
		  - stress echocardiography (3%, n=4).
			High: 21.1% (28/133) vs. 21.1% (28/133)	Chest pain: 100% vs. 100%
				- Typical angina: NR
				- Atypical angina: NR
				- Nonspecific chest pain: NR
				Dyspnea: NR
				Prior MI: NR
				Prior revascularization: NR
				Known CAD: 12% vs. 17%
				Chest pain frequency: NR
				Hypertension: 46% vs. 41%
				Hyperlipidemia: 29% vs.25%
				Diabetes: 16% vs. 19%
				Current smoking: 17% vs. 23%
				
				Low vs. Intermediate vs. High pretest probability
				Mean age (SD): 53 (15) vs. 59 (13) vs. 62 (12) years; p<0.001
				Female: 38% vs. 42% vs. 32%
				Chest pain: 100% vs. 100% vs. 100%
				- Typical angina: NR	

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
				- Atypical angina: NR - Nonspecific chest pain: 100% vs. 100% vs. NR Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: 7% vs. 14% vs. 29% Chest pain frequency: NR Hypertension: 34% vs. 49% vs. 54%; p = 0.001 Hyperlipidemia: 20% vs. 30% vs 34%; p = 0.049 Diabetes: 11% vs. 20% vs. 23%; p = 0.041 Current smoking: 19% vs. 20% vs. 23%	
CATCH trial Linde, 2013, 2015, & 2014 RCT (Single center) Denmark Non-profit	Population: Suspected ACS; Acute chest pain Setting: Outpatient (Hospitalized and discharged within 24 hours; randomization occurred after discharge) Inclusion:	**A. CCTA (320 slice MDCT) (n=299 randomized; 285 analyzed)** Stressor: NA Contrast: NR Protocol: Upon hospital admission patients underwent ECG and troponin testing and were discharged within 24 hours. Following hospital discharge, patients were contacted to participate in the study. Those agreeing underwent CCTA within	A vs. B According to Diamond and Forrester Low: 21.4% (61/285) vs. 21.3% (62/291) Intermediate: 69.1% (197/285)	A vs. B Subgroup: None N randomized: 600 Mean age (SD): 56 (12) vs. 55 (12) years Female: 44% vs. 42% Race: NR Chest pain: - Typical angina: 12% vs. 12%	120 days (4 months): 96% (576/600) Long-term followup, median (IQR) duration: 18.7 (16.8 to 20.1) months: 100% for clinical events Crossover: - 4.6% (13/285) of patients in group A did

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	Normal or non-diagnostic electrocardiogram (ECG), normal troponins, clinical indication for further non-invasive, outpatient, cardiac evaluation, based on the risk factor profile, symptom description and an overall clinical assessment Exclusion: New diagnostic ECG changes with ST-segment elevation or depression >0.5 mm or T-wave inversion >4 mm in ≥2 contiguous leads, increased levels of plasma-troponins, age <18 years, women of childbearing age not using approved contraception, patients with geographical residence or mental or physical conditions that could complicate follow-up, known allergy to iodinated contrast agents, serum creatinine >130 mg/l, abnormal chest x-ray or blood test tests that could explain the chest pain, former	seven days of initial admittance. Identification of significant CAD led to a referral for ICA. In patients with coronary stenoses between 50 and 70% or a non-diagnostic CCTA, a further evaluation plan was determined based on an integrated evaluation of coronary lesion location (proximal versus distal), stress test results and indices of clinical presentation. Test that determined the treatment strategy during index evaluation CCTA alone: 82% (233/285) CCTA + functional test: 14% (39/285) Functional test alone: 5% (13/285) Definition of positive test: - Stenosis >50% in the left main artery, and ≥70% in other large coronary arteries (left anterior descending artery and diagonals, circumflex artery and marginals and right coronary artery) ("significant stenosis") - Stenoses between 50% and 70% or a non-diagnostic CCTA, went on to further evaluation that involved an integrated evaluation of coronary lesion	vs. 69.1% (201/291) High: 9.5% (27/285) vs. 9.6% (28/291)	- Atypical angina: 39% vs. 40% - Non-anginal chest pain: 49% vs. 49% Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: 15% vs. 12% Chest pain frequency: NR Hypertension: 36% vs. 47%, p=0.008 Hyperlipidemia: 41% vs. 35% Diabetes: 12% vs. 10% Current or ex-smoker: 15% vs. 12% Family history of heart disease: 24% vs. 26% Median BMI: 28 vs. 28	not undergo CCTA (no specific reasons as to why were provided). At least 2 of these patients underwent bicycle treadmill testing. - 2.4% (7/291) of patients in group B did not undergo any functional testing.

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	coronary artery bypass graft (CABG) operation	location (proximal versus distal), stress test results and indices of clinical presentation. - Diameter stenoses b50% were considered non-significant **B. Any functional testing (n=301 randomized; 291 analyzed)** Stressor: Dipyridamole (for SPECT only) Contrast: NR Protocol: Patients underwent an exercise bicycle test unless they were unable to reach at least 85% of the expected heart rate, in which case they were referred for stress SPECT Test that determined the treatment strategy during index evaluation Exercise ECG alone: 76% (221/291) SPECT alone: 22% (63/291) Clinical assessment only without any functional test: 2% (7/291) Definition of positive test: An exercise bicycle test with signs of ischemia led to referral for ICA, and patients with reversible perfusion defects on SPECT or non-diagnostic test results were referred for ICA.			

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
ROMICAT-II trial Hoffman, 2012 Truong, 2013 (subgroup analysis) Truong, 2016 (subgroup analysis) Reinhardt, 2018 (subgroup analysis) RCT (Multi-center; 9 sites) US Government	Population: Symptoms suggestive of acute coronary syndromes Setting: Emergency department Inclusion: Chest pain (or anginal equivalent) of at least 5 minutes' duration within 24 hours before presentation; age 40 to 74 years; sinus rhythm; warranted further risk stratification to rule out acute coronary syndromes. Exclusion: History of known coronary artery disease; new diagnostic ischemic changes on initial ECG; initial troponin level > 99th percentile of local assay; impaired renal function (creatinine >1.5 mg/dL [132.6 µmol/L]); hemodynamic or clinical instability; known allergy to an iodinated contrast agent; BMI > 40; currently symptomatic asthma.	**A: CCTA (n=501)** - CCTA not performed in 5.6% (28/501) Stressor: NA Contrast: NR Protocol: All test results were provided to emergency department physicians in real time. Additional care was not mandated by the study protocol in either group. The discharge diagnosis was based on the local physicians' assessment. Definition of positive test: NR **B: Any functional testing or no testing (n=499)** Patients received either no testing or functional testing such as exercise ECG, stress radionuclide imaging, or stress echocardiography - SPECT: 25% (124/499) - Stress echo: 20% (102/499) - ETT: 29% (147/499) - No testing at index visit: 22% (109/499) - Unknown: 3% (17/499)	A vs. B Number of cardiovascular risk factors: 0 or 1: 36% vs. 38% 2 or 3: 54% vs. 52% ≥ 4: 10% vs. 10%	A vs. B Subgroup: None N randomized: 1000 Mean age (SD): 54 vs. 54 years Female: 48% vs. 46% Race: - Black: 28% vs. 28% - White: 66% vs. 66% - Asian: 4% vs. 23% - Other: 2% vs. 4% Ethnicity: - Non-Hispanic: 87% vs. 85% Chest pain: 100% vs. 100% -Typical angina: 89% vs. 91% -Atypical angina: 11% vs. 9% Dyspnea: 1% vs. 2% Prior MI: NR Prior revascularization: NR Known CAD: NR Chest pain frequency: NR Hypertension: 54% vs. 54% Hyperlipidemia: 46% vs. 45%	28 days: 98.7% (987/1000) (Patients assessed by telephone for occurrence of MACE and health care utilization)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
				Diabetes: 17% vs. 17% Current or former smoker: 50% vs. 49% Family history of premature CAD: 27% vs. 27% Mean BMI: 29.4 vs. 29.1	
ACRIN-PA trial Litt, 2012 Hollander, 2016 RCT (Multi-center; 5 sites) US Government and Non-profit	Population: Symptoms suggestive of acute coronary syndromes Setting: Emergency department Inclusion: Chest pain, signs or symptoms consistent with possible acute coronary syndrome; age ≥ 30 years; ECG without evidence of acute ischemia; initial TIMI score of 0 to 2 Exclusion: Symptoms clearly noncardiac; coexisting condition necessitating admission regardless of acute coronary syndrome; normal findings on CCTA or invasive angiography in the previous year; or contraindications to CCTA	**A: CCTA (≥64 slice MDCT) (n=908)**** - Underwent CCTA: 84% (767/908) - Underwent stress testing 14% (124/908) - No imaging or provocative testing: 9% (80/908) [Most common reason for not receiving CCTA was because of persistent elevation of the heart rate (27%)] Stressor: NA Contrast: NR Protocol: Reported results included a calcium score and both cardiac and noncardiac findings. After CCTA, a second measurement of troponin levels was obtained 90 to 180 minutes after arrival in the emergency department. Local interpretations of CT studies were used for "real time" clinical decision making. Definition of positive test:	A vs. B All patients low to intermediate risk as stated by authors Thrombolysis in Myocardial Infarction risk score: 0: 51% vs. 51% 1: 36% vs. 36% ≥ 2: 13% vs. 13%	A vs. B Subgroup: Low to intermediate risk N randomized: 1,392 Mean age (SD): 49 vs. 50 years Female: 51% vs. 56% Race/Ethnicity: -Black: 58% vs. 62% -White: 40% vs. 35% -Asian: 1% vs. 2% -American Indian or Alaska Native: 1% vs. 1% -Native Hawaiian or Pacific Islander: <1% vs. 0% -Unknown: 1% vs. 1% -Hispanic or Latino: 2% vs. 2% Chest pain: 100% vs. 100% Dyspnea: NR Prior MI: 1% vs. 1%	(Patients assessed by telephone for MI, CV hospitalization, revascularization, cardiac testing, seen by cardiologist, and medicines. Medical record review if reported hospitalization or adverse effects) 30 days: 98.4% (1370/1392) 12 months: 92.3% (1285/1392)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
		≥ 50% coronary artery stenosis Positive stress test: Test shows ST-segment elevation or depression of more than 1 mm or reversible ischemia on imaging **B: Any functional testing or no testing (n=462)**** Stressor: Graded exercise or pharmacologic stress according to local institution's protocol. Contrast: NR Protocol: Physician decided which tests to perform, if any. - Underwent stress testing with imaging: 56% (258/462) - Stress testing without imaging: 2% (9/462) - Underwent CCTA: 6% (26/462) - No testing: 36% (167/462) Definition of positive test: ≥ 50% coronary artery stenosis Positive stress test: Test shows ST-segment elevation or depression of more than 1 mm or reversible ischemia on imaging		Prior revascularization: NR Known CAD: NR Chest pain frequency: NR Hypertension: 51% vs. 50% Hypercholesterolemia: 27% vs. 26% Diabetes: 14% vs. 14% Current smoking: 32% vs. 34% Heart failure: 1% vs. 2% Family history of CAD: 30% vs. 27%	
BEACON trial Dedic, 2016	Population: Acute chest pain or symptoms suggestive of acute coronary syndrome	The initial standard clinical work-up at the ED included a 12-lead electrocardiogram and blood analysis for all patients. If the initial	A vs. B Grace risk score	A vs. B	30 days: 98% (490/500)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
RCT (Multi-center; 7 sites) Netherlands University funded	Setting: Emergency department Inclusion: Patients with chest pain, signs or symptoms consistent with possible acute coronary syndrome, 30 years of age and older, with a maximum age of 75 years for men and 80 years for women Exclusion: Symptoms clearly of noncardiac origin or a coexisting condition already necessitated hospital admission. History of known CAD, clinical need for urgent invasive coronary angiography (ICA), clinical instability, serum troponin levels above 3 times the upper limit of the 99th percentile of the local assay, impaired renal function (estimated glomerular filtration rate <60% of age-corrected normal values), pregnancy, known allergy to	clinical work-up did not reveal either an evident acute coronary syndrome or an evident noncardiac cause, eligible and consenting patients were randomized. In both groups, hs-troponins were available. Participants from both groups who were discharged from the ED, without prolonged observation (<8 h) were asked to return to the outpatient clinic after 48 to 72 h for repeated measurement of cardiac biomarkers and a 12-lead ECG. This study focused on initial ED management without protocol-mandated medical management during the remaining clinical course. **A: CCTA (≥64 slice MDCT) (n=250)** - Underwent CCTA: 97% (243/250) - Did not undergo CCTA: 3% (7/250) Stressor: NA Contrast: NR Protocol: CCTA was performed after the initial clinical work-up. Treating physicians were informed directly at the point of care regarding the result of CCTA and imaging-based recommendations	Low: 84% (211/250) vs. 83% (208/250) Intermediate: 12% (31/250) vs. 16% (39/250) High: 3% (8/250) vs. 1% (3/250)	Subgroup: Mostly low risk according to Grace risk score (84%) N randomized: 500 Mean age (SD): 55 (8) vs. 53 (9) years Female: 49% vs. 45% Race: NR Chest pain: 100% vs. 100% Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: NR Chest pain frequency: NR Hypertension: - >150 mm Hg systolic or >90 mm Hg diastolic: 17% vs. 17% - Treated: 26% vs. 28% Hyperlipidemia: NR Diabetes: NR Current smoking: 37% vs. 31% History of peripheral artery disease: 3% (8/250) vs. 3% (7/250) History of transient ischemic	

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	an iodinated contrast agent, severe arrhythmias, and body mass index >40 kg/m2.	were issued. Final medical management decisions were left to the treating physicians. Definition of positive test: ≥50% coronary artery stenosis **B: Any functional testing** - Underwent CCTA: 2% (6/250) Stressor: NR Contrast: NR Protocol: Attending physicians made clinical decisions regarding further testing, including repeated cardiac marker assessment, hospital admission, noninvasive tests, and referral to ICA, according to current guidelines. Definition of positive test: NR		attack/cerebrovascular accident: 7% vs. 7%	
Miller, 2011 RCT (Single center) US Government	Population: Acute chest pain patients with suspected CAD Setting: Emergency department Inclusion: Chest pain consistent with ischemia within previous 12 hours; ≥ 35 years old; low to intermediate risk of MI and／or complications; Normal or indeterminate ECG; negative cardiac biomarkers; required	**A: CCTA (64 slice MDCT) (n=30)** Stressor: NA Contrast: type NR Protocol: A nonenhanced ECG-gated scan was acquired for a coronary artery calcium (CAC) score followed by a contrast enhanced CCTA. Treatment decisions were made based on test results. Patients with no identified CAD were discharged home, patients with non-obstructive CAD were prescribed Statins, aspirin and/or Plavix, blood pressure medication, and were referred for	A vs. B Low to intermediate risk for myocardial infarction and/or complications (according to Goldman risk)	A vs. B Subgroup: Low to intermediate risk N randomized: 60 Mean age (SD): 51 vs. 51 years Female: 57% vs. 43% Race: - African American: 47% vs. 47% - Asian: 0% vs. 1% - White: 23% vs. 13% - Hispanic: 30% vs. 37%	90 days: 100% (60/60) (Patients assessed by telephone interview. Medical record review for in-network resource utilization. Out-of-network resource use predicted with utilization and cost-chest pain (UAC-CP) participant self-reporting.)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	admission at time of risk stratification per ED physician; required cardiology consult in ED; able to hold breath ≥ 15 seconds (required for CCTA); heart rate <70 beats ⁄ min (initially or after beta-blocker) Exclusion: Contraindication to iodinated and ⁄ or beta-blocking drugs; creatinine ≥ 1.2 mg⁄ dL; pregnant or suspected; vulnerable population (e.g., incarcerated); documented CAD (by prior ICA, CCTA, PCI, or CABG); cardiac imaging within the past year that excluded CAD; clinically unstable; ECG diagnostic of ischemia or MI; atrial fibrillation or markedly irregular rhythm; contrast administered within previous 24 hours; unable to have 18-gauge antecubital IV access; medical care home out-of-network (to control for follow-up care).	further testing. Patients with obstructive CAD or a nondiagnostic scan were referred immediately for further testing. Definition of positive test: Positive (obstructive): > 50% coronary artery stenosis. Positive (nonobstructive): presence of plaque without stenosis > 50% **B: Any functional testing (n=30)** Stressor: NA Contrast: type NR Protocol: All patients (including those in Group A) were treated according to an algorithm that included 12-lead ECG, coronary biomarkers, and continuous ECG monitoring. All subjects received aspirin, sublingual nitroglycerin, and cardiology consultation. If indicated, additional testing included exercise stress test, nuclear perfusion testing, stress echocardiography, transesophageal echocardiography, and/or interventional catheterization. Definition of positive test: NR		Chest pain: 100% vs. 100% -Typical angina: NR -Atypical angina: NR Dyspnea: NR Prior MI: 0% vs. 0% Prior revascularization: 0% vs. 0% Known CAD: 0% vs. 0% Chest pain frequency: NR Hypertension: NR Hyperlipidemia: NR Diabetes: NR Current smoking: NR	

ACS = acute coronary syndrome, BMI = body mass index, CABG = coronary artery bypass graft, CAC = coronary artery calcium, CACS = coronary artery calcium scoring, CAD = coronary artery disease, CCTA = coronary computed tomography, CT = computed tomography, ECG = electrocardiogram, ECHO = echocardiography, ED = emergency department, ExECG = exercise electrocardiogram, f/u = follow-up, ICA = invasive coronary angiogram, IQR = inter-quartile range, IV = intravenous, MDCT = multi-detector computed tomography, mg = milligram, MI = myocardial infarction, mL = milliliter, mm = millimeter, MPI = myocardial perfusion imaging, NA = not applicable, NR = not reported, PCI = percutaneous coronary intervention, RCT = randomized control trial, SD = standard deviation, SPECT = single photon emission computed tomography.

* p-values non-significant unless reported

† 2 patients discharged themselves against medical advice and were excluded from analysis. Unclear to which group they belonged initially.

‡ Baseline risk Based on "Tatum et al. Comprehensive strategy for the evaluation and triage of the chest pain patient. Ann Emerg Med 1997;29:116-25"

§ Reported as MDCT, n = 51 and SOC, n = 49, with total as n = 99. Presumed correction for MDCT, n = 50.

** It appears that patients could undergo more than one test at index visit though this is not explicitly stated.

Appendix Table F2. Data abstraction for CCTA vs. any functional testing: Efficacy Outcomes

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Suspected CAD							
PROMISE trial CCTA vs. functional testing Subgroup analyses: Y Formal test for interaction: Y	**Disposition** NR **Test Results, % (n/N)** From index publication (Douglas 2015) Abnormal (positive for CAD): 10.7% (517/4840) vs. 11.7% (556/4759), p=0.1178 Normal: NR Indeterminate: NR *Test results not stratified by specific types of functional testing* From Ladapo 2016 Positive: 11.1% (553/4996) vs.	**All-cause mortality (component of primary composite endpoint) , % (n/N)** 12 months 0.4% (21/4996) vs. 0.6% (32/5007), RR 0.66 (95% CI 0.38 to 1.14), p=0.1318 Median 25 months follow-up 1.5% (74/4996) vs. 1.5% (75/5007), RR 0.99 (95% CI 0.72	**Nonfatal MI (component of primary composite endpoint) , % (n/N)** 12 months 0.4% (18/4996) vs. 0.5% (27/5007), p=NR Median 25 months follow-up 0.6% (30/4996) vs. 0.8% (40/5007), p=NR	**Revascularization any, % (n/N)** 60 days 6.1% (304/4996) vs. 3.1% (154/5007), p=NR 90 days 6.2% (311/4996) vs. 3.2% (158/5007), RR 1.97 (95% CI 1.63 to 2.38). p<0.0001 **Revascularization (CABG only), % (n/N)** 90 days 1.4% (72/4996) vs. 0.75% (38/5007), RR 1.9 (95% CI 1.3 to 2.3), p=0.0011 **Proportion of patients who initiated a preventive**	**Invasive Coronary Angiography, % (n/N)** 60 days 12.0% (600/4996) vs. 8.1% (403/5007), p=NR 90 days 12.2% (609/4996) vs. 8.1% (406/5007), RR 1.50 (95% CI 1.33 to 1.69), p<0.0001 - Cardiac catheterization test results of no obstructive CAD: 27.9% (170/609) vs. 52.5% (213/406), p=NR	**Primary composite end point (includes death from any cause, nonfatal MI, hospitalization for unstable angina, or major procedural complication), % (n/N)**[*] 12 months: 1.8% (88/4996) vs. 1.8% (91/5007), adjusted HR 0.94 95% CI 0.70 to 1.26), p=0.682 Median 25 months follow-up 3.3% (164/4996) vs. 3.0% (151/5007), adjusted HR 1.04 (95% CI 0.83 to 1.29), p=0.75	**Hospitalization for unstable angina (component of composite endpoint), % (n/N)** 12 months: 1% (49/4996) vs. 0.7% (34/5007), p=NR Median 25 months follow-up: 1.2% (61/4996) vs. 0.8% (41/5007), p=NR **Duke Activity Status Index (DASI) (scale 0-58.2; higher=increased QOL, Mean (SD)** Baseline 25.5 (17.7) vs. 25.5 (17.8), p= NR 6 months 30.4 (17.8) vs. 30.5 (17.7), MD –0.1 (95% CI –1.0 to 0.8), p=NR 12 months

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	11.6% (582/5007), p=NR Negative: 82.0% (4096/4996) vs. 82.6% (4136/5007), p=NR Indeterminate: 3.8% (188/4996) vs. 0.8% (39/5007), p=NR Incomplete: 0.1% (3/4996) vs. 0.0% (2/5007), p=NR	to 1.36), p=0.9450 **Cardiac mortality** NR		**medication, and who were not initially using the medication at baseline, % (n's and N's NR)** By the 60-day visit Aspirin: 11.8% vs. 7.8%, p<0.0001 Statin: 12.7% vs. 6.2%, p<0.0001 Beta-blocker: 8.1% vs. 5.3%, p<0.0001 Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker: 3.6% vs. 3.3%, p=NS **Proportion of patients who discontinued a preventive medication, and who were initially using the medication at**		**Secondary composite end point (primary composite end point plus catheterization showing no obstructive CAD) , % (n/N)*** 12 months 5.1% (256/4996) vs. 5.9% (296/5007), adjusted HR 0.85 (95% CI 0.72 to 1.00), p=0.055 Median 25 months follow-up 6.6% (332/4996) vs. 7.1% (353/5007) (adjusted HR 0.91 (95% CI 0.78 to 1.06) (p=0.22) **Death or nonfatal MI, % (n/N)*** 12 months 7.8% (39/4996) vs. 11.4% (57/5007),	29.9 (17.8) vs. 30.7 (17.7), MD –0.6 (95% CI –1.6 to 0.3), p=NR 24 months 31.2 (17.4) vs. 31.1 (17.4), MD 0.1 (95% CI –0.9 to 1.1), p=NR **Seattle Angina Questionnaire (SAQ) Angina Frequency Scale (higher=less frequent angina), Mean (SD)** Baseline 78.5 (16.9) vs. 78.2 (17.2), p=NR 6 months 93.1 (12.1) vs. 92.9 (13.1), MD 0.2 (95% CI –0.4 to 0.9), p=NR 12 months 94.0 (11.8) vs. 94.1 (11.6), MD –0.1 (95% CI –0.7 to 0.5), p=NR 24 months 95.0 (11.2) vs. 95.1 (10.8), MD –0.2 (95% CI –0.8 to 0.4), p=NR

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				baseline, % (n's and N's NR) By the 60-day visit Aspirin: 2.7% vs. 2.9% Statin: 2.2% vs. 2.1% Beta-blocker: 2.3% vs. 1.9% Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker: 2.5% vs. 2.52% **Proportion of patients who continued a preventive medication, and who were initially using the medication at baseline,% (n's and N's NR)** By the 60-day visit Aspirin: 43.1% vs. 42.1%		adjusted HR 0.66 (95% CI 0.44 to 1.00), p=0.049 Median 25 months follow-up 2.1% (104/4996) vs. 2.2% (112/5007), adjusted HR 0.88 (95% CI 0.67 to 1.15), p=0.35 **Death, nonfatal MI or hospitalization for unstable angina, % (n/N)*** 12 months 1.7% (86/4996) vs. 1.8% (88/5007), adjusted HR 0.95 (95% CI 0.71 to 1.28), p=0.736 Median 25 months follow-up 3.2% (162/4996) vs. 3.0% (148/5007), adjusted HR 1.04	**Seattle Angina Questionnaire (SAQ) QOL scale (scale 0-100; higher=increased QOL), Mean (SD)** Baseline 56.3 (22.7) vs. 56.0 (22.8), p=NR 6 months 80.4 (19.7) vs. 80.6 (20.1), MD –0.2 (95% CI –1.2 to 0.9), p=NR 12 months 81.7 (19.1) vs. 82.4 (18.8), MD –0.5 (95% CI –1.5 to 0.6), p=NR 24 months 82.8 (18.8) vs. 83.0 (18.6), MD –0.2 (95% CI –1.3 to 0.9), p=NR **Seattle Angina Questionnaire (SAQ) Physical Limitation Score (scale 0-100; higher=increased physical functioning), Mean (SD)** Baseline

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				Statin: 44.6% vs. 43.7% Beta-blocker: 22.9% vs. 23.8% Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker: 41.8% vs. 41.8% **Proportion of patients who never used a preventive medication, and who were not initially using the medication at baseline, % (n's and N's NR)** <u>By the 60-day visit</u> Aspirin: 42.4% vs. 47.2% Statin: 40.5% vs. 47.9% Beta-blocker: 66.7% vs. 69.0%		(95% CI 0.84 to 1.31), p=0.70	78.6 (21.5) vs. 79.1 (22.0), p=NR <u>6 months</u> 93.6 (14.6) vs. 94.0 (13.9), MD –0.4 (95% CI –1.2 to 0.4), p=NR <u>12 months</u> 94.3 (14.1) vs. 95.0 (12.4), MD –0.8 (95% CI –1.6 to -0.0), p=NR <u>24 months</u> 95.3 (12.1) vs. 94.8 (13.2), MD –0.7 (95% CI –1.5 to 0.1), p=NR **Seattle Angina Questionnaire (SAQ) Angina Stability (scale 0-100; lower scores indicate more frequent angina, higher scores less frequent angina, a score of 50 indicates no change in angina frequency at most strenuous level of activity), Mean (SD)** <u>Baseline</u>

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker: 52% vs. 52.4% **Overall use of medication adjusted for patients' demographic and clinical characteristics and physician specialty, % (%, n's and N's NR)** <u>60-days</u> Aspirin: adj. OR 1.54 (95% CI 1.34 to 1.76), p<0.0001 Statin: adj. OR 2.03 (95% CI 1.76 to 2.35) p<0.0001 Beta-blocker: adj. OR 1.32 (95% CI 1.13 to 1.54), p<0.0001			44.2 (23.9) vs. 43.8 (25.2), p=NR <u>6 months</u> 54.4 (16.5) vs. 53.7 (15.5), MD 0.7 (95% CI –0.1 to 1.6), p=NR <u>12 months</u> 52.2 (14.5) vs. 52.8 (14.8), MD –0.7 (95% CI –1.5 to 0.1), p=NR <u>24 months</u> 95.0 (12.9) vs. 51.3 (12.0), MD –0.1 (95% CI –0.8 to 0.6), p=NR **Proportion of patients with moderate to severe depression on PHQ-9 (score ≥15), % (n/N)** <u>Baseline</u> 19.2% (2899/2982) vs. 18.2% (2895/3003), p=0.34 <u>6 months</u> 14.8% (2669/2982) vs. 13.1% (2550/3003), p=0.07 <u>12 months</u>

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker: adj. OR 1.04 (95% CI 0.87 to 1.25), p=NS **Prevalence of medication use among patients adjusting for Initial Test Results and Revascularization, % (n's and N's NR)** <u>60 days</u> Aspirin: 54.8% vs. 49.7% adj. OR 1.43 (95% CI 1.24 to 1.65), p<0.001 Statin: 57.1% vs. 49.6% adj. OR 2.08 (95% CI 1.78 to 2.43) Beta-blocker: 30.9% vs. 28.9% adj. OR 1.17 (95%			13% (2585/2982) vs. 11.5% (2392/3003), p=0.12 <u>24 months</u> 11.5% (2238/2982) vs. 10.7% (2001/3003), p=0.45 **Depression PHQ-9 (scale 0-27, higher=greater depression), Mean (SD)** <u>Baseline</u> 5.6 (5.2) vs. 5.4 (5.4), p=NR <u>6 months</u> 4.3 (5.0) vs. 4.5 (4.9), MD 0.1 (95% CI –0.2 to 0.3), p=NR <u>12 months</u> 4.2 (4.9) vs. 3.9 (4.6), MD 0.2 (95% CI –0.0 to 0.5), p=NR <u>24 months</u> 3.8 (4.7) vs. 3.7 (4.5), MD 0.1 (95% CI –0.2 to 0.4), p=NR

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				CI 0.99 to 1.38), p=0.064 Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker: adj. OR 1.01 (95% CI 0.83 to 1.22), p=0.935			**EQ-5D Health Status Index, Mean (SD)** Baseline 72.0 (19.5) vs. 72.4 (19.8), p=NR 6 months 75.1 (18.9) vs. 75.0 (20.0), MD -0.0 (-0.9 to 0.9), p=NR 12 months 74.7 (20.3) vs. 74.9 (21.2), MD -0.7 (-1.6 to 0.2), p=NR 24 months 73.2 (24.1) vs. 72.7 (24.9), MD 0.1 (-0.9 to 1.1), p=NR **Treatment Satisfaction** 6 months 89.4 (18.6) vs. 88.2 (20.9), MD 1.4 (95% CI 0.3 to 2.4), p=NR 12 months 89.4 (18.4) vs. 88.7 (20.0), MD 1.0 (95% CI –0.1 to 2.1), p=NR 24 months

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							89.8 (17.6) vs. 89.4 (18.6), MD 1.0 (95% CI –0.1 to 2.1), p=NR
Suspected ACS							
Chang, 2008 CCTA vs. functional testing Subgroup analyses: Y Formal test for interaction: N	**Disposition, % (n/N)** Discharged from ED**:** 59% (78/133) vs. 50% (66/133), p=NR Admitted to hospital: 41% (55/133) vs. 50% (67/133), p=0.14 **Test result, % (n/N)** Diagnosed with ACS: 29% (39/133) vs. 29% (39/133), p=NR Stenosis >50%: 0.75% (1/133) vs. NR Perfusion abnormality	**All-cause mortality, % (n/N)** 30 days 0% (0/133) vs. 0% (0/133), p=NR **Cardiac mortality, % (n/N)** 30 days 0% (0/133) vs. 0% (0/133), p=NR	**Nonfatal MI, % (n/N)** 30 days 0% (0/133) vs. 0.75% (1/133), p=NR	**Revascularization, % (n/N)** Index visit 20% (26/133) vs. 21% (28/133), p=NR **Necessary admission for ACS**: Index visit 29% (39/133) vs. 29% (39/133); p=1.0 ○ Admission for NSTEMI: 8% (11/133) vs. 11% (15/133), p=NR ○ Admission for Unstable Angina: 25% (28/113) vs. 18% (24/133), p=NR	**Invasive Coronary Angiography, % (n/N)** Index visit 35% (47/133) vs. 43% (57/133), p=NR **Stress testing, % (n/N)** Index visit 10% (13/133) vs. 50% (67/133)[†] Test modality among SOC patients receiving stress testing in ER (n = 67): ○ Exercise treadmill: 78%% (52/67) ○ Myocardial stress perfusion imaging: 16% (11/67)	NR	**ED length of stay (hours), median (IQR)** 4.8 (3.1 to 7.6) vs. 4.6 (3.2 to 7.1), p=0.98 ○ Intermediate risk: 4.5 (3.2 to 7.7) vs. 6.0 (4.1 to 8.9), p=0.055 ○ Low and high-risk: no difference **Hospital length of stay (hours), median (IQR)[‡]** 7.1 (4.1 to 97.5) vs. 26.6 (4.8 to 131.1), p=0.049 ○ High risk: 94.7 (56.9 to 159.9) vs. 155.2 (95.5 to 266.1), p=0.036) ○ Low and intermediate risk: no difference

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	without significant stenosis: 0.75% (1/133) vs. NR			**Unnecessary admissions[§]:** Index visit 5% (6/133) vs. 16% (21/133); p=0.007[**]	○ Stress ECHO: 6% (4/67)		
CATCH trial Linde 2013, 2015 CCTA vs. functional testing Subgroup analyses: Y Formal test for interaction: N	**Disposition, % (n/N)** All patients had already been discharged prior to randomization and returned for testing only **Test Results, % (n/N)** **CCTA test results for group A** Severe stenosis (>70%): 11% (31/272) No significant CAD: 74% (202/272)	**All-cause mortality, % (n/N)** 120 days NR Median 18.7 month followup 0.7% (2/285) vs. 0% (0/291) **Cardiac mortality (component of composite endpoint), % (n/N)** 120 days 0% (0/285)	**Acute MI (component of composite endpoint), % (n/N)** 120 days 0% (0/285) vs. 1% (3/291) Median 18.7 month followup 0.7% (2/285) vs. 2% (7/291), p=0.18 **STEMI, % (n/N)**	**Revascularization performed (PCI or CABG) (component of composite endpoint), % (n/N)** 120 days 10% (29/285) vs. 4% (12/291), p=0.005 Median 18.7 month followup 0% (0/285) vs. 0.7% (2/291), p=1.0 **Revascularization performed (PCI only), % (n/N)** 120 days	**Referred for Invasive Coronary Angiography, % (n/N)** 120 days 17% (49/285) vs. 12% (36/291), p=0.10 [††] *[14% (7/49) vs. 6% (2/36) underwent fractional flow reserve due to an intermediate diameter stenosis]* ICA test results - Normal ICA: 29% (14/49) vs. 64% (23/36), p=0.002 **Post-index repeated elective diagnostic**	**Proportion of patients experiencing a MACE (includes cardiac death, myocardial infarction, unstable angina pectoris, and revascularization), % (n/N)** 120 days NR Median 18.7 month followup 2% (5/285) vs. 5% (14/291), HR 0.36 (95% CI 0.16 to 0.95), p=0.04	**Unstable angina pectoris (component of composite endpoint), % (n/N)** 120 days 0.4% (1/285) vs. 0% (0/291), p=NR Median 18.7 month followup 1% (3/285) vs. 2% (5/291), p=0.72 **Readmitted for chest pain (component of composite endpoint), % (n/N)** 120 days 2% (7/285) vs. 4% (11/291), p=NR **Probability of event free survival, % (n/N)[‡‡]**

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	- No atherosclerosis: 52% (106/202) - Maximal stenosis <25%: 22% (44/202) - Maximal stenosis of 25% to 49%: 26% (52/202) Borderline stenosis (50% to 69%): 9% (25/272) Non-diagnostic CCTA: 5% (14/272) *No CCTA performed in 13 of the 285 patients in group A* **Exercise ECG/SPECT results for group B** Ischemia: 10% (29/284)	vs. 0.3% (1/291) Median 18.7 month followup 0% (0/285) vs. 0.3% (1/291), p=1.0	Median 18.7 month followup 0% (0/285) vs. 0.7% (2/291), p=NR **NSTEMI, % (n/N)** Median 18.7 month followup 0.7% (2/285) vs. 1.7% (5/291), p=NR	9% (25/285) vs. 3% (8/291), p=0.002 Median 18.7 month followup NR **Revascularization performed (CABG only), % (n/N)** 120 days 1.4% (4/285) vs. 1.4% (4/291), p=1.0 Median 18.7 month followup NR **Referral to medical treatment only (not further described), % (n/N)** 120 days 2% (6/285) vs. 0.3% (1/291), p=NR	**testing during follow-up, % (n/N)** - Bicycle exercise ECG: 0.7% (2/285) vs. 1.4% (4/291), p=0.69 - SPECT: 1.4% (4/285) vs. 1.7% (5/291), p=1.0 - CCTA: 0.4% (1/285) vs. 0% (0/291), p=0.49 - ICA: 2.5% (7/285) vs. 1% (3/291), p=0.87	**Proportion of patients experiencing a primary composite endpoint (includes MACE plus readmission for chest pain), % (n/N)** 120 days NR Median 18.7 month followup 11% (30/285) vs. 16% (47/291), HR 0.62 (95% CI 0.40 to 0.98), p=0.04, adj. HR 0.57 (95% CI 0.36 to 0.91), p=0.02[§§]	120 days 97.5% vs. 95%, Log-rank p=0.10

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	No Ischemia: 85% (240/284) Non diagnostic test: 5% (15/284) *No ECG or SPECT performed in 7 of the 291 patients in group B* **Functional Test Results, % (n/N)**[***] Type of test received: - Exercise bicycle test: 75% (213/285) vs. 76% (221/291) - SPECT stress: 22% (64/285) vs. 22% (63/291) - No functional stress performed: 3% (8/285) vs. 2% (7/291) [†††] (*Results for each of the above tests*			**Medication prescribed after index visit, % (n/N)** - Aspirin: 47% (134/285) vs. 36% (106/291), p=0.01 - Statin: 44% (125/285) vs. 38% (110/291), p=0.15 - Beta-blocker: 24% (67/285) vs. 19% (54/291), p=0.15 - Calcium-blocker: 18% (52/285) vs. 11% (33/291), p=0.03 - Nitrates: 17% (49/285) vs. 11% (33/291), p=0.016 - Diuretics: 21% (61/285) vs. 14% (41/291), p=0.02 - ACE-inhibitors/AT2-antagonist: 27% (76/285) vs. 24% (69/291), p=0.44			

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	are reported below) <u>Positive for ischemia on exercise bicycle test</u>: 8% (16/213) vs. 6% (14/221) - Positive based on ECG only: 44% (7/16) vs. 36% (5/14) - Positive based on ECG and chest pain: 31% (5/16) vs. 57% (8/14) - Positive based on chest pain only: 25% (4/16) vs. 7% (1/14) <u>Non-diagnostic exercise bicycle test</u>: 9% (19/213) vs. 7% (15/221) <u>Normal exercise bicycle test</u>: 84% (178/213) vs. 87% (192/221)			- Platelet inhibitors: 14% (40/285) vs. 6% (18/291), p=0.002			

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	Reversable defects identified on SPECT: 22% (14/64) vs. 24% (15/63) No reversable defects identified on SPECT: 78% (50/64) vs. 76% (48/63)						
ROMICAT-II trial Hoffman 2012 CCTA vs. functional testing or no testing Subgroup analyses: Y Formal test for interaction: Y	**Disposition, % (n/N)** - Direct discharge from emergency department: 47% (233/501) vs. 12% (62/499) - Admission to observation unit: 30% (153/501) vs. 60% (301/499) - Admission to hospital: 21% (107/501) vs. 25% (125/499) - Left against medical advice:	**All-cause mortality , % (n/N)** 28 days 0% (0/501) vs. 0% (0/499)	**Myocardial infarction (part of MACE composite outcome) , % (n/N)** Index 1.6% (8/501) vs. 3.0% (15/499), p=NR 28 days 0.2% (1/501) vs. 0.4% (4/499), p=NR	**Received Any Revascularization, % (n/N)** At index visit 6% (29/501) vs. 4% (18/499), p=NR At index plus 28 day followup visit 6% (32/501) vs. 4% (21/499), p=NR **Received Percutaneous Coronary Intervention, % (n/N)** At index visit	**Received Invasive Coronary Angiography, % (n/N)** At index visit 11% (54/501) vs. 7% (36/499), p=0.06 At index plus 28 day followup visit 12% (59/501) vs. 8% (40/499), p=0.06 **Additional functional testing performed, % (n/N)** At index visit - SPECT: 10% (50/501) vs. NA	**Major adverse cardiovascular event (including death, myocardial infarction, unstable angina, or urgent coronary revascularization), % (n/N)** 28 days 0.4% (2/501) vs. 1.2% (6/499), p=0.18	**Unstable angina pectoris requiring percutaneous coronary intervention (part of MACE composite outcome) , % (n/N)** 28 days 0.2% (1/501) vs. 0.4% (2/499), p=NR **Hospital length of stay, mean (SD)** All patients in intention-to-treat analysis 23.2 (37.0) vs. 30.8 (28.0) hours, p<0.001 Patients with final diagnosis other than

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	2% (8/501) vs. 2% (11/499) p<0.001 across all **Test results, % (n/N)** NR			5% (24/501) vs. 3% (14/499), p=0.14 At index plus 28 day followup visit 5% (27/501) vs. 3% (17/499), p=0.16 **Received Coronary Artery Bypass Graft, % (n/N)** At index visit 1% (5/501) vs. 1% (4/499), p=0.99 At index plus 28 day followup visit 1% (5/501) vs. 1% (4/499), p=0.99	- Stress echo: 4% (20/501) vs. NA - ETT: 2% (12/501) vs. NA At index plus 28 day followup visit - SPECT: 10% (50/501) vs. 2% (9/499) - Stress echo: 4% (20/501) vs. 0% (0/499) - ETT: 2% (12/501) vs. 3% (15/499) **Total number of diagnostic tests performed (including index test), % (n/N)** 28 day follow-up No testing: 2% (9/501) vs. 18% (89/499) 1 test: 72% (359/501) vs. 70% (350/499) ≥2 tests: 27% (133/501) vs. 12% (60/499) p<0.001		acute coronary syndrome 17.2 (24.6) vs. 27.2 (19.5) hours, p<0.001 Patients with final diagnosis of acute coronary syndrome 86.3 (72.3) vs. 83.8 (61.3) hours, p=0.87 **Follow-up for recurrent chest pain, % (n/N)** within 28 days - Repeat visit to the ED: 2.8% (14/501) vs. 3.8% (19/499) - Repeat hospitalization: 1.4% (7/501) vs. 1.4% (7/499) p=0.38 **Discharge diagnosis after index emergency department visit or hospitalization, % (n/N)** Normal (diagnosis of non-cardiac chest pain): 85% (426/501) vs. 89% (445/499), p=NR

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							Abnormal: 15% (75/501) vs. 11% (54/499), p=NR - Noncoronary cardiac pain: 1% (7/501) vs. 2% (8/499) , p=NR - Coronary chest pain not associated with acute coronary syndrome: 5% (25/501) vs. 3% (14/499), p=NR - Acute coronary syndrome: 9% (43/501) vs. 6% (32/499), p=NR
ACRIN-PA trial Litt, 2012 Hollander, 2016 CCTA vs. functional testing Subgroup analyses: N	**Disposition, % (n/N)** Index visit Discharged: 50% (450/908) vs. 23% (105/462), difference 26.8% (95% CI 21.4% vs. 32.2%), p=NR Admission or observation: 50% (458/908) vs. 77% (357/462), p=NR	**All-cause mortality, % (n/N)** Index visit 0% (0/908) vs. 0% (0/908) 30 days 0% (0/908) vs. 0% (0/908) 12 months	**Acute myocardial infarction, % (n/N)** Index visit 1.0% (9/908) vs. 0.9% (4/462), difference 0.1% (95% CI -5.5% to 5.7%), p=NR 30 days	**Revascularization, % (n/N)** Index visit 3% (23/908) vs. 1% (4/462), difference 1.7% (-3.9% to 7.3%), p=NR 30 days 3% (24/893) vs. 1% (6/457), difference 1.4%	**Total number of diagnostic tests used (includes testing completed at index evaluation), % (n/N)**‡‡‡ From randomization to 30 days CCTA: 85% (767/905) vs. 6% (27/454) Stress test without imaging: 1% (11/886) vs. 2% (10/454)	**Major adverse cardiovascular event (including cardiac death and Acute myocardial infarction), % (n/N)** Index Visit NR 30 days NR 12 months 1.4% (12/870) vs. 1.1% (5/443),	**Hospital length of stay (hours), Median (IQR)** Index visit - Across all patients: 18.0 (7.6 to 27.2) vs. 24.8 (19.2 to 30.5), p<0.001 - Across patients with a negative test: 12.3 (7.0 to 24.3) vs. 24.7 (19.7 to 29.6), p<0.001

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	Test results for tests performed at index visit, % (n/N) Index visit For CCTA - Normal: 83.4% (640/767) vs. 76.9% (20/26), p=NR - Abnormal (≥50% stenosis): 10.4% (80/767) vs. 15.4% (4/26), p=NR - Indeterminate or nondiagnostic: 6% (47/767) vs. 8% (2/26), p=NR For Stress testing (with or without imaging) - Normal: 79.0% (98/124) vs. 91.8% (245/267), p=NR - Abnormal: 12.1% (15/124)	0.2 (2/907) vs. 0.7% (3/461), difference –0.4% (95% CI –6.0% to 5.2%), p=NR **Cardiac Mortality, % (n/N)** Index visit 0% (0/908) vs. 0% (0/908) 30 days 0% (0/908) vs. 0% (0/908) 12 months 0.1% (1/906) vs. 0.1% (0/460), difference 0.1% (95% CI –5.5% to 5.7%), p=NR	1.10% (10/908) vs. 1.08% (5/462), difference 0.02% (95% CI -5.6% to 5.7%), p=NR 12 months 1.3% (11/870) vs. 1.1% (5/444), difference 0.1% (95% CI –5.6 to 5.9), p=NR **Acute coronary syndrome without acute myocardial infarction, % (n/N)** Index visit 3% (28/908) vs. 2% (7/462),	(95% CI -4.3% to 7.0%), p=NR 12 months 2.9% (25/872) vs. 1.6% (7/444), difference 1.3% (95% CI –4.4 to 7.0), p=NR	Stress test with imaging: 16% (140/891) vs. 58% (264/458) Resting echocardiogram: 6% (55/888) vs. 7% (30/454), difference -0.4% (95% CI -6.1% to 5.2%) From ED or hospital discharge through 12 months CCTA: 0.2% (2/822) vs. 1% (5/422), difference –0.9% (95% CI –6.8% to 4.9%), p=NR Stress test without imaging: 2% (19/827) vs. 0.5% (2/424), difference 1.8% (–4.0% to 7.7%), p=NR Stress test with imaging: 7% (60/824) vs. 8% (33/422), difference –0.5% (95% CI –6.4% to 5.3%), p=NR	difference 0.3% (95% CI –5.5% to 6.0%)	**Hospital admission after index visit, %(n/N)** From ED or hospital discharge to 30 days 3% (28/889) vs. 2% (11/456), difference 0.7% (95% CI -4.95% to 6.4%), p=NR From ED or hospital discharge through 12 months 16% (137/843) vs. 17% (74/432), difference –0.9% (95% CI –6.7 to 4.9), p=NR **Emergency department revisit, % (n/N)** From ED or hospital discharge to 30 days 8% (71/885) vs. 8% (34/452); 0.5% (95% CI -5.2 to 6.2), p=NR From ED or hospital discharge through 12 months 36% (305/852) vs. 38% (166/438), difference –

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	vs. 6.0% (16/267), p=NR - Indeterminate or nondiagnostic: 9% (11/124) vs. 2% (6/267), p=NR For ICA - Normal: 24.3% (9/37) vs. 55.6% (10/18), p=NR - Abnormal: 75.7% (28/37) vs. 44.4% (8/18), p=NR - Indeterminate or nondiagnostic: NR **Diagnosis of coronary disease, % (n/N)** Index visit 9% (82/908) vs. 3% (16/462), difference 5.6% (0% to 11.2%, p=NR		difference 1.6% (95% CI -4.0% to 7.2%), p=NR 30 days NR 12 months NR		Resting echocardiogram: 6% (49/824) vs. 6% (26/425), difference –0.2% (95% CI –6.0 to 5.7), p=NR **Cardiac Catheterization, % (n/N)** At index visit 4% (37/908) vs. 4% (18/462), p=NR From ED or hospital discharge to 30 days 0.9% (8/887) vs. 4% (1/454), p=NR From ED or hospital discharge through 12 months 3% (24/829) vs. 3% (13/432), difference –0.2% (95% CI –6.0% to 5.7%), p=NR **Medication use, % (n/N)** Prescribed at index visit		2.1% (95% CI –7.9% to 3.7%), p=NR **Cardiologist office visit, % (n/N)** From ED or hospital discharge to 30 days 7% (62/878) vs. 4% (17/451), difference 3.3% (95% CI –2.4% to 9.0%), p=NR From ED or hospital discharge through 12 months 18% (148/821) vs. 13% (53/423), difference 5.5% (95% CI –0.4% to 11.3%)

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
					- Aspirin: 26% (233/908) vs. 24% (110/462), difference 1.9% (95% CI -3.8% to 7.5%), p=NR - Thienopyridines: 3% (24/908) vs. 2% (7/462), difference 1.1% (95% CI -4.5% to 6.7%), p=NR - Statins: 17% (153/908) vs. 16% (75/462), difference 0.6% (95% CI -5.0% to 6.2%), p=NR <u>Being used at 30 day followup</u> - Aspirin: 22% (196/884) vs. 25% (113/452), difference -2.8% (95% CI -8.5% to 2.8%), p=NR - Thienopyridines: 4% (31/884) vs. 2% (8/452), difference 1.7% (95% CI -3.9% to 7.4%), p=NR - Statins: 14% (120/885) vs. 11% (48/452), difference		

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
					2.9 % (95% CI -2.7% to 8.6%), p=NR <u>Being used at 12 month followup</u> - Aspirin: 34% (283/843) vs. 37% (159/433), difference –3.2% (95% CI –8.9% to 2.7%), p=NR - Thienopyridines: 4% (37/830) vs. 3% (12/430), difference 1.7% (95% CI –4.2% to 7.5%) - Statins: 24% (198/835) vs. 18% (78/431), difference 5.6% (95% CI –0.2% to 11.4%), p=NR		
BEACON trial Dedic 2016 CCTA vs. functional testing Subgroup analyses: N	**Disposition, % (n/N)** - Discharged from the emergency department: 65% (159/250) vs. 59% (144/250), p=0.16 - Admitted to hospital: 35%	**All-cause mortality, % (n/N)** <u>30 days</u> 0.4% (1/250) vs. 0% (0/250), p=1.0	**MI, any, % (n/N)** <u>Index (at discharge)</u> 6% (14/250) vs. 6% (14/250), p=NR	**Revascularization, % (n/N)** <u>30 days</u> 9% (22/250) vs. 7% (17/250), p=0.40 - Percutaneous coronary intervention: 9%	**Received Invasive Coronary Angiography, % (n/N)** <u>Index visit</u> 14% (34/250) vs. 0% (25/250), p=0.21	**MACE (including death, acute coronary syndrome, and coronary revascularization), %(n/N)** <u>30 days</u>	**Occurrence of undetected acute coronary syndrome after index visit, % (n/N)** <u>30 days</u> 0.5% (1/250) vs. 1% (3/250), p=0.62

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	(86/250) vs. 41% (101/250) p=0.16 **Test results for CCTA arm only, % (n/N)** - No detectable CAD: 42% (106/250) - Atherosclerotic plaque with <50% luminal narrowing: 28% (71/250) - 50% to 70% luminal narrowing in 1 or more coronary Arteries: 14% (35/250) - ≥70% luminal narrowing in 1 or more coronary arteries: 5% (13/250) - Non-diagnostic: 7% (18/250) *(No test results were*			(22/250) vs. 5% (13/250), p=NR - Coronary artery bypass graft surgery: 0% (0/250) vs. 2% (4/250)	<u>30 days (includes tests done at index visit)</u> 17% (41/250) vs. 13% (31/250), p=0.20 **Diagnostic testing utilization, % (n/N)** <u>At Index visit</u> - Exercise electrocardiography: 9% (23/250) vs. 53% (130/250), p<0.01 - SPECT: 1% (2/250) vs. 3% (7/250), p=0.18 - Cardiac magnetic resonance imaging: 0.4% (1/250) vs. 0.4% (1/250), p=1.0 <u>30 days</u> - Exercise electrocardiography: 13% (32/250) vs. 58% (143/250), p<0.01 - SPECT: 1% (2/250) vs. 7% (16/250), p<0.01	10% (25/250) vs. 9% (21/250), p=0.54	**Emergency department revisit, % (n/N)** <u>30 days</u> 5% (13/250) vs. 8% (19/250), p=0.27 **Repeat hospital admission, % (n/N)** <u>30 days</u> 3% (7/250) vs. 6% (14/250), p=0.12 **Hospital length of stay (hours), Median (IQR)** <u>Index visit</u> 6.3 (4.8 to 11.1) vs. 6.3 (4.5 to 25.5), p=0.80

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	provided for patients randomized to group B) **Diagnosis of Acute Coronary Syndrome, % (n/N)** <u>At hospital discharge</u> 9% (22/250) vs. 7% (17/250), p=0.40 - Unstable angina: 3% (8/250) vs. 1% (3/250), p=NR - Myocardial infarction: 6% (14/250) vs. 6% (14/250), p=NR				- Cardiac magnetic resonance imaging: 0.4% (1/250) vs. 1% (3/250), p=0.62 <u>After index visit</u> - CCTA: 0.4% (1/250) vs. 1% (2/250), p=1.0 **Additional diagnostic testing in an outpatient setting after index ED visit (total of Exercise electrocardiography, SPECT, Cardiac magnetic resonance, and CCTA), % (n/N)** <u>After index visit</u> 4% (10/250) vs. 11% (26/250), p<0.01		
Miller 2011 CCTA vs. functional testing Subgroup analyses: N	**Disposition, % (n/N)** - Admitted to hospital: 20% (6/30) vs. 53% (16/30), p=0.007	NR	NR	**Proportion of patients receiving stents, % (n/N)** <u>90 days</u> 3% (1/30) vs. 0% (0/30), p=1.0	**Proportion of patients requiring additional testing, % (n/N)** <u>90 days</u> 37% (11/30) vs. 57% (17/30), p=0.121		**Proportion of patients requiring an emergency department revisit, % (n/N)** <u>90 days</u> - None: 83% (25/30) vs. 67% (20/30)

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	Test results. % (n/N) NR **Final diagnosis, % (n/N)** <u>90 days</u> - CAD present: 64% (18/28) vs. 17% (1/6) - CAD not present: 36% (10/28) vs. 83% (5/6) p=0.032 [No diagnosis made: 7% (2/30) vs. 80% (24/30), p<0.001] Gfdh				**Specific type of additional testing required by patients, % (n/N)** <u>90 days</u> - Transthoracic echocardiogram: 7% (2/30) vs. 17% (5/30), p=0.424 - Stress echocardiography: 10% (3/30) vs. 3% (1/30), p=0.612 - Exercise stress test: 7% (2/30) vs. 20% (6/30), p= 0.612 - Transesophageal echocardiogram: 0% (0/30) vs. 0% (0/30), p=0.278 - Coronary catheterization: 13% (4/30) vs. 13% (4/30), p=1.0		- ≥ 1: 17% (5/30) vs. 33% (10/30) p=0.136 **Number of emergency department revisits, mean (SD)** <u>90 days</u> 2.0 (2.2) vs. 3.3 (4.0) **Number of hospital days, Mean (SD)** <u>90 days</u> 3.0 (3.1) vs. 3.7 (3.9), p=0.704 **Proportion of participants hospitalized at least once during 90-day follow-up (admitted/readmitted), % (n/N)** <u>90 days</u> 20% (6/30) vs. 53% (16/30), p=0.007

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							Proportion of patients with ≥1 return visit to cardiology, % (n/N) 90 days 105 (3/30) vs. 17% (5/30), p=0.706

ACE =Angiotensin-converting enzyme, ACS = acute coronary syndrome, CABG = coronary artery bypass graft, CAD = coronary artery disease, CCTA = coronary computed tomography, CI = confidence interval, ECHO = echocardiography, ED = emergency department, EQ-5D = European Quality of Life Five Dimension, ETT = exercise treadmill test, HR = hazard ratio, ICA = invasive coronary angiogram, IQR = inter-quartile range, MACE = major adverse cardiovascular events, MD = mean difference, MDCT = multi-detector computed tomography, MI = myocardial infarction, N = no, NA = not applicable, NR = not reported, NS = not significant, NSTEMI = Non-ST-Segment Elevation Myocardial Infarction, OR = odds ratio, PCI = percutaneous coronary intervention, PHQ = patient health questionnaire, QOL = quality of life, RR = risk ratio, SD = standard deviation, SOC = standard of care, SPECT = single photon emission computed tomography, STEMI = ST-Segment Elevation Myocardial Infarction, vs. = versus, Y = yes.

* All hazard ratios were adjusted for age, sex, CAD risk equivalent (history of either diabetes, peripheral arterial disease, or cerebrovascular disease), and the pre-specification of the intended functional test if randomized to the functional testing arm.

† No MDCT group patients received stress testing in ED; 10% (13/133) has additional stress testing either as inpatient or outpatient, with no detail about which setting. All reported stress testing in SOC patients occurred in the ED

‡ Time from ED presentation to hospital discharge

§ Unnecessary admission: Admission for a medical condition that should not have led to hospitalization, which was ultimately confirmed to be neither ACS nor any medical conditions requiring hospitalization (determined by consensus of the outcome panel).

** Number for all controls reported in one table as n = 21; however, sum of values reported in another table for each of three pre-test probability levels n = 20.

†† Adjusting for hypertension or other

risk factors in a multivariate regression model did not change the outcome.

‡‡ Events were cardiac death, myocardial infarction, unstable angina pectoris, revascularization, and readmission for chest pain.

§§ Adjusted for baseline hypertension and hyperlipidemia

*** In this trial, all patients underwent both CCTA and a functional test (bicycle exercise-ECG and/or MPI) in addition to a clinical evaluation by an experienced cardiologist. However, in the standard care group CCTA results remained blinded for patients and clinical staff, and in the CCTA-guided group clinical decision making was based on CCTA-findings overruling stress test results.

††† Due to logistical reasons, a functional stress test was not performed in 8 patients in the CCTA-guided group and 2 patients in the standard care group. In addition, 3 patients in the standard care group had myocardial infarction before the test was performed, and one was considered to be at high risk-risk on the scheduled test-day, and therefore referred directly for invasive coronary angiography.

‡‡‡ Calculation of the between-group difference is not applicable, since testing disparities were dictated by the study design.

Appendix Table F3. Data abstraction for CCTA vs. any functional testing: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Suspected CAD			
PROMISE trial CCTA vs. functional testing	**Proportion of all as tested patients experiencing a major* complication, % (n/N)[†]** <u>Within 24 hours after index test</u> CCTA vs. any functional test: 0% (0/4633) vs. 0% (0/4837), p>0.05 **Proportion of all as randomized patients experiencing a major[‡] complications, % (n/N)[§]** <u>Within 72 hours of index test</u> CCTA vs. any functional test 0.1% (4/4996) vs. 0.1% (5/5007), p=NR Stroke: 0.02% (1/4996) vs. 0.04% (2/5007), p=NR Major bleeding: 0.06% (3/4996) vs. 0.06% (3/5007), p=NR Anaphylaxis: 0% (0/4996) vs. 0% (0/5007), p=NR Renal failure requiring dialysis: 0% (0/4996) vs. 0% (0/5007), p=NR **Proportion of all as tested patients experiencing any minor‡‡ complication, % (n/N)** <u>Within 24 hours after index test</u> CCTA vs. any functional test: 0.8% (37/4633) vs. 0.6% (27/4837), p=0.15 CCTA vs. Nuclear Stress: 0.8% (37/4633) vs. 0.7% (23/3263), p=NR CCTA vs. Stress Echo: 0.8% (37/4633) vs. 0.3% (3/1083), p=NR	**Proportion of all as tested patients with a potentially significant incidental finding, % (n/N)** <u>On Index test</u> CCTA vs. any functional test: 11.6% (539/4633) vs. 0.7% (34/4837), p<0.001 CCTA vs. Nuclear Stress: 11.6% (539/4633) vs. 0.4% (13/3263), p=NR CCTA vs. Stress Echo: 11.6% (539/4633) vs. 1.9% (21/1083), p=NR NR for exercise electrocardiography	**Cumulative radiation dose among all patients as randomized, Mean (SD) (N=10003; n=4996 vs. 5007)** <u>≤90 days</u> CCTA vs. any functional test: 12.0 (8.5) mSv vs. 10.1 (9.0) mSv, p<0.001 **Stratified by physician's intended functional test before randomization**** CCTA vs. nuclear stress testing: 12.0 (8.4) mSv vs. 14.1 (7.6) mSv, p<0.001 CCTA vs. stress echo: 12.6 (9.0) mSv vs. 1.3 (4.3) mSv, p<0.001 CCTA vs. exercise electrocardiography: 10.4 (7.8) vs. 2.3 (5.4), p<0.001 **Cumulative radiation dose among all patients as tested[††], Mean (SD) (N=9470; n=4633 vs. 4837)** <u>≤90 days</u> CCTA vs. any functional test: 12.5 (8.4) mSv vs. 10.6 (8.9) mSv, p<0.001 **Subgroup intended for nuclear stress testing before randomization[**]** CCTA vs. nuclear stress testing (n=3146 vs. 3203): 13.6 (9.2) vs. 16.2 (7.7), p<0.001 **Cumulative radiation dose among all patients as randomized, Median (IQR) (N=10003; n=4996 vs. 5007)**

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
	CCTA vs. Exercise electrocardiography: 0.8% (37/4633) vs. 0.2% (1/491), p=NR **Type of minor complication occurring during functional testing amongst patients as tested, % (n/N)**[§§] Within 24 hours after index test Nuclear Stress vs. Stress Echo vs. Exercise electrocardiography Hypotension: 0.2% (6/3263) vs. 0.2% (2/1083) vs. 0% (0/491) Stress induced symptoms: 0.1% (4/3263) vs. 0% (0/1083) vs. 0% (0/491) Ventricular tachycardia: 0.2% (5/3263) vs. 0% (0/1083) vs. 0% (0/491) Rapid atrial fibrillation: 0% (0/3263) vs. 0% (0/1083) vs. 0% (0/491) **Type of minor complications occurring during CCTA amongst patients as tested, % (n/N)** Within 24 hours after index test Mild contrast reaction: 0.5% (22/4633) Extravasation of contrast: 0.3% (12/4633) Hemodynamic instability: 0.1% (3/4633) Acute bronchospasm: 0% (0/4633) **Proportion of all as tested patients experiencing hospital admission related to test complication, % (n/N)** Within 24 hours after index test CCTA vs. any functional test: 0% (0/4633) vs. 0.1% (5/4837), p=NR		≤90 days CCTA vs. any functional test: 10.0 (5.6 to 17.2) mSv vs. 11.3 (0.0 to 13.5) mSv, p=NR **Stratified by physician's intended functional test before randomization**[**] Nuclear stress testing: 10.1 (5.7 to 17.1) mSv vs. 12.6 (11.1 to 16.0) mSv, p=NR Stress Echo: 10.6 (5.5 to 18.3) mSv vs. 0.0 (0.0 to 0.0) mSv, p=NR Exercise electrocardiography: 8.5 (4.8 to 15.7) mSv vs. 0.0 (0.0 to 0.0) mSv, p=NR **Cumulative radiation dose among all patients as tested**[††]**, Median (IQR) (N=9470; n=4633 vs. 4837)** ≤90 days CCTA vs. any functional test: 10.3 (6.1 to 17.4) vs. 11.5 (0.0 to 13.8), p=NR **Subgroup intended for nuclear stress testing before randomization**[**] CCTA vs. nuclear stress testing (n=3146 vs. 3203): 11.6 (6.7 to 18.5) vs. 13.1 (11.5 to 19.4), p=NR **Proportion of patients receiving no radiation exposure (these patients are factored into the *as randomized* data above, but not the *as tested* data), % (n values NR)** ≤90 days 4.0% vs. 32.6%, p=NR

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
	CCTA vs. Nuclear Stress: 0% (0/4633) vs. 0.1% (3/3263), p=NR CCTA vs. Stress Echo: 0% (0/4633) vs. 0.1% (1/1083), p=NR CCTA vs. Exercise electrocardiography: 0% (0/491) vs. 0.2% (1/491), p=NR		**Radiation dose for index test only among subgroup intended for nuclear stress testing before randomization** analyzed as tested[††]** **(n=3146 vs. 3203)** Index test Mean (SD): 10.4 (6.6) vs. 14.1 (5.6), p<0.001 Median (IQR): 8.8 (5.3 to 14.6) vs. 12.6 (11.3 to 14.6), p=NR ≤9 mSv, % (n/N): 51.2% (1611/3146) vs. 7.0% (223/3203), p<0.001
Suspected ACS			
Chang, 2008 CCTA vs. functional testing	**Skin rash**: 1.5% (2/133) vs. NR [resolved spontaneously] **Contrast-induced nephropathy:** 0% (0/133) vs. 0% (0/133)	NR	**Radiation exposure, mean (SD)** Index test 12.5 (2.0) mSV vs. NR
CATCH trial CCTA vs. functional testing	NR	NR	**Effective radiation dose for SPECT rest and stress:** 8.2 mSV **Radiation dose for ICA, Median (IQR)**: 6.2 mSV (3.8 to 12.5) **Radiation dose for CCTA+CACS, Median (IQR)** Index test 4.7 (3.8 to 6.0) mSv **Cumulative radiation does (mSv), Median (IQR)**: 6.1 (4.2 to 12.6) vs. 0 (0 to 5.7), p<0.0001

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
ROMICAT-II trial CCTA vs. functional testing or no testing	**Transient increase in the creatinine level without the need for dialysis** Index test 0.2% (1/501) vs. 0% (0/499), p=NR	NR	**Cumulative radiation exposure, Mean (SD) mSv/patient (includes exposure from CCTA, SPECT, and ICA)** 28 days 14.3 (10.9) vs. 5.3 (9.6), p<0.001
ACRIN-PA trial CCTA vs. functional testing	**Bradyarrhythmia** Index test 0.1% (1/908) vs. 0.2% (1/462) (Presumed to be related to medications to control heart rate)	NR	NR
BEACON trial CCTA vs. functional testing	**Minor complications** Index test Any complication: 4% (9/250) vs. 0.4% (1/250), p=NR - Transient increases in creatinine levels: 1% (3/250) vs. 0.4% (1/250), p=NR - Contrast medium extravasation without clinical consequences: 2% (4/250) vs. 0% (0/250), p=NR - Mild medically treated allergic skin reaction: 1% (2/250) vs. 0% (0/250), p=NR	NR	**Cumulative radiation dose (mSv), Mean (SD)** 30 days 7.3 (6.6) mSv vs. 2.6 (6.5) mSv, p=NR
Miller 2011 CCTA vs. functional testing	NR	NR	NR

ACS = acute coronary syndrome, CACS = coronary artery calcium scoring, CAD = coronary artery disease, CCTA = coronary computed tomography, ECHO = echocardiography, ICA = invasive coronary angiogram, IQR = inter-quartile range, mSv = millisieverts, NR = not reported, SD = standard deviation, SPECT = single photon emission computed tomography.

* Major complications were defined as death, renal failure requiring dialysis, or anaphylaxis requiring emergency respiratory and/or circulatory support

† Data abstracted from Lu 2017 Table 2

‡ Major complications were defined as stroke, major bleeding, anaphylaxis, or renal failure requiring dialysis

§ Data abstracted from Douglas 2015 Supplemental Table S5
** Prior to randomization, treating physicians specified which functional test the patient should receive if he or she were randomized to the functional arm, with randomization stratified by this preference.
†† All PROMISE subjects who had functional testing or CTA as their first test were included. Patients who had no test or who had invasive coronary angiography (ICA) as their first test were excluded. Computed tomography (CT) protocols commonly include a non-contrast CT for assessment of coronary artery calcium score before contrast-enhanced CTA to assess coronary artery stenosis. Some sites chose not to proceed with CTA in patients with a high calcium score; these participants were excluded as the radiation dose from calcium score CT alone is substantially lower than for CTA.
‡‡ For CCTA, minor complications included mild intravenous contrast reactions, contrast extravasation, and adverse reactions to nitroglycerin or beta blockers administered during the examination. For functional testing, minor complications included hemodynamic instability or hypotension, arrhythmia, and adverse drug reactions.
§§ The types of minor complications reported for CCTA differed from those reported for the functional tests (except for hospital admission which is reported separately). Therefore, no direct comparisons can be made.

Appendix Table F4. Data abstraction for CCTA vs. Exercise ECG: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
Suspected CAD					
SCOT-HEART trial SCOT-HEART investigators Multi-center (12 sites) Scotland Government and Foundation	Population: Stable suspected angina due to coronary heart disease Setting: Cardiology chest pain clinics Inclusion: Patients aged 18–75 years and referred by a primary-care physician to a dedicated cardiology chest pain clinic with stable suspected angina due to coronary heart disease Exclusion: Inability to undergo CT scanning, renal failure (serum creatinine >250 µmol/L or estimated glomerular filtration rate <30 mL/min), previous recruitment to the trial, major allergy to iodinated contrast media, inability to give informed consent, known pregnancy, and acute coronary syndrome within 3 months	**A: CCTA (64 and 320 slice) + CACS + Exercise ECG (n=2073)** - CCTA: 85.8% (1778/2073) - Exercise ECG only: 14.2% (295/2073) Stressor: NA Contrast: Iodinated contrast Protocol: All patients underwent routine clinic assessment including, if deemed appropriate, symptom-limited exercise electrocardiography with the standard Bruce protocol. Symptoms (typical, atypical, or non-anginal chest pain according to the National Institute for Health and Care Excellence [NICE] definition), diagnosis, investigations, and treatment strategy were documented at the end of the clinic attendance, before randomization. This included categorizing (no, unlikely, probable, or yes) the likelihood of the diagnosis of coronary heart disease and angina due to coronary heart disease and documentation of the need for additional stress imaging, such as stress echocardiography, and	A vs. B Predicted 10-year risk of coronary heart disease according to the ASSIGN score, Mean % (SD) 18% (11%) vs. 17% (12%) Estimated pretest probability (according to NICE 2010) (n=3770) <10%: 11% 10% to 29%: 19% 30% to 59%: 26% 60% to 89%: 25% >90%: 19%	A vs. B Subgroup: None N randomized: 4146 Mean age (SD): 57 (9.7) vs. 57 (9.7) years Female: 44% vs. 44% Race: NR Chest pain: - Typical: 36% vs. 35% - Atypical: 24% vs. 23% - Non-anginal: 40% vs. 41% Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: NR Previous coronary heart disease: 9% vs. 9% Previous cerebrovascular disease: 4% vs. 2% Previous peripheral vascular disease: 2% vs. 1% Chest pain frequency: NR Hypertension: 34% vs. 33% Hyperlipidemia: NR Hypercholesterolaemia:53% vs. 53% Diabetes: 11% vs. 11% Current and former smokers: 53% vs. 53%	6 weeks 5 years Median follow-up for the 2015 publication: 1.7 (range 0.1 to 4.1) years Median follow-up for the 2018 publication: 4.8 (range 3 to 7) years [comprising 20,254 patient-years of follow-up] % followed at 5 years: 98.4% (4080/4146)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
		radionuclide or magnetic resonance myocardial perfusion imaging, and invasive coronary angiography. Definition of positive test: - Obstructive coronary artery disease: a luminal stenosis >70% in one or more major epicardial vessels or >50% in the left main stem - Moderate non-obstructive: 50% to 70% luminal cross-sectional area stenoses - Mild non-obstructive: 10% to 49% luminal cross-sectional area stenoses - Normal: <10% luminal cross-sectional area stenoses **B: Exercise ECG (n=2073)** - Exercise ECG: 99.8% (2070/2073) - CCTA: 0.2% (3/2073) Stressor: Exercise Contrast: NR Protocol: Same as above Definition of positive test: NR			
CAPP trial McKavanagh, 2014	Population: Suspected CAD Setting: Rapid Access Chest Pain Clinics	**A: CCTA (64 slice) + CACS (n=250)** - CCTA+CACS: 98% (246/250) - Other test (not specified): 2% (4/250) Stressor: NA	A vs. B **Diamond and Forrester pretest**	A vs. B Subgroup: None N randomized: 500	3 months, 12 months

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
Multi-center (2 sites) UK, Ireland Government	Inclusion: Present with symptoms of stable chest pain, which is defined as troponin negative without symptoms suggestive of unstable angina. Exclusion: Standard contraindications to both exercise stress test and cardiac CT	Contrast: Ioversal, Optiray 350 mg/mL Protocol: All diagnoses at the clinics were made by the clinicians and considered both the clinical picture and the test result. All further investigations ordered were at the discretion of the clinicians and determined by clinical need. Patients with a CACS score >400 were considered high risk and referred for ICA. Definition of positive test: Coronary diameter stenosis >50% in a major epicardial artery >2 mm was considered significant. Such results were deemed positive and could involve either calcified or non-calcified disease **B: Exercise ECG (n=250)** - Exercise ECG: 98% (245/250) - Other test (not specified): 2% (5/250) Stressor: Treadmill (Bruce protocol) Contrast: NA Protocol: Same as above Definition of positive test: Defined according to previous guidelines (Fox et al. Guidelines or management of stable angina	**likelihood of CAD, % (n/N)** Low-risk (patients estimated to have <30% likelihood of disease): 43.6% (107/245) vs. 41.5% (101/243) Intermediate-risk (30-60%): 25.3% (62/245) vs. 21.8% (53/243) High-risk (>60%): 31.0% (76/245) vs. 36.6% (89/243)	Mean age (SD): 59 (10) vs. 58 (10) Female: 43% vs. 47% Race: NR Chest pain: - Typical angina: 34.6% vs. 27.8% - Atypical angina: 6.6% vs. 8.2% - Non-anginal pain: 58.8% vs. 63.7% Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: 0% vs. 0% Chest pain frequency: NR Hypertension: 31.6% vs. 29.7% Hyperlipidemia: NR Diabetes: 5.7% vs. 4.8% Current smoking: 18.9% 19.2%	% followed at 12 months: 97.6% (488/500)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
		pectoris: executive summary. Eur Heart K 2006;27:1341-81.)			
Suspected ACS					
CT-COMPARE trial Hamilton-Craig, 2014 Single center Australia Government and Foundation	Population: Possible ACS Setting: Emergency department Inclusion: Males ≥ 30 and females ≥ 40 years of age presenting to the ED with acute undifferentiated chest pain. Other inclusion criteria included intermediate probability of coronary artery disease according to the Cardiac Society of Australia and New Zealand guidelines, initial 12-lead ECG without evidence of acute ischemia, TIMI risk score <4, and a negative first serum sensitive troponin-I with 99th centile at <0.04 ng/mL. To be eligible for randomization, subjects needed to be pain-free and potentially able to exercise on a treadmill. Exclusion: Previous diagnosis of CAD, confirmed pregnancy of lactating	**A: CCTA (n=322)** Stressor: NR Contrast: Iomeron 350 (non-ionic isomolar contrast) Protocol: Negative (normal CCTA) subjects were discharged without repeat troponin. Patients with mild CCTA disease had a 6-hour troponin before being discharged with a letter to their family physician. Moderate disease (50–70%) was admitted for a second troponin, and managed at the discretion of the treating cardiologist. Severe disease (>70%) subjects were admitted to the coronary care unit, treated as ACS according to current guidelines, and managed by the treating cardiologist with open access to CCTA data. Definition of positive test: >50% stenosis considered positive **B: Exercise ECG (n=240)** Stressor: standard Bruce treadmill exercise ECG protocol Contrast: NA	All patients were low to intermediate risk	A vs. B Subgroup: None N randomized: 562 Mean age (SD): 52 (10.7) vs. 52 (9.8) Female: 43% vs. 42% Race: Chest pain: -Typical angina: 89% vs. 91% -Atypical angina: 11% vs. 9% Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: 0% vs. 0% Chest pain frequency: NR Hypertension: 31% vs. 31% Hyperlipidemia: 25% vs. 24% Diabetes: 7% vs. 6% Current smoking: 24% vs. 23% Family history of CAD: 33% vs. 33%	30 days (via telephone), 6 and 12 months % followed at 12 months: 100% (562/562)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	female; history of severe reactive airway disease or current exacerbation, allergy or contraindication to iodinated contrast or beta-blockade medication; current atrial fibrillation; and renal impairment (eGFR <50 ml/min using the MDRD equation).	Protocol: A cardiologist independently adjudicated the Exercise ECG result using standard criteria for myocardial ischemia. Subjects without Exercise ECG evidence of myocardial ischemia were discharged. Subjects with positive or equivocal ExECG results were managed at the discretion of the treating cardiologist. Definition of positive test: NR			

ACS = acute coronary syndrome, CACS = coronary artery calcium scoring, CAD = coronary artery disease, CCTA = coronary computed tomography, CT = computed tomography, ECG = electrocardiogram, ExECG = exercise electrocardiogram, f/u = follow-up, ICA = invasive coronary angiogram, MI = myocardial infarction, mL = milliliter, NA = not applicable, NICE = National Institute for Health and Care Excellence, NR = not reported, SD = standard deviation, TIMI = Thrombolysis in Myocardial Infarction.

* p-values non-significant unless reported

† CTCAs were mainly done with the 320 detector row scanner (n=1343)

‡ Patients with acute chest pain are not seen in such clinics but are referred directly to the emergency department.

Appendix Table F5. Data abstraction for CCTA vs. Exercise ECG: Efficacy Outcomes

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Suspected CAD							
SCOT-HEART trial The SCOT-HEART investigators 2015, 2018 CCTA (+ CACS) + Exercise ECG vs. Exercise ECG alone Subgroup analyses: Y Test for interaction: Y	**Disposition, % (n/N)** NR **Test results, % (n/N)** • Electrocardiogram - Normal: 85% (1757/2073) vs. 84% (1735/2073) - Abnormal: 14% (292/2073) vs. 15% (316/2073) p=NR • Stress electrocardiograph (received in 1764 and 1753 patients - Normal: 63% (1103/1764) vs. 62% (1085/1753) - Abnormal (i.e., evidence of myocardial ischemia): 15% (264/1764) vs. 15% (265/1753)	**All-cause mortality, % (n/N)** Median follow-up 1.7 years 0.8% (17/2073) vs. 1.0% (20/2073), HR 0.860 (95% CI 0.450 to 1.642), p=0.6468 Median follow-up 4.8 years 2.1% (43/2073) vs. 2.1% (43/2073), HR 1.02 (95% CI 0.67 to 1.55), p=NR	**Non-fatal myocardial infarction (all NSTEMI), % (n/N)** Median follow-up 1.7 years 1.1% (22/2073) vs. 1.7% (35/2073), HR 0.627 (95% CI 0.367 to 1.069), p=0.0862 Median follow-up 4.8 years 2.1% (44/2073) vs. 3.5% (73/2073), HR 0.60	**Proportion of patients undergoing any coronary revascularization, % (n/N)** Median follow-up 1.7 years • Any revascularization: 11.2% (233/2073) vs. 9.7% (201/2073), HR 1.198 (95% CI 0.992 to 1.448), p=0.0611* **- PCI:** 8.9% (184/2073) vs. 7.7% (160/2073), p=0.1075 **- CABG:** 2.6% (54/2073) vs. 2.2% (45/2073), HR 1.190 (95% CI 0.963 to 1.472), p=0.1075 Median follow-up 4.8 years • Any revascularization:	**Proportion of patients receiving any further investigation, % (n/N)** 6 weeks 31% (633/2073) vs. 33% (682/2073) **Proportion of patients receiving invasive coronary angiography, % (n/N)** 6 weeks 12% (255/2073) vs. 13% (260/2073) Median follow-up 4.6 years 23.6% (491/2073) vs. 24.2% (502/2073), HR 1.00 (95% CI 0.88 to 1.13), p=NR Hazard ratio for the rate of ICAs beyond	**Coronary heart disease death and non-fatal myocardial infarction, % (n/N)** Median follow-up 1.7 years 1.3% (26/2073) vs. 2.0% (42/2073), HR 0.616 (95% CI 0.378 to 1.006), p=0.0527 Median follow-up 4.6 years 2.3% (48/2073) vs. 3.9%	**Rehospitalizations for cardiac chest-pain, % (n/N)** Median follow-up 1.7 years 3.7% (76/2073) vs. 3.3% (69/2073), HR 1.115 (95% CI 0.805 to 1.545), p=0.5130 **Rehospitalizations for non-cardiac chest-pain, % (n/N)** Median follow-up 1.7 years 8.8% (183/2073) vs. 10.0% (208/2073), HR 0.864 (95% CI 0.708 to 1.054), p=0.1498 **Non-fatal stroke, % (n/N)** Median follow-up 1.7 years

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	- Inconclusive: 16% (284/1764) vs. 16% (282/1753) p=NR • CACS (for group A patients only) - Low (<100 Agatston Units): 65% (1159/1778) - Medium (100-400 Agatston Units): 17% (303/1778) - High (>400 Agatston Units): 18% (315/1778) • CCTA (for group A patients only) - Normal: 37% (654/1778) - Mild (<50%): 21% (372/1778) - Moderate (50–70%): 17% (300/1778) - Obstructive (>70%): 25% (452/1778) One vessel: 12% (207/1778) Two vessel: 7% (128/1778)	**Death from coronary heart disease (all deaths from fatal myocardial infarction), % (n/N)** Median follow-up 1.7 years 0.2% (4/2073) vs. 0.3% (7/2073), HR 0.574 (95% CI 0.167 to 1.971), p=0.3776 Median follow-up 4.8 years 0.2% (4/2073) vs. 0.4% (9/2073), HR 0.46 (95% CI	(95% CI 0.41 to 0.87), p=NR	13.5% (279/2073) vs. 12.9% (267/2073), HR 1.07 (95% CI 0.91 to 1.27), p=NR† - **PCI**: 10.6% (219/2073) vs. 10.2% (212/2073), HR1.06 (95% CI 0.88 to 1.28), p=NR - **CABG**: 3.3% (69/2073) vs. 3.0% (62/2073), p=NR Hazard ratio for the rate of revascularizations occurring beyond 12 months: HR 0.59 95% (CI 0.38 to 0.90), p=NR **Changes in recommended treatments compared to what clinicians recommended at baseline prior to randomization, % (n/N)** 6 weeks Preventive treatment	12 months: HR 0.70 95% (CI 0.52 to 0.95), p=NR **Proportion of patients receiving additional stress imaging, % (n/N)** 6 weeks - Radionuclide: 9% (176/2073) vs. 10% (213/2073) - Other: 1% (16/2073) vs. 1% (14/2073) **Changes in further investigations compared to what clinicians recommended at baseline prior to randomization, % (n/N)** 6 weeks Stress imaging	(81/2073), HR 0.59 (95% CI 0.41 to 0.84), p=0.004 **Coronary heart disease death, myocardial infarction and stroke, % (n/N)** Median follow-up 1.7 years 1.5% (31/2073) vs. 2.3% (48/2073), HR 0.644 (95% CI 0.410 to 1.012), p=0.0561 Median follow-up 4.8 years	0.1% (5/2073) vs. 0.2% (7/2073), HR 0.727 (95% CI 0.228 to 2.315), p=0.5900 Median follow-up 4.8 years 0.7% (15/2073) vs. 1.0% (20/2073), HR 0.74 (95 % CI 0.38 to 1.44), p=NR **Seattle Angina Questionnaire. Mean (SD)** Change from baseline at 6 weeks - Physical limitation: −0.5 (0.5) vs. −0.0 (0.5), MD −0.72 (95% CI −2.08 to 0.63), p=0.2957 - Angina stability: 16.7 (0.9) vs. 15.8 (0.9), MD 1.03 (95% CI −0.61 to 2.68), p=0.2184 - Angina frequency: 11.2 (0.6) vs. 11.8 (0.6), MD −0.84

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	Three vessel: 7% (117/1778) **Final diagnosis of coronary heart disease, % (n/N) (using all available information including that from subsequent testing)‡** <u>6 weeks</u> 23% (476/2073) vs. 11% (221/2073) **Final diagnosis of angina due to coronary heart disease, % (n/N) (using all available information including that from subsequent testing)‡** <u>6 weeks</u> 11% (231/2073) vs. 7% (143/2073)	0.14 to 1.48), p=NR		• Any change in preventative treatment: 18% vs. 4%, p<0.0001 - Cancelled: 3.7% (77/2073) vs. 0.4% (8/2073) - New order: 14% (293/2073) vs. 4% (84/2073) • Any change in antianginal treatment: 9% vs. 1%, p<0.0001 - Cancelled: 5.4% (112/2073) vs. 0.3% (6/2073) - New order: 4.0% (82/2073) vs. 0.5% (11/2073) **Proportion of patients that commenced preventative therapies during follow-up, % (n/N)** <u>Median follow- up 4.8 years</u> 19.4% (402/2073) vs. 14.7% (305/2073), OR	- Cancelled: 5.8% (121/2073) vs. 0% (0/2073) - New order: 0.2% (5/2073) vs. 0.3% (6/2073) Invasive Coronary Angiography - Cancelled: 1.4% (29/2073) vs. 0.05% (1/2073) - New order: 4.5% (94/2073) vs. 0.4% (8/2073)	3.0% (63/2073) vs. 4.7% (97/2073), HR 0.65 (95% CI 0.47 to 0.89), p=NR	(−2.20 to 0.54), p=0.2277 - Treatment satisfaction: −7.0 (0.4) vs. −7.0 (17.1), MD 0.03 (95% CI −1.07 to 1.14), p=0.9525 - Quality of life: 8.7 (0.5) vs. 9.9 (0.6), MD −1.31 (95% CI −2.66 to 0.05), p=0.0585 <u>Change from baseline at 6 months</u> - Physical limitation: 1.6 (0.6) vs. 3.0 (0.6), MD −1.74 (95% CI −3.34 to −0.14), p=0.0329 - Angina stability: 13.4 (0.9) vs. 12.5 (0.9), MD 1.27 (95% CI −0.27 to 2.80), p=0.1059 - Angina frequency: 18.3 (0.6) vs. 19.2 (0.6), MD −1.55

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				1.40 (95% CI 1.19 to 1.65), p=NR **Proportion of patients that commenced anti-anginal therapies during follow-up, % (n/N)** Median follow- up 4.8 years 13.2% (273/2073) vs. 10.7% (221/2073), OR 1.27 (95% CI 1.05 to 1.54), p=NR			(95% CI −2.85 to −0.25), p=0.0198 - Treatment satisfaction: −5.0 (0.4) vs. −4.3 (0.4), MD −0.97 (95% CI−2.14 to 0.21), p=0.1060 - Quality of life: 15.5 (0.6) vs. 18.6 (0.6), MD −3.48 (95% CI −4.95 to −2.01), p<0.0001 **SF-12 Physical component summary score, Mean (SD)** Baseline 44.2 (0.2) vs. 44.0 (0.2), MD 0.1 (95% CI −0.5 to 0.8), p=0.70 6 weeks 44.3 (0.3) vs. 44.5 (0.3), MD −0.2 (95% CI −0.9 to 0.6), p=0.66 6 months

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							45.0 (0.3) vs. 46.0 (0.3), MD −1.0 (95 % CI −1.8 to −0.2), p=0.01 **SF-12 Mental component summary score, Mean (SD)** <u>Baseline</u> 46.1 (0.3) vs. 46.7 (0.3), MD −0.6 (95% CI −1.3 to 0.2), p=0.12 <u>6 weeks</u> 47.2 (0.3) vs. 47.0 (0.3), MD 0.2 (95% CI −0.6 to 1 0), p=0.57 <u>6 months</u> 47.8 (0.3) vs.48.6 (0.3), MD -0.8 (95% CI -1..6 to 0.0), p=0.05
CAPP trial McKavanagh 2015	**Test results, % (n/N)** - Negative: 43.6% (106/243) vs. 53.9% (132/245), p=0.0021	**All-cause mortality, % (n/N)** <u>12 months</u>	**Myocardial infarction, % (n/N)** <u>12 months</u>	**Proportion of patients receiving revascularization, % (n/N)**	**Proportion of patients receiving any additional**	NR	**Seattle Angina Questionnaire. Mean Difference in**

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
CCTA + CACS vs. Exercise ECG Subgroup analyses: N	- Positive: 54% (131/243) vs. 19.2% (47/245), p=0.0054 - Inconclusive: 2.5% (6/243) vs. 27% (66/245), p<0.0001	0.4% (1/243) vs. 0.4% (1/245), p=NR **Cardiac-related mortality, % (n/N)** <u>12 months</u> 0% (0/243) vs. 0% (0/245), p=NR	0.41% (1/243) vs. 0.82% (2/245)	<u>12 months</u> Any revascularization: 15.2% (37/243) vs. 7.7% (19/245), p=NR -CABG: 3.3% (8/243) vs. 2.9% (7/245), p=NR -PCI: 11.9% (29/243) vs. 4.9% (12/245), p=NR **Proportion of patients undergoing medical management only, % (n/N)** <u>12 months</u> 40.7% (99/243) vs. 14.3% (35/245), p=NR **Proportion of patients receiving no further intervention, % (n/N)** <u>12 months</u> 44% (107/243) vs. 78% (191/245), p=NR	**downstream testing, % (n/N)** <u>12 months</u> Any further testing: 29.6% (72/243) vs. 52.2%(128/245), p<0.0001 -MPI: 2.5% (6/243) vs 24.5% (60/245), p=NR -ICA§: 27.2% (66/243) vs 20.8% (51/245), p=NR -CCTA: 0% vs. 6.5% (16/245), p=NR -DSE: 0% vs. 0.4% (1/245), p=NR		**Change Scores from Baseline (95% CI)** <u>3 months</u> - Quality of life: -5.7 (-10.3 to -1.2), p=0.014 - Angina frequency: -2.7 (-6.8 to 1.3), p=0.184 - Angina stability: -11.1 (-17.4 to -4.8), p=0.001 - Physical limitations: 20.54 (-4.3 to 3.3), p=0.779 - Treatment satisfaction:-2.12 (-5.3 to 1.2), p=0.213 <u>12 months</u> - Quality of life: -4.8 (-9.6 to -0.19), p=0.041 - Angina frequency:-1.9 (-6.0 to 2.2), p=0.365 - Angina stability: -6.8 (-12.8 to -0.7), p=0.028

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							- Physical limitations: 0.33 (-4.3 to 5.0), p=0.889 - Treatment satisfaction: -1.4 (-5.2 to 2.3), p=0.446 **Outpatient cardiology visits, % (n/N)** 12 months 1.5% (28/243) vs. 22.9% (56/245), p=NR **Unstable angina, % (n/N)** 12 months 0.41% (1/243) vs. 1.2% (3/245), p=NR **Hospitalization for chest pain, % (n/N)** 12 months 0.82% (2/243) vs. 6.9% (17/245), p=0.009

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							(Resulting in unplanned days in hospital: 7 days vs. 56 days) **Chest pain clinical revisits, % (n/N)** 12 months 3.3% (8/243) vs. 13.1% (32/245)
Suspected ACS							
CT-COMPARE trial Hamilton-Craig 2014 CCTA vs. Exercise ECG Subgroup analyses: N	**Disposition, % (n/N)** Inpatient admission: 10.2% (33/322) vs. 10.8% (26/240), OR 1.1 (95% CI 0.6 to 1.8), p=0.800 **Test results, % (n/N)** Negative: 89.1% (287/322) vs. 88.8% (213/240), p=NR Positive: 10.6% (34/322) vs. 11.3% (27/240), p=NR Inconclusive: 0.3% (1/322) vs. 0% (0/240)	**All-cause mortality, % (n/N)** 30 days 0% (0/332) vs. 0% (0/240), p=NR 12 months 0.6% (2/332) vs. 0.4% (1/240), p=NR	**MI (NSTEMI), % (n/N)** Index 1.9% (6/322) vs. 1.3% (3/240), p=NR 30 days 0% (0/332) vs. 0% (0/240), p=NR	**Proportion of patients receiving revascularization, % (n/N)** 12 months **Any Revascularization**: 4.3% (14/322) vs. 1.3% (3/240) - **PCI**: 3.7% (12/322) vs. NR - **CABG**: 0.62% (2/322) vs. NR	**Proportion of patients receiving any additional downstream testing, % (n/N)** 12 months - **ICA**: 9.0% (29/322) vs 4.2% (10/240), OR 2.3 (95% CI 1.1 to 4.7), p=0.028 - **Stress echocardiography**: 2.2% (7/322) vs.1.3% (3/240), p=0.30	NR	**Proportion of patients with acute coronary syndrome, % (n/N)** Index visit Any Acute Coronary Syndrome: 5.3% (17/322) vs. 2.9% (7/240), p=NR - NSTEMI: 1.9% (6/322) vs. 1.7% (4/240), p=NR - Unstable angina: 3.4% (11/322) vs. 1.7% (4/240), p=NR 30 days

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
					- **SPECT**: 2.2% (7/322) vs. 7.5% (18/240), p=NR		No major coronary events were identified (0% prevalence of acute coronary syndrome) <u>6 months</u> 0.3% (1/322) vs. 0% (0/240), p=NR **Proportion of patients re-presenting to the Emergency Department, % (n/N)** <u>12 months</u> 12.7% (41/322) vs. 10.5% (25/240), OR 1.3 (95% CI 0.8 to 2.3) p=0.300 **Hospital length of stay (hours), Mean (95% CI)** <u>Index visit</u> 13.5 (11.2 to 15.7) vs. 19.7 (17.3 to 22.0), p=0.003

ACS = acute coronary syndrome, CABG = coronary artery bypass graft, CACS = coronary artery calcium scoring, CAD = coronary artery disease, CCTA = coronary computed tomography, CI = confidence interval, DSE = dobutamine stress echocardiography, ECG = electrocardiogram, HR = hazard ratio, ICA = invasive coronary angiogram, MD = mean difference, MI = myocardial infarction, MPI = myocardial perfusion imaging, N = no, NR = not reported, NSTEMI = Non-ST-Segment Elevation Myocardial Infarction, OR = odds ratio, PCI = percutaneous coronary intervention, SD = standard deviation, vs. = versus, Y = yes.

* Nine patients had percutaneous coronary intervention followed by coronary artery bypass surgery.

† 12 patients had percutaneous coronary intervention followed by coronary-artery bypass grafting, and 4 patients had coronary-artery bypass grafting followed by percutaneous coronary intervention.

‡Clinicians were asked to diagnose both coronary heart disease, and angina due to coronary heart disease, in view of all available information. They were asked to categorize this according to the level of confidence in their diagnosis (yes, probable, unlikely, or no) both at baseline and at 6 weeks after the result of the CCTA (standard care and CCTA) and ASSIGN score (standard care).

§ Coronary revascularization may have occurred at the same time as ICA

Appendix Table F6. Data abstraction for CCTA vs. Exercise ECG: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Suspected CAD			
SCOT-HEART trial CCTA (+ CACS) + ETT vs. ETT alone	**Adverse events for patients in group A (NR for group B), % (n/N)** Index visit Any: 1.7% (31/1778) - Contrast reaction: 0.7% (13/1778) - Contrast extravasation: 0.4% (7/1778) - Vasovagal reactions: 0.2% (4/1778) - Headaches: 0.2% (4/1778) - Other: 0.2% (3/1778) [All adverse events were mild and self-limiting with no cases of anaphylaxis or renal failure]	**Incidental findings on CCTA (group A only), % (n/N)** Index visit Other cardiac findings: 28.2% (501/1778) Non-cardiac findings: 38.1% (677/1778)	**Radiation dose for CCTA (mSv), Median (IQR) [No data for group B)]** Index test 4.1 (3.0 to 5.6) [37% of the dose was attributable to the measurement of the coronary artery calcium score]
CAPP trial CCTA + CACS vs. Exercise ECG	There were no complications after any investigation in this study.	NR	**Effective radiation dose (mSv), Mean (SD NR)** Index test 5.31 vs. 0.00, p=NR
Suspected ACS			
CT-COMPARE trial CCTA vs. Exercise ECG	NR	NR	**Radiation exposure (mSv), mean (95% CI)** Index test 3.8 (3.5 to 4.1) vs. NR

ACS = acute coronary syndrome, CACS = coronary artery calcium scoring, CAD = coronary artery disease, CCTA = coronary computed tomography, CI = confidence interval, ECG = electrocardiogram, ETT = exercise treadmill test, mSv = millisieverts, NR = not reported, SD = standard deviation.

Appendix Table F7. Data abstraction for CCTA vs. ICA: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
Suspected CAD					
CAD-Man trial Dewey 2016 Single center Germany Non-profit	Population: Suspected CAD Setting: Hospital admission status at time of randomization: - Inpatient: 57% - Outpatient: 43% Inclusion: Patients 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. Exclusion: History of CAD (including PCI, stents, and bypasses), STEMI, CKMB above 34 U/l on initial testing, pulmonary edema most likely due to ischemia, age below 30 years, women of childbearing potential, atrial fibrillation, uncontrolled tachycardia, or other non-sinus rhythms, inability to	**A: CCTA + CACS (n=168)†** - Underwent CCTA: 98.2% (165/168) - Withdrew informed consent and did not undergo CT: 0.6% (1/168) - Underwent ICA per clinician: 1.2% (2/162) Stressor: NA Contrast: Iodinated contrast agents Protocol: Patients with suspected obstructive coronary artery disease subsequently underwent late enhancement magnetic resonance imaging to identify those with more than 50% transmural extent of non-viable myocardium in the area supplied by a stenosed artery and thus considered unlikely to benefit from revascularization. Patients with non-calcified coronary plaques on CT were recommended for intensified risk factor modification and statin treatment as this management might reduce cardiovascular death and myocardial infarction.	A vs. B <10%: 11.4% vs. 15.4% 10 to 60%: 74.2% vs. 60.5% >60%: 14.4% vs. 24.1% Mean (SD) pretest probability of coronary artery disease: 34.6% (23.5%)	A vs. B Subgroup: None N randomized: 340 Mean age (SD): 60.4 (11.3) vs. 60.4 (11.4) Female: 52.7% vs. 48.1% Race: NR Chest pain: - Atypical angina: 38.9% vs. 48.8% - Non-anginal chest pain: 58.1% vs. 49.4% - Other chest discomfort: 3.0% vs. 1.8% Dyspnea: NR Prior MI: 0% vs. 0% Prior revascularization: 0% vs. 0% Known CAD: - Carotid artery disease: 5.4% vs. 6.2%	Median (IQR) follow-up: 3.3 (1.3 to 4.6) years % followed: 96.8% (329/340)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	hold breath for 5 seconds, renal insufficiency with dialysis, prior myocardial infarction, two or more positive functional tests.	Definition of positive test: at least one 50% diameter stenosis in the left main coronary artery or at least one 70% diameter stenosis in other coronary arteries. **B: ICA (n=172)** - Underwent ICA: 94.2% (162/172) - Withdrew informed consent and did not undergo ICA: 5.8% (10/172) Stressor: NA Contrast: NA Protocol: Treated according to the 2014 ESC/EACTS Guidelines on myocardial revascularization Definition of positive test: at least one 50% diameter stenosis in the left main coronary artery or at least one 70% diameter stenosis in other coronary arteries.		- Peripheral artery disease: 1.2% vs. 0.0% - Positive functional test within 6 months before randomization: 25.7% vs. 27.7% Chest pain frequency: NR Hypertension: NR Hyperlipidemia: 56.9% vs. 51.0% Diabetes: 66.5% vs. 69.1% Current smoking: 24.5% vs. 21.0% Mean BMI (SD): 27.5 (4.7) vs. 27.0 (4.6) Family history of premature CAD: 14.4% vs. 9.9%	
CONSERVE trial Chang 2019 Multi-center	Population: Suspected CAD Setting: Outpatient, non-emergent Inclusion: 1. Moderate or severe angina, which improves to mild with medical therapy	**A: CCTA (n=823)** - Did not receive allocated test: 4.7% (39/823) (26 patient decision, 2 physician decision, 11 unspecified) Stressor: NA Contrast: Iodinated contrast agents	A vs. B Mean (SD) pretest probability of coronary artery disease: 51% (30%) vs. 52% (30%); "Largely	A vs. B Subgroup: Stable patients N randomized: 1,611	Median (IQR) follow-up: 12.3 (11.7 to 13.2) months Follow-up measures taken

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
Norther America, East Asia, Europe, India	2. Mild or moderate angina, which is intolerant to medical therapy 3. Any angina, not evaluable by non-invasive stress testing 4. Heart failure with normal ejection fraction of unknown etiology 5. Symptomatic (chest pain) + Abnormal NIST (non-invasive stress testing) 6. Asymptomatic +2 Risk Factors (RF) + Abnormal NIST 7. Worsening NIST 8. Recurrent hospitalization for Chest Pain + Abnormal/equivocal NIST 9. Low-risk surgery, stable angina 10. Low risk surgery, medically stabilized moderate or severe stable angina 11. High-risk surgery with equivocal NIST 12. Asymptomatic, high-risk occupation 13. Vascular surgery with >2 RF 14. Perioperative MI 15. High risk for coronary disease when other cardiac surgical procedures are planned (e.g., pericardiectomy or removal of chronic pulmonary emboli) 16. Prospective immediate cardiac transplant donors whose risk profile increases the likelihood of coronary disease 17. Asymptomatic patients with Kawasaki disease who have coronary artery aneurysms on echocardiography 18. Before surgery for aortic aneurysm/dissection in patients without known coronary disease	Protocol: All sites were instructed to perform ICA and CCTA in accordance with local site practice and societal guidelines. Definition of positive test: stenosis ≥50% **B: ICA (n=808)** - Did not receive allocated test: 11.0% (89/808) (71 patient decision, 3 physician decision, 15 unspecified) Stressor: NA Contrast: NA Protocol: All sites were instructed to perform ICA and CCTA in accordance with local site practice and societal guidelines. Definition of positive test: stenosis ≥50%	intermediate risk" per authors	Mean age (SD): 59.9 (12.1) vs. 60.8 (11.5) years Female: 48.3% vs. 43.9% Race: - Asian:85.6% vs. 84.0% - White: 13.1% vs. 14.2% - African American: 0.5% vs. 1.4% - Hispanic: 0.5% vs. 0.4% - Unknown: 0.3% vs. 0.0% Chest pain: - Typical angina: 31.0% vs. 30.1% - Atypical angina: 40.2% vs. 38.7% - Noncardiac chest pain: 2.3% vs. 1.4% - Asymptomatic: 11.5% vs. 10.6% Dyspnea: 13.5% vs. 17.7% Prior MI: 0% vs. 0%	at 6 and 12 months % followed at 6 months: 91.4 %(1472/1611) % followed at 12 months: 79.3% (1278/1611)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	19. Recent blunt chest trauma and suspicion of acute MI, without evidence of preexisting CAD Exclusion: 1. Known CAD (past MI, PCI, CABG, or diagnosed by cardiac catheterization without intervention) 2. Acute coronary syndrome or myocardial infarction at time of enrollment 3. Planned intervention or bypass surgery 4. Known complex congenital heart disease 5. Planned invasive angiography for reasons other than CAD 6. Non-cardiac illness with life expectancy < 2 years 7. Inability to provide written informed consent 8. Concomitant participation in another clinical trial in which subject is subject to investigational drug or device 9. Pregnant women 10. Allergy to iodinated contrast agent 11. Serum creatinine >1.5 mg/dl or GFR <30 ml/min 12. Baseline irregular heart rhythm 13. Heart rate ≥100 beats per minute 14. Systolic blood pressure ≤90 mm Hg 15. Contraindications to β blockers or nitroglycerin 16. Body mass index >35kg/m^2 17. Known complex congenital heart disease			Prior revascularization: 0% vs. 0% Known CAD: 0% vs. 0% Chest pain frequency: NR Hypertension: 56.9% vs. 59.0% Hyperlipidemia: 33.0% vs. 34.6% Diabetes: 25.9% vs. 29.5% Current smoking: 13.8% vs. 13.63% Mean BMI (SD): 25.6 (4.0) vs. 25.7 (4.0)	

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	18. Age <18 years				

BMI = body mass index, CABG = coronary artery bypass graft, CACS = coronary artery calcium scoring, CAD = coronary artery disease, CCTA = coronary computed tomography, CT = computed tomography, f/u = follow-up, ICA = invasive coronary angiogram, IQR = inter-quartile range, MI = myocardial infarction, mm = millimeter, NA = not applicable, NIST = non-invasive stress testing, NR = not reported, PCI = percutaneous coronary intervention, SD = standard deviation,
STEMI = ST-Segment Elevation Myocardial Infarction.

* p-values non-significant unless reported

† Coronary calcium scoring was used to individually adjust the acquisition length of CT angiography but was not used to defer CCTA.

Appendix Table F8. Data abstraction for CCTA vs. ICA: Efficacy Outcomes

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Suspected CAD							
CAD-Man trial Dewey 2016 CCTA vs. ICA Subgroup analyses: N	**Patient disposition, % (n/N)** Index visit Discharged after index test: 86.7% (143/165) vs. 84.6% (137/162) **Test results, % (n/N)** Index visit - Obstructive CAD: 12.1% (20/165) vs. 15.4% (25/162) - No CAD: 87.9% (145/165) vs. 84.6% (137/162), p=NR	**Cardiac-related mortality (component of composite outcome), % (n/N)** Median 3.3 year follow-up 0% (0/167) vs. 0.6% (1/162), p=NR	**Myocardial infarction (component of composite outcome), % (n/N)** Median 3.3 year follow-up 0.6% (1/167)* vs. 0% (0/162)	**Proportion of patients receiving revascularization, % (n/N)** Index visit Any revascularization: 9.6% (16/167) vs. 14.2% (23/162), p=NR - PCI: 7.8% (13/167) vs. 13.6% (22/162), p=NR - CABG: 1.8% (3/167) vs. 0.6% (1/162), p=NR **Proportion of patients receiving re-revascularization or first revascularization more than two months after randomization (component of composite outcome), % (n/N)**	**Proportion of patients in group A undergoing follow-up ICA, % (n/N)** Index visit 14.4% (24/167) vs. 100% (162/162) - ICA revealing obstructive CAD: 75% (18/24) vs. 15.4% (25/162) - ICA associated with revascularization of obstructive CAD: 66.7% (16/24) vs.14.2% (23/162) **Rate of ICAs per patient** During the first six months after randomization	**MACE (including MI, cardiac death, stroke, unstable angina pectoris, re-revascularization or first revascularization more than 2 months after randomization), % (n/N)** Median 3.3 year follow-up 4.2% (7/167) vs. 3.7% (6/162), adj. HR 0.90 (95% CI 0.30 to 2.69), p=0.86	**Hospital length of stay (hours), Median (IQR)** Index visit All patients: 30.0 (3.5 to 77.3) vs. 52.9 (49.5 to 76.4), p<0.001 - Inpatients at time of randomization: 60.3 (32.6 to 98.5) vs. 68.0 (50.2 to 105.8), p=0.12 **Stroke (component of composite outcome), % (n/N)** Median 3.3 year follow-up

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				Median 3.3 year follow-up 3.6% (6/167) vs. 3.1% (5/162), adj. HR 0.89 (95% CI 0.27 to 2.90), p=0.84	0.25 vs. 1.1, p<0.001 6 to 12 months after randomization 0.027 vs. 0.013, RR 0.78 (95% CI NR), p=0.56 During second year of observation NR vs. NR, RR 0.81 (95% CI NR), p=0.56 **Cumulative relative risk adjusted for observation time for coronary angiography** During the first six months after randomization ICA vs. CCTA: RR 4.2 (95% CI 3.0 to 5.8), p<0.001		0% (0/167) vs. 0.6% (1/162), p=NR **Unstable angina pectoris, % (n/N)** Median 3.3 year follow-up 1.2% (2/167) vs. 0% (0/162), p=NR

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
					Median follow-up 3.3 years ICA vs. CCTA: RR 3.1 (95% CI 2.3 to 4.0), p<0.001		
CONSERVE trial Chang 2019 CCTA vs. ICA Subgroup Analyses: N	**Patient disposition, % (n/N)** NR **Test results, % (n/N)** Index visit - No CAD: 34.4% (269/784) vs. 24.2% (174/719), p=NR - Nonobstructive CAD: 37.6% (294/784) vs. 36.9% (265/719), p=NR - Obstructive CAD: 27.9% (219/784) vs. 39.0% (280/719), p<0.001	**All-cause mortality (component of composite outcome), % (n/N)** Median 12.3 month follow-up 0.3% (2/784) vs. 0.1% (1/719), p=NR	**Acute myocardial infarction (component of composite outcome), % (n/N)** Median 12.3 month follow-up 0.3% (2/784) vs. 0.3% (2/719), p=NR	**Proportion of patients receiving revascularization, % (n/N)** Median 12.3 month follow-up Any revascularization: 13% (98/784) vs. 18 %(127/719), p=0.007 - PCI: 11% (89/784) vs. 15% (109/719), p<0.001 - CABG: 1% (9/784) vs. 3% (18/719), p=0.075 Revascularization as a result of obstructive CAD on index test: 34% (74/219) vs. 43% (120/280), p=0.04	**Proportion of patients undergoing downstream follow-up testing** Median 12.3 month follow-up - ICA: 23% (179/784) vs. 4% (30/719), p<0.001 - Fractional Flow Reserve: 0% (0/784) vs. 6% (41/719), p<0.001 - CCTA: 0.4% (3/784) vs. 0.1% (1/719), p=0.36 - Exercise ECG: 14% (108/784) vs. 11% (79/784), p=0.12	**MACE (including death, acute non-fatal MI, unstable angina, cardiac hospitalization, or stroke), % (n/N)** Median 12.3 month follow-up 4.6% (36/784) vs. 4.6% (33/719), HR 0.99 (95% CI 0.62 to 1.58), p=0.99	**Cardiac hospitalization (component of composite outcome), % (n/N)** Median 12.3 month follow-up 4.2% (33/784) vs. 4.3% (31/719), p=NR **Stroke (component of composite outcome), % (n/N)** Median 12.3 month follow-up 0.3% (2/784) vs. 0.3% (2/719), p=NR

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	- 1-vessel CAD: 16.1% (126/784) vs. 17.7% (127/719), p=NR - 2-vessel CAD: 6.6% (52/784) vs. 11.4% (82/719), p=NR - 3-vessel or left main stenosis: 5.2% (41/784) vs. 9.9% (71/71),p=NR				- Stress nuclear: 2% (14/784) vs. 1% (10/719), p=0.67 - Stress echocardiogram: 1% (9/784) vs. 1% (9/719), p=0.95 - Rest echocardiogram: 36% (281/784) vs. 13% (95/271), p<0.001 No obstructive CAD on ICA: 25% (24/114) vs. 61% (439/719), p<0.001		**Unstable angina (component of composite outcome), % (n/N)** Median 12.3 month follow-up 1.1% (9/784) vs. 1.1% (8/719), p=NR **Angina-free** Median 12.3 month follow-up 60% (470/784) vs. 62% (446/719), p=0.52)

adj. = adjusted, CABG = coronary artery bypass graft, CAD = coronary artery disease, CCTA = coronary computed tomography, CI = confidence interval, ECG = electrocardiogram, HR = hazard ratio, ICA = invasive coronary angiogram, IQR = inter-quartile range, MACE = major adverse cardiovascular events, NR = not reported, PCI = percutaneous coronary intervention, RR = risk ratio, SD = standard deviation, vs. = versus, Y = yes.

* Single procedure related myocardial infarction occurred after percutaneous coronary intervention in computed tomography (CT) group: during primary stent implantation, a dissection of the left anterior descending coronary artery occurred, leading to implantation of a second stent with over-stenting of a side branch.

Appendix Table F9. Data abstraction for CCTA vs. ICA: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Suspected CAD			
CAD-Man trial Dewey 2016 CCTA vs. ICA	**Proportion of patients with complications prolonging hospital stay by at least 24 hours** 0% (0/165) vs. 0% (0/162) **Minor procedural complications, % (n/N)** Within 48 hours after last procedure related to CCTA or ICA Any minor complication: 3.6% (6/165) vs. 10.5% (17/162), p=0.014 [Of the minor procedural complications in the CT group, four occurred after coronary angiography and two after CT. The two that occurred after CT were one allergoid reaction and one bradycardia] - Hematoma at puncture site: 0.6% (1/165) vs. 8.6% (14/162), p<0.001 - Secondary bleeding at puncture site: 0.6% (1/165) vs. 0.6% (1/162), p=1.00 - Bradycardia: 1.2% (2/165) vs. 0% (0/162), p=0.50 - Angina without infarction: 0.6% (1/165) vs. 0% (0/162), p=1.00 - Allergoid reaction to contrast agent: 0.6% (1/165) vs. 0% (0/162), p=1.00 - Stent migration: 0% (0/165) vs. 0.6% (1/162), p=0.49 - Hypotension requiring treatment: 0% (0/165) vs. 0.6% (1/162), p=0.49	NR	**Overall exposure to radiation (mSv) (including from ICAs and revascularizations), Median (IQR)** Median follow-up 3.3 years 5.0 (4.2 to 8.7) vs. 6.4 (3.4 to 10.7), p=0.45
CONSERVE trial Chang 2019 CCTA vs. ICA	**Major bleeding, % (n/N)** Median 12.3 month follow-up 0% (2/784) vs. 0.3% (2/719), p=NR - Requiring major transfusion: 0% (0/784) vs. 0.1% (1/719), p=NR	NR	**Effective radiation dose (mSv), Median (IQR NR)** Index test 6.5 vs. NR

AE = adverse events, CAD = coronary artery disease, CCTA = coronary computed tomography, CT = computed tomography, ICA = invasive coronary angiogram, IQR = inter-quartile range, mSv = millisieverts, NR = not reported.

Appendix Table F10. Data abstraction for CCTA vs. SPECT MPI: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
Suspected CAD					
IAEA-SPECT/CTA trial Karthikeyan, 2017 Multi-center (6 sites) Brazil, Czech Republic, India, Mexico, Slovenia, and Turkey Funding: International organization	Population: Stable, Symptomatic (89%) or Asymptomatic; suspected CAD Setting: Outpatient, non-emergent (tertiary care hospitals) Inclusion: Patients above 21 years, who were mildly symptomatic (those in class II New York Heart Association) and had 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 criteria Exclusion: Known CAD, history of myocardial infarction or coronary revascularization, patients who were severely symptomatic (class III or IV NYHA), had chronic renal impairment precluding contrast injection, severe medical disease with limited life-expectancy, known contraindication or allergy to	**A: CCTA (≥64 slice) (n=152)** - 93% (142/152) received calcium scoring as planned - 3% (4/152) of received calcium scoring only - 4% (6/152) no test Stressor: NA Contrast: used, but type NR Protocol: Calcium scoring was performed prior to contrast injection. Definition of positive test: - Normal: no coronary stenoses or any luminal narrowing less than 30% of the reference vessel diameter - Mild stenoses: 30%-49% luminal narrowing - Moderate stenosis: 50%-69% luminal narrowing - Severe stenosis: ≥70% luminal narrowing **B: SPECT MPI (n=151)** 5% (8/151) of patients did not receive stress MPI Stressor: Exercise treadmill: 33% Exercise bike: 25% Dipyridamole: 34%	A vs. B All symptomatic patients had an intermediate likelihood of having CAD, and all asymptomatic patients determined to be at intermediate or high risk of coronary events by the Framingham criteria	A vs. B Subgroup: None N randomized: 303 Mean age (SD): 60 (11) vs. 60 (12) Female: 51% vs. 54% Race: - Caucasian: 73% vs. 69% - Hispanic: 25% vs. 20% - Indian: 5% vs. 5% - African: 1% vs. 1% - Other: 0% vs. 1% Chest pain: 80% vs. 80% Dyspnea or other ischemic symptoms: 10% vs. 9% Prior MI: 0% vs. 0% Prior revascularization: 0% vs. 0% Known CAD: 0% vs. 0%	6 months: 98.0% (297/303) 12 months: % followed NR

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	pharmacologic stress agents or contrast agents, or had an abnormal cardiac rhythm (including persistent atrial fibrillation) which precluded ECG gating, very obese patients, and pregnant or lactating women.	Adenosine: 3% Contrast: NR Protocol: 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. Definition of positive test: - Normal: not defined - Abnormal: any perfusion defect (either at rest or stress) or wall motion abnormality (not explained by left bundle branch block) - Inconclusive: not defined		Chest pain frequency: NR Hypertension: 64% vs. 64% Hyperlipidemia: 59% vs. 55% Diabetes: 28% vs. 29% Current smoking: 24% vs. 17% Family history of CAD: 32% vs. 30%	
Min, 2012 Multi-center (2 sites) US Industry	Population: Suspected CAD; stable chest pain Setting: Outpatient cardiology clinics Inclusion: ≥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; and a determination by the referring	**A: CCTA (64 slice) (n=91)** Stressor: NA Contrast: iodinated Protocol: NR Definition of positive test: Normal: NR Abnormal: ≥50% stenosis **B: SPECT MPI (n=89)** Stressor: exercise (treadmill) or pharm (adenosine) Contrast: technetium-99m sestamibi (25-40 mCi) (some	A vs. B **Pretest Likelihood** Low: 4.1% (4/91) vs. 9.0% (8/89) Intermediate: 62.6% (57/91) vs. 67.4% (60/89) High: 33.0% (30/91) vs. 23.6% (21/89) **Framingham pre-test likelihood scores,**	A vs. B Subgroup: None N randomized: 180 Mean age (SD): 56 (10) vs. 59 (9.5), p=0.04 Female: 57% vs. 52%, p=0.04 Race: NR Chest pain: -Typical angina: 31.9% vs. 22.5%	Mean (SD) follow-up: 55 (34) days % followed: 96.1% (173/180)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	physician that CAD evaluation with noninvasive imaging was warranted. Exclusion: suspected acute coronary syndrome; noncardiac illness with life expectancy <2 years; pregnant state or possible pregnant state, allergy to iodinated contrast agent; serum creatinine R 1.7 mg/dL; irregular heart rhythm; heart rate ≥100 beat/min; systolic blood pressure ≤90 mm Hg; contraindication to beta-blocker or nitroglycerin; concomitant participation in another clinical trial; inability to provide written informed consent; or class I American College of Cardiology/American Heart Association indication for urgent or emergent invasive coronary angiography	patients underwent dual isotope imaging thallium-201 [3-4.5 mCi]) Protocol: NR Definition of positive test: Normal: <5% of myocardium abnormal Abnormal: ≥5% of myocardium abnormal (Categorized according to reporting guidelines from the American Society of Nuclear Cardiology)	**Mean (SD)**: 18.3 (12.7) vs. 9.2 (13.7)	-Atypical angina: 23.1% vs. 24.7% - Noncardiac angina: 27.5% vs. 24.7% Dyspnea: NR Prior MI: 0% vs. 0% Prior revascularization: 0% vs. 0% Known CAD: 0% vs. 0% Chest pain frequency: Hypertension: 62% vs. 59% Hyperlipidemia: 53% vs. 61% Diabetes: 23% vs. 21% Smoker (ever): 58% vs. 44%, p=0.053	
RESCUE trial Stillman, 2020 Multi-center (44 sites)	Population: Suspected CAD; stable angina or angina equivalent Setting: Outpatient Inclusion:	**A: CCTA (≥64 slice) (n=516)** - CCTA: 91.7% (473/516) - No test: 8.3% (43/516) Stressor: NA Contrast: 80 mL of iodinated contrast	NR	A vs. B Subgroup: None N randomized: 1050 Mean age (SD): 57 vs. 58 years	Mean (SD) follow-up time: 16.2 (7.9) months Participants with positive cardiac-

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
US, Germany, the Netherlands Government	Willing and able to provide a written informed consent, 40 years or older, Presentation with symptoms of stable angina (CCS 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, to performed at an ACRIN-qualified facility with a RESCUE-qualified scanner Exclusion: Prior revascularization; not suitable to undergo CT with an iodinated contrast agent because of a known allergy-like reaction to contrast media as defined by the American College of Radiology, renal failure or insufficiency as determined by glomerular filtration rate (GFR) < 30 mL/min/1.73 m2 based on a serum creatinine level obtained within 28 days prior to registration; 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	Protocol: Patients without left main disease were treated with optimal medical treatment. Definition of positive test: ≥50% stenosis **B: SPECT MPI (n=531)** - SPECT: 87.4% (464/531) - No test: 12.6% (67/531) Stressor: NR Contrast: NR Protocol: Patients with ≥10% reversible defect were directed to ICA, and patients without left main disease by ICA were treated with optimal medical treatment. Definition of positive test: ≥10% reversible defect		Female: 45% vs. 46% Race: - American Indian or Alaskan Native: 2% vs. 1% - Asian: 2% vs. 3% - Black or African American: 14% vs. 15% - Native Hawaiian or other: <1% vs. <1% - White: 78% vs. 78% - Multiple races: 2% vs. 1% - Unknown: 2% vs. 2% Ethnicity: - Hispanic or Latino: 9% vs. 11% Chest pain: 100% vs. 100% Dyspnea: NR Prior MI: NR Prior revascularization: 0% vs. 0% Prior history of CAD: 11% vs. 10%	related findings on their CCTA or SPECT/MPI were contacted at a minimum of 4 time points (at 2 weeks and 2, 6, and 12 months). Participants with negative findings on CCTA or SPECT MPI were contacted at a minimum of 2 time points (6 and 12 months). Participants were then contacted every 6 months until the conclusion of the trial. 10.5% (110/1047) participants did not have the randomized scan. % followed: NR

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	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 CCS Class IV); history of known left ventricular ejection fraction < 45%; pulmonary edema or 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 (e.g., SPECT MPI or CCTA within the previous 72 hours); BMI			Chest pain frequency: NR Hypertension: 62% vs. 60% Hyperlipidemia: NR Diabetes: 20% vs. 21% Current smoking: 14% vs. 16% Mean BMI: 30 vs. 29	

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	> 40 kg/m2 because of likely limited examination quality; pregnancy or intent to become pregnant (if a female is of childbearing potential—defined as a premenopausal female capable of becoming pregnant.				
Suspected ACS					
CT-STAT trial Goldstein, 2011 Multi-center (16 sites) US Industry	Population: Acute chest pain; suspected ACS Setting: Emergency department Inclusion: 1) acute chest pain suspicious for angina based on an ED physician's history taking and physical examination; 2) age ≥25 years; 3) time from onset of chest pain to presentation ≤12 h; 4) time from emergency department presentation to randomization ≤24 h; 5) normal or nondiagnostic rest ECG at the time of enrollment, without ECG evidence of ischemia (i.e., ST-segment elevation or depression ≥1mm in 2 or more contiguous leads, and/or T-wave inversion ≥2mm);	**A: CCTA + CACS (n=375)** - CCTA: 96% (361/375) - Excluded or withdrew consent and excluded: 4% (14/375) Stressor: NA Contrast: 60 to 100 ml Ultravist 300 Protocol: The CCTA could be done immediately after enrollment and results were read immediately by an experienced physician and findings were communicated to the ED physician. Patients with coronary arterial stenoses 0% to 25% and/or calcium score <100 Agatston units were eligible for discharge home; patients with stenoses >70% were referred for ICA; and patients with intermediate lesions (stenosis 26% to 70% or calcium score >100 Agatston units) or uninterpretable scans were recommended to cross over for a rest-stress MPI. All patients underwent serial ECGs and cardiac biomarkers before enrollment and	A vs. B Low- to intermediate-risk patients (not clearly defined) Mean (SD) Thrombolysis In Myocardial Infarction risk score 1.04 (0.87) vs. 0.99 (0.84)	A vs. B Subgroup: None N randomized: 749 Mean age (SD): 50 (10) vs. 50 (10) years Female: 55% vs. 53% Race: NR Chest pain: 100% vs. 100% - unstable angina: 2% vs. 3% Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: NR Chest pain frequency: NR Hypertension: 39% vs. 36%	6 months: 83.7% (627/749) (Mortality rates were from the Social Security Death Index for 99.9% of patients)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	6) thrombolysis in myocardial infarction risk score ≤4 for unstable angina or non-ST segment elevation myocardial infarction Exclusion: 1) known CAD; 2) elevated serum biomarkers including creatine kinase-myocardial band, myoglobin, and/or troponin I (e.g., Adiva Centaur assay, Bayer Healthcare, Tarrytown, New York); 3) ischemic ECG changes, as denoted in the preceding text; 4) previously known cardiomyopathy, with an estimated ejection fraction ≤45%; 5) contraindication to iodinated contrast and/or beta-blocking drugs; 6) atrial fibrillation or markedly irregulat rhythm; 7) body mass index ≥39 kg/m2; 8) elevated serum creatinine levels (creatinine ≥1.5 mg/dl); 9) CT imaging or contrast imaging within the past 48 h	at 4 and 8 hours thereafter before discharge. All clinical management was at the discretion of the attending physician. Definition of positive test: Abnormal: >25% stenosis. Severity categories: 0= no stenosis 1= 1-25% stenosis 2= 26-50% stenosis 3= 51-70% stenosis 4= 71-99% stenosis 5= total occlusion **B: SPECT MPI (n=374)** - SPECT: 90% (338/374) - Excluded or withdrew consent: 10% (36/374) Stressor: Exercise (treadmill) or pharm (adenosine or dipyridamole) Contrast: Tc-99m sestamibi Protocol: Rest imaging studies could be done immediately after enrollment. Stress testing was done only if the resting studies were normal. Definition of positive test: Images categorized as abnormal; probably abnormal; equivocal, probably normal, or normal (based on stress/rest perfusion imaging, functional data, hemodynamic response to stress, symptoms, ECG		Hyperlipidemia: 31% vs. 36% Diabetes: 8% vs. 6% Current smoking: 25% vs. 20% Family history of CAD: 31% vs. 30% Mean BMI (SD): 28.1 (4.7) vs. 28.7 (5.1)	

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
		response, exercise duration, and blood pressure response). Details of each category were NR and the American Society of Nuclear Cardiology consensus statement (J Nucl Cardiol 2003: 10:705) was cited			
Goldstein, 2007 Single center US Industry	Population: Acute chest pain or angina equivalent symptoms; suspected ACS Setting: Emergency department Inclusion: 1) chest pain or angina equivalent symptoms compatible with ischemia during the past 12 hours; 2) age ≥25 years; and 3) a prediction of a low risk of infarction and/or complications according to established criteria. Exclusion: 1) known coronary artery disease; 2) electrocardiograms diagnostic of cardiac ischemia and/or infarction (significant Q waves, ST-segment deviations >0.5 mm, or T-wave inversion); 3) elevated serum biomarkers including creatine kinase-MB, myoglobin, and/or	**A: CCTA (n=99)** Stressor: NA Contrast: Visipaque Protocol: NR Definition of positive test: Lesions were classified by the maximal luminal diameter stenosis according to the following severity scale: 0= no stenosis 1= 1% to 25% stenosis 2= 26% to 50% stenosis 3= 51% to 70% stenosis 4= 71% to 99% stenosis 5= total occlusion **B: SPECT MPI (n=98)** Stressor: Exercise (type NR) Contrast: Tc99m-sestamibi Protocol: NR Definition of positive test: Images categorized as abnormal; probably abnormal; equivocal, probably normal, or normal. Details of each category were NR but categories were based on:	A vs. B Goldman Riley criteria: 0=Very low risk: 100% (99/99) vs. 99.0% (97/98) 1= Low risk: 0% (0/99) vs. 1.0% (1/98) 2= Moderate risk: 0% vs. 0% Mean (SD) Thrombolysis In Myocardial Infarction risk score 1.24 (0.8) vs. 1.33 (0.8)	A vs. B Subgroup: None N randomized: 203 Mean age (SD): 48 (11) vs. 51 (12) Female: 57% vs. 47%, p=0.05 Race: NR Chest pain: 100% vs. 100% Dyspnea: NR Prior MI: 0% vs. 0% Prior revascularization: NR Known CAD: 0% vs. 0% Chest pain frequency: 0% vs. 0% Hypertension: 39% vs. 38% Hyperlipidemia: 34% vs. 38%	6 months (Clinical records reviewed) % followed: NR

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	cardiac troponin I on initial and 4-hour testing; 4) previously known cardiomyopathy, with estimated ejection fraction ≤45%; 5) contraindication to iodinated contrast and/or beta-blocking drugs; 6) atrial fibrillation or markedly irregular rhythm; 7) body mass index ≥39 kg/m2; 8) renal insufficiency (creatinine ≥1.5 mg/dl); or 9) computed tomography imaging or contrast administration within the past 48 hours.	1) symptoms (typical angina pectoris during exercise); 2) electrocardiographic response (>1 mm flat or down sloping ST-segment depression 80 ms after the J point or >1 mm of ST-segment elevation 80 ms after the J point or sustained ventricular tachycardia); and 3) SPECT evidence of perfusion defects with qualitative and semiquantitative visual analysis and a standard 17-segment model		Diabetes: 8.2% vs. 12.2%: Current smoking: 15% vs. 20% Mean BMI (SD): 29 (5) vs. 29 (5) Family history of CAD: 8% vs. 12%	
PROSPECT trial Levsky, 2009 Levsky, 2015 Single center US Non-profit, Government	Population: Acute chest pain, no MI or ischemia on ECG/biomarkers; suspected ACS Setting: Hospital telemetry unit/Inpatient Inclusion: Patients without known coronary artery disease, ECG or serum cardiac biomarkers showed no acute myocardial infarction or ischemia. At least 1 intermediate-risk criterion for death or myocardial infarction in the short term was required: 1) pain for more than 20 minutes, 2) pain onset at	**A: CCTA (64 slice) (n=200)** - CCTA: 93.5% (187/200) - SPECT: 3.5% (7/200) - No test: 2% (4/200) Stressor: NA Contrast: iodixanol-320 Protocol: Coronary calcium was scored. Scans were interpreted with complete access to clinical information and without blinding. After imaging, the managing physicians made all clinical care decisions without restriction. Definition of positive test: NR **B: SPECT MPI (n=200)** - SPECT: 94.5% (189/200)	A vs. B Patients considered to be at intermediate-risk per authors. Diamond—Forrester pretest probability, mean: 36% vs. 37% Thrombolysis in Myocardial Infarction Risk Score, Mean (SD): 1.3 (1.0) vs. 1.2 (1.0)	A vs. B Subgroup: None N randomized: 400 Mean age (SD): 56.8 (11.8) vs. 56.3 (10.5) Female: 63% vs. 63% Race/Ethnicity: - Hispanic: 53% vs. 55% - African American: 39% vs. 34% - Asian: 5% vs. 4% - White: 4% vs. 5% - Other: 1% vs. 1%	12 months Median followup for safety outcomes: 41.7 (Group A) and 39.0 (Group B) months % followed: NR

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	exertion within the previous 2 weeks, 3) age older than 70 years, 4) subthreshold elevation of serum troponin T, or 5) nonspecific ST-segment or T-wave changes on ECG at presentation. Exclusion: CCTA, MPI, or cardiac catheterization within the preceding 6 months and contraindications to CCTA, including renal insufficiency, active asthma, poor venous access, allergy to intravenous contrast material or other serious allergy, and dysrhythmia that precluded cardiac gating.	- No test: 5.5% (11/200) Stressor: Default stressor was treadmill exercise per the Bruce protocol. Patients unable to exercise received intravenously administered adenosine or regadenoson with or without low-level exercise. Contrast: Radionuclide stress MPI was generally performed by using 1-day dual-isotope (201-Tl rest/99m-Tcsestamibi stress) or 99m-Tc-sestamibi rest/stress imaging Protocol: Single photon-emission CT, with gated and attenuation-corrected images, was performed. One of several experienced, certified nuclear cardiologists or nuclear medicine physicians interpreted the findings by using standard quantification algorithms. Definition of positive test: NR		Chest pain >20 minutes: 62% vs. 63% Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: 0% vs. 0% Chest pain frequency: NR Hypertension: 72% vs. 75% Hyperlipidemia: 49% vs. 55% Diabetes: 33% vs. 31% Current smoking: 17% vs. 15% Mean BMI: 30.5 vs. 30.7	
Nabi, 2016 Single center US Funding NR	Population: Patients with acute chest pain who were hospitalized and under observational status waiting for evaluation; suspected ACS Setting: SPECT/CT department	**A: CCTA + CACS (64 slice) (n=288)** - CCTA: 98.6% (284/288) - SPECT: 1.4% (4/288) Stressor: NA Contrast: Visapaque Protocol: Patients had CACS followed by CCTA Definition of positive test:	A vs. B **Framingham Risk Score, % (n/N)** Low: 76% vs. 77% Intermediate: 19% vs. 18% High: 5% vs. 5%	A vs. B Subgroup: None N randomized: 598 Mean age (SD): 54 vs. 53 years Female: 55% vs. 56%	Clinical follow-up was prospectively obtained by telephone interview at predefined intervals of 1 week, 1 month,

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	Inclusion: Patients older than 18 years who were hospitalized under observational status awaiting SPECT for evaluation of acute chest pain Exclusion: Contradiction to CCTA, Prior history of CAD, Elevated initial troponin (>0.10ng/km), known cardiomyopathy, underlying comorbidity limiting follow-up, inability to obtain informed consent, duplicate emergency department visits, patient/physician refusal to participate	Significant coronary artery disease: >50% stenosis Moderate: 51%–69% stenosis Severe: 70%–90% stenosis Subtotal/total occlusion: >90% stenosis **B: SPECT MPI (n=310)** - SPECT: 100% (310/310) Stressor: Pharmacologic stress testing: 73% (223/310) - Adenosine: 24% (74/310) - Regadenoson: 48% (148/310) - Dobutamine: 0.3% (1/310) Treadmill exercise stress testing: 27% (84/310) Contrast: NR Protocol: SPECT was performed as recommended by the American Society of Nuclear Cardiology Definition of positive test: Normal test consisted of homogeneous left ventricular myocardial perfusion, normal cavity size, and ejection fraction was 50% or greater with normal wall motion	p=0.95 Thrombolysis in Myocardial Infarction risk score, % (n/N) 0: 50% vs. 55% 1: 29% vs. 32.3% 2: 15% vs. 14% 3: 3% vs. 2% p=0.67	Race/Ethnicity: - Black: 27% vs. 33% - White: 56% vs. 56% - Hispanic: 14% vs. 10% - Asian: 2% vs. 0.3% - Other: 1% vs. 2% p=0.05 Chest pain: 100% vs. 100% - Severe angina within the last 24 hours: 6% vs. 5% Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: 0% vs. 0% Chest pain frequency: NR Hypertension: 50% vs. 51% Hyperlipidemia: 39% vs. 37% Diabetes: 15% vs. 15%	and more than 6 months Median follow-up: 6.5 months 4 patients randomized to CCTA crossed over to SPECT % followed: 99.2% (593/598)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
				Current smoking: 26% vs. 27% Mean BMI (SD): 30.5 (7.4) vs. 31.8 (9.1), p=0.05 Family history of CAD: 25% vs. 21%	

ACS = acute coronary syndrome, BMI = body mass index, CACS = coronary artery calcium scoring, CAD = coronary artery disease, CCTA = coronary computed tomography, CT = computed tomography, ECG = electrocardiogram, ED = emergency department, f/u = follow-up, MI = myocardial infarction, mL = milliliter, MPI = myocardial perfusion imaging, NA = not applicable, NR = not reported, SD = standard deviation, SPECT = single photon emission computed tomography.

* p-values non-significant unless reported.

Appendix Table F11. Data abstraction for CCTA vs. SPECT MPI: Efficacy Outcomes

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Suspected CAD							
IAEA-SPECT/CTA trial Karthikeyan, 2017 CCTA vs. SPECT Subgroup Analyses: Y Test for interaction: Y	**Disposition, % (n/N)** NR **Test results, % (n/N)** Index test - Normal stenosis (0% to 29%): 43.9% (62/141) - Abnormal (≥30% stenosis): 56.1% (79/141) - Mild stenosis (30% to 49%): 23.4% (33/141) - Moderate stenosis (50% to 69%): 14.9% (21/141) - Severe stenosis (≥70% stenosis): 17.7% (25/141)	**All-cause mortality, % (n/N)** 12 months 0.7% (1/152) vs. 0% (0/151), p=NR	**Nonfatal MI % (n/N)** 12 months 0% (0/152) vs. 0% (0/151), p=NR	**Planned coronary revascularization (CABG/PCI), % (n/N)** 12 months 6.5% (8/148) vs. 7.8% (10/149), adj. OR 1.29 (95% CI 0.48 to 3.42), p=0.61 (adjusted for recruiting centers, symptom status, and physician preference of procedure at baseline) [One additional patient in the MPI arm underwent unplanned PCI]	**Proportion of patients having additional testing with another modality (Rest-stress MPI, CCTA, stress ECG, CMR, or stress ECHO), or invasive coronary angiography, % (n/N)** 6 months 27.7% (41/148) vs. 16.8% (25/149) vs. adj. OR 0.50 (95% CI 0.28 to 0.89), p=0.019 (adjusted for recruiting centers and symptom status) adj. OR 0.51 (95% CI 0.28 to 0.91), p=0.023 (adjusted for recruiting centers, symptom status, and physician preference of procedure at baseline)	**Composite of death, nonfatal MI, recurrent ischemia, or unplanned revascularization, % (n/N)** 12 months 1.6% (2/152) vs. 2.3% (3/151), p=NR	**Proportion of patients with recurrent ischemia, % (n/N)** 12 months 0.7% (1/152) vs. 1.3% (2/151), p=NR

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	[7% (11/152) of patients did not receive CCTA] **Test results for Group B (SPECT), % (n/N)** <u>Index test</u> - Normal: 70.6% (101/143) - Abnormal: 28.7% (41/143) - Inconclusive: 0.7% (1/143) [5% (8/151) of patients did not receive stress MPI]				**Proportion of patients having additional non-invasive testing with another modality (Rest-stress MPI, CCTA, stress ECG, CMR, or stress ECHO)** <u>6 months</u> 17.6% (26/148) vs. 4.7% (7/149), adj. OR 0.19 (95% CI 0.08 to 0.48), p<0.001 (adjusted for recruiting centers and symptom status) adj. OR 0.18 (95% CI 0.07 to 0.46), p<0.001 (adjusted for recruiting centers, symptom status, and physician preference of procedure at baseline) **Proportion of patients having an elective coronary angiography, % (n/N)**		

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
					6 months 14.2% (21/148) vs. 12.1% (18/149), adj. OR 0.83 (95% CI 0.42 to 1.60), p=0.60 (adjusted for recruiting centers and symptom status) adj. OR 0.86 (95% CI 0.44 to 1.71), p= 0.67 (adjusted for recruiting centers, symptom status, and physician preference of procedure at baseline) *ORs are for the comparison in the reverse direction*		
Min, 2012 CCTA vs. SPECT Subgroup Analyses: Y	**Disposition, % (n/N)** NR **Test Results, % (n/N)** Index test	**All-cause mortality, % (n/N)** Mean 55 day follow-up 0% (0/91) vs. 0% (0/89)	**Myocardial infarction, % (n/N)** Mean 55 day follow-up	**Need for subsequent revascularization (PCI or CABG), % (n/N)** Mean 55 day follow-up	**Invasive coronary angiography, % (n/N)** Mean 55 day follow-up 13% (12/91) vs. 8% (7/89), p=0.25	NR	**CAD-related hospitalization, % (n/N)** Mean 55 day follow-up

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Test for interaction: N	- Normal: 70% (64/91) vs. 64% (57/89) - Abnormal: 30% (27/91) vs. 36% (32/89) p=0.29		0% (0/91) vs. 0% (0/89)	8% (7/91) vs. 1% (1/89), p=0.03 **Percent change in medication use, Mean change from baseline (SD)** <u>Mean 55 day follow-up</u> - Aspirin: 21.8% (47%) vs. 8.1% (35%), p=0.04 - Statin: 6.9% (45%) vs. –3.5% (28%), p=0.03 - Non-statin-lipid lowering: –1.1% (32%) vs. –1.2% (36%), p=0.95 - Beta-blocker: 4.6% (43%) vs. 0% (31%), p=0.25 - ACE inhibitors: –1.1% (24%) vs. –2.3% (31%), p=0.94 - Angiotensin receptor antagonists: 1.1%	**Use of any noninvasive cardiac imaging test, % (n/N)** <u>Mean 55 day follow-up</u> 3% (3/91) vs. 10% (9/89), p=0.07 **Any resource utilization, % (n/N)** <u>Mean 55 day follow-up</u> 20.9% (19/91) vs. 20.2% (18/89), p=0.91		12% (11/91) vs. 11% (10/89), p=0.86 **Seattle Angina Questionnaire (range 0-100, higher=increased health status), Mean change from baseline (SD)** <u>Mean 55 day follow-up</u> - Quality of life/disease perception: 13.5 (22.6) vs. 11.6 (19.0), p=0.80 - Physical limitation: 2.5 (21.3) vs. 4.1 (19.0), p=0.58 - Angina stability: 30.0 (37.0) vs. 22.9 (30.1), p=0.11 -Angina frequency: 10.2

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				(24%) vs. 1.2% (24%), p=0.96 - Calcium channel blockers: –1.1% (24%) vs. –2.3% (22%), p=0.99			(16.4) vs. 7.6 (14.8), p=0.31 -Treatment satisfaction: 4.5 (17.8) vs. 0.6 (18.2), p=0.26
RESCUE trial Stillman, 2020 CCTA vs. SPECT	**Disposition, % (n/N)** NR **Test Results, % (n/N)** Index test - Positive: 23.6% (122/516) vs. 24.3% (23/531), p=NR - Negative: 66.9% (345/516) vs. 82.1% (436/531), p=NR - Uninterpretable: 1.2% (6/516) vs. 1.0% (5/531), p=NR - Scan not performed: 8.3% (43/516) vs. 12.6% (67/531), p=NR	**All-cause mortality, % (n/N)** Mean follow-up 16.2 months 0.01% (10/1047) (NR by group; 7 malignancies, 1 stroke, 1 cocaine drug overdose, and 1 pulmonary end-stage chronic obstructive pulmonary Disease) **Cardiac death, % (n/N)**	**Myocardial infarction, % (n/N)** Mean follow-up 16.2 months 0.4% (2/516) vs. 1.5% (8/531), p=NR	**Any revascularization, % (n/N)** Mean follow-up 16.2 months 5.2% (27/516) vs. 3.7% (20/531), p=NR CCTA and SPECT arm: no left main disease = OMT Adherence to OMT (i.e., antihypertensives, medication for DM, blood thinners and nonsmoking)† 6 months 36.1% (39/108) vs. 25.0% (5/20)	NR	**MACE (including cardiac-related death, acute myocardial infarction, and revascularization), % (n/N)** Mean follow-up 16.2 months NR vs. NR: HR 1.03 (95% CI, 0.61 to 1.75), p=0.19	**Stroke, % (n/N)** Mean follow-up 16.2 months 0.001% (1/1047)

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
		Mean follow-up 16.2 months 0% (0/516) vs. 0% (2/531), p=NR		12 months 38.1% (37/97) vs. 38.1% (8/21) 18 months 41.9% (31/74) vs. 57.1% (8/14) 24 months 40% (16/40) vs. 42.9% (3/7) Cumulative 38.6% (123/319) vs. 38.7 (24/62)			
Suspected ACS							
CT-STAT trial Goldstein, 2011 CCTA vs. SPECT Subgroup Analyses: N	**Disposition, % (n/N)** Discharged from ED within ≤6 hours after index visit: 72.6% (262/361) vs. 80.1% (271/338), p=NR **Test results for Group A (CCTA), % (n/N)** Index test - Minimal or no stenosis (0% to	**All-cause mortality, % (n/N)** At index visit 0% (0/361) vs. 0% (0/338), p=NA Between discharge and 6 months 0% (0/361) vs. 0% (0/337), p=NA	**Myocardial infarction, % (n/N)** At index visit 0.3% (1/361) vs. 1.5% (5/338), p=0.11 Between discharge and 6 months	**Percutaneous Coronary Intervention, % (n/N)** At index visit 2.5% (9/361) vs. 2.4% (8/338), p= 0.90 Between discharge and 6 months 0.3% (1/330) vs. 0% (0/297), p=0.12	**Invasive Coronary Angiography, % (n/N)** At index visit 6.7% (24/361) vs. 6.2% (21/338), p=0.80 Between discharge and 6 months 0.6% (2/330) vs. 0.3% (1/297), p=1.0 **Rest/stress SPECT** At index visit 10.9% (37/361) vs. NA	NR	**Additional unstable angina, % (n/N)** At index visit 0.8% (3/361) vs. 0.9% (3/338), p=1.0 Between discharge and 6 months 0% (0/330) vs. 0% (0/297), p=NA

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	25%): 82.2% (297/361) - Intermediate stenosis (25% to 70%): 10.2% (37/361) - Severe stenosis (>70%): 3.6% (13/361) - Indeterminant/non-diagnostic: 3.7% (14/361) **Test results for Group B (SPECT), % (n/N)** Index test - Normal or probably normal: 89.9% (304/338) - Abnormal, probably abnormal, or equivocal: 10.1% (34/338)		0% (0/330) vs. 0% (0/297), p=NA	**Coronary Artery Bypass Graft, % (n/N)** At index visit 1.1% (4/361) vs. 0% (0/338, p=1.0 Between discharge and 6 months 0% (0/330) vs. 0% (0/297), p=NA	**CCTA** At index visit NA vs. 1.8% (6/338)		**Repeat cardiovascular hospitalization, % (n/N)** Between discharge and 6 months 0% (0/330) vs. 0% (0/297), p=NA **Repeat cardiovascular emergency department visit, % (n/N)** Between discharge and 6 months 0.6% (2/330) vs. 1.3% (4/297), p=0.43

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Goldstein, 2007 CCTA vs. SPECT Subgroup Analyses: N	**Disposition, % (n/N)** Directly discharged from ED after index test: 88.1% (88/99) vs. 96.9% (96/98), p=0.03 **Test results for Group A (CCTA), % (n/N)** Index test - Minimal or no stenosis (0% to 25%): 67.7% (67/99) - Intermediate stenosis (25% to 70%): 13.1% (13/99) - Severe stenosis (>70%): 8.1% (8/99) - Indeterminant/non-diagnostic:11% (11/99) **Test results for Group B (SPECT), % (n/N)**	**All-cause mortality, % (n/N)** At index visit 0% (0/99) vs. 0% (0/98), p=NR Between discharge and 6 months 0% (0/99) vs. 0% (0/98), p=NR	**Myocardial infarction, % (n/N)** At index visit 0% (0/99) vs. 0% (0/98), p=NR Between discharge and 6 months 0% (0/99) vs. 0% (0/98), p=NR	**Percutaneous Coronary Intervention, % (n/N)** At index visit 3.0% (3/99) vs. 1.0% (1/98), p=0.62 Between discharge and 6 months 1.0% (1/99) vs. 0% (0/98), p=NR **Coronary Artery Bypass Graft, % (n/N)** At index visit 2.0% (2/99) vs. 0% (0/98), p=0.50 Between discharge and 6 months 0% (0/99) vs. 0% (0/98), p=NR	**In-hospital diagnostic catheter, % (n/N)** At index visit 11.1% (11/99)‡ vs. 3.1% (3/98), p=0.03 Between discharge and 6 months 1.0% (1/99) vs. 4.1% (4/98), p=NR **Rest/stress SPECT, % (n/N)** At index visit 24.2% (24/99) vs. NA Between discharge and 6 months 1.0% (1/99) vs. 3.2% (3/98), p=0.37 **Any additional cardiac testing, % (n/N)** Between discharge and 6 months 2.0% (2/99) vs. 7.1% (7/98), p=0.10	NR	**Additional unstable angina, % (n/N)** Between discharge and 6 months 0% (0/99) vs. 0% (0/98), p=NA **Repeat cardiovascular emergency department visit, % (n/N)** Between discharge and 6 months 6.1% (6/99) vs. 6.1% (6/98), p=1.0 **Repeat cardiovascular office visit, % (n/N)** Between discharge and 6 months

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	Index test - Normal or probably normal: 94.9% (93/98) - Abnormal: 5.1% (5/98)						2.0% (2/99) vs. 2.0% (2/98), p=NR
PROSPECT trial Levsky, 2009 Levsky, 2015 CCTA vs. SPECT Subgroup Analyses: N	NR	**All-cause mortality, % (n/N)** 12 months 0.5% (1/200) vs. 3% (6/200), difference -2.5% (95% CI -6.3% to 0.7%), p=0.122	NR	**Coronary Artery Bypass Graft, % (n/N)** 12 months 4% (7/200) vs. 0.5% (1/200), difference 3.0% (95%CI -0.3% to 6.9%), p=0.068 **Percutaneous Coronary Intervention, % (n/N)** 12 months 4% (8/200) vs. 5.5% (11/200), difference -1.5% (95% CI -6.4% to 3.3%), p=0.64 Median followup of 41.7 (Group A) and	**Proportion of patients undergoing one or more cardiac catheterization** 12 months 15% (30/200) vs. 16% (32/200), difference −1.0% (95% CI −8.5% to 6.5%), p=0.89 - Cardiac catheterization without revascularization: 7.5% (15/200) vs. 10% (20/200), HR 0.77 (95% CI 0.40 to 1.49), p=0.44 Median followup of 41.7 (Group A) and 39.0 (Group B) months	**Major adverse cardiovascular events (consisting of myocardial infarction, stroke, and cardiac arrest), % (n/N)** 12 months 5% (9/200) vs. 5% (9/200), difference 0% (95% CI -4.7% to 4.7%), p=1.0 **Major adverse cardiovascular events (consisting of myocardial infarction, stroke, and cardiac arrest) + death from any cause, % (n/N)**	**Hospital length of stay (hours), Median (IQR)** Index visit 28.9 (11.0 to 48.4) vs. 30.4 (23.9 to 51.3), p=0.057 **Rehospitalization for any reason, % (n/N)** Median followup of 41.7 (Group A) and 39.0 (Group B) months 43% (86/200) vs. 49% (98/200), difference -6.0% (95% CI -16% to 4.1%), p=0.27

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				39.0 (Group B) months 5% (9/200) vs. 7% (14/200), difference -2.5% (-7.7% to 2.6%), p=0.39 **New aspirin prescription, % (n/N)** Median followup of 41.7 (Group A) and 39.0 (Group B) months 40% (79/200) vs. 34% (63/200), difference 5.5% (95% CI -4.3% to 15%), p=0.30 **New statin prescription, % (n/N)** Median followup of 41.7 (Group A) and 39.0 (Group B) months	18% (36/200) vs. 19% (38/200), difference 1.0% (95% CI -7.0% to 9.0%), p=0.90	12 months 5% (9/200) vs. 7.55% (15/200), difference -3.0% (95% CI -8.3% to 2.2%), p=0.29	**Cardiac rehospitalization, % (n/N)** Median followup of 41.7 (Group A) and 39.0 (Group B) months 25% (50/200) vs. 31% (61/200), difference -5.5% (95% CI -15% to 3.6%), p=0.26 **Emergency Department revisit for any reason, % (n/N)** Median followup of 41.7 (Group A) and 39.0 (Group B) months 63% (126/200) vs. 57.5% (115/200), difference -5.5% (95% CI -4.4% to 15%), p=0.31 **Cardiac-related Emergency**

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				25% (50/200) vs. 18% (36/200), difference 7.0% (95% CI -1.4% vs. 15%), p=0.113 **Increased statin dose, % (n/N)** Median followup of 41.7 (Group A) and 39.0 (Group B) months 3% (6/200) vs. 3% (6/200), difference 0% (95% CI -4.1% to 4.1%), p=1.0			**Department revisit, % (n/N)** Median followup of 41.7 (Group A) and 39.0 (Group B) months 21% (41/200) vs 20% (40/200), difference -0.5% (95% CI -7.7% to 8.7%), p=1.0 **Primary care visit, % (n/N)** Median followup of 41.7 (Group A) and 39.0 (Group B) months 57% (114/200) vs. 56% (112/200), difference 1.0% (95% CI -9.0% to 11%), p=0.92 **Cardiology outpatient visit, % (n/N)** Median followup of 41.7 (Group A)

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							and 39.0 (Group B) months 23% (46/200) vs. 21% (42/300), p=0.72 **Proportion of patients reporting continued chest pain, % (n/N)** On 6 or 12 month follow-up call 36% (64/186) vs. 36% (64/188), p=NR (pain was of the same or worse in 28 recipients in Group A and 23 recipients in Group B)
Nabi, 2016 CCTA vs. SPECT	NR	**Cardiac mortality, % (n/N)** Index	NR	**Coronary Revascularization, % (n/N)** Median 6.5 month follow-up	**Proportion of patients requiring additional testing, % (n/N)** Median 6.5 month follow-up	**Cardiac event (including cardiac death, unstable angina, or myocardial infarction), % (n/N)**	**Time to diagnosis (hours), Mean (SD)** From randomization

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Subgroup Analyses: N		0% (0/283) vs. 0% (0/300), p=NR <u>Median 6.5 month follow-up</u> 0% (0/283) vs. 0% (0/300), p=NR		0.7% (2/283) vs. 1.0% (3/300), p=1.0	- SPECT: 7.4% (21/283) vs. 4.0% (12/300), p=NR - CCTA: 0% (0/283) vs. 0.6% (2/300), p=NR - ICA: 2.5% (7/283) vs. 4.0% (12/300), p=NR **Total # of follow-up Cardiac Tests (including ICA), % (n/N)** <u>Median 6.5 month follow-up</u> - 0: 89.8% (254/283) vs. 92.0% (276/300) - 1: 10.2% (29/283) vs. 7.0% (21/300) - 2: 0% (0/283) vs. 1.0% (3/300) p=0.08	<u>Median 6.5 month follow-up</u> 4.6% (13/283) vs. 3.0% (9/300), p=0.39 [All of the events were unstable angina, except 1 of the 22 total events was an MI, but group NR]	8.1 (8.5) vs. 9.4 (7.4), p=0.0002 **Hospital length of stay (hours), Mean (SD)** <u>From randomization to discharge</u> 19.7 (27.8) vs. 23.5 (34.4), p=0.002 **Chest pain outpatient visit, % (n/N)** <u>Median 6.5 month follow-up</u> 2.8% (8/283) vs. 1.7% (5/300), p=0.41 **Hospital readmission for chest pain, % (n/N)** <u>Median 6.5 month follow-up</u>

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							8.5% (24/283) vs. 9.0% (27/300), p=0.88 **Emergency department visit for reoccurring chest pain, % (n/N)** Median 6.5 month follow-up 9.9% (28/283) vs. 12.3% (37/300), p=0.43

ACE = Angiotensin-converting enzyme, ACS = acute coronary syndrome, CABG = coronary artery bypass graft, CAD = coronary artery disease, CI = confidence interval, CMR = cardiac magnetic resonance, ECG = electrocardiogram, ECHO = echocardiography, ED = emergency department, ICA = invasive coronary angiogram, IQR = inter-quartile range, MACE = major adverse cardiovascular events, MI = myocardial infarction, MPI = myocardial perfusion imaging, N = no, NA = not applicable, NR = not reported, OMT = optimal medical therapy, OR = odds ratio, PCI = percutaneous coronary intervention, SD = standard deviation, SPECT = single photon emission computed tomography, Y = yes.

* In exploratory analyses, the results were consistent (interaction P values in parentheses) across subgroups defined by symptom status (P = 0.6), angina as presenting symptom (P = 0.71), presence of diabetes (P = 0.18), and participating site (P = 0.10). (No other data provided)

† In both arms, patients without left main disease were given OMT.

‡ For CCTA, of these 11, 8 received ICA as the result of severe CAD according to CCTA; 3 tested abnormal on SPECT that was received from intermediate or non-diagnostic CCTA results.

Appendix Table F12. Data abstraction for CCTA vs. SPECT MPI: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Suspected CAD			
IAEA-SPECT/CTA trial Karthikeyan, 2017 CCTA vs. SPECT	**Test complications, % (n/N)** Index test 2.1% (3/146) vs. 0% (0/143), p=NR (all 3 events in Group A were allergic reactions)	NR	**Effective radiation dose (mSv), median (IQR)** Initial diagnostic procedure 5.0 (3.8 to 10) vs. 9.3 (8.5 to 9.7), p<0.001 All diagnostic procedures at 12 months 8.8 (I4.0 to 13.2) vs. 9.6 (8.9 to 12.5), p=0.040 All diagnostic and therapeutic procedures at 12 months* 8.8 (I4.0 to 13.2) vs. 9.6 (8.9 to 12.5), p=0.041
Min, 2012 CCTA vs. SPECT	NR	NR	**Estimated effective radiation dose (mSv), median (IQR)** Index test 6.5 (5.1 to 13.3) vs 13.3 (13.1 to 38.0), p<0.0001 **Estimated radiation from down stream testing (mSv), median (IQR)** Mean 55 day follow-up 0.0 (0.0 to 0.0) vs. 0.0 (0.0 to 0.0), p=0.31 **Cumulative radiation (mSv), median (IQR)** Mean 55 day follow-up

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
			7.3 (5.1 to 13.7) vs 13.3 (13.1 to 38.0), p<0.0001
RESCUE trial Stillman, 2020 CCTA vs. SPECT	**Mild to moderate adverse events that were considered to be possibly, probably, or definitely associated with imaging, % (n/N)** Index test 4% (4/473) vs. 0% (0/468), p=NR	**Incidental findings, % (n/N)** Index test 32.8% (169/516) vs. 1.7% (9/531), p=NR - Proportion requiring additional follow-up imaging: 33.1% (59/169) vs. 22.2% (2/9), p=NR	NR
Suspected ACS			
CT-STAT trial Goldstein, 2011 CCTA vs. SPECT	NR	NR	**Radiation dose (mSv), median (IQR)** Index test 11.5 (6.8 to 16.8) vs. 12.8 (11.6 to 13.9), p=0.02
Goldstein, 2007 CCTA vs. SPECT	**Test complications, % (n/N)** Index test 0% (0/99) vs. 0% (0/98), p=NA	NR	NR
PROSPECT trial Levsky, 2009 Levsky, 2015 CCTA vs. SPECT	**Serious complications of imaging, % (n/N)** Index test 0% (0/200) vs. 0% (0/200), p=1.0 **Proportion of patients reporting one or more general adverse reactions, % (n/N)** Index test Any adverse reaction: 24% (45/186) vs. 24% (46/188), p=NR (most commonly headache, nausea, dizziness, and feeling of warmth) - Chest pain, shortness of breath, or palpitations: 0.5% (1/186) vs. 16% (30/188), p<0.001 - Rash or pruritus: 1.5% (3/186) vs. 0% (0/186), p=0.25	**Proportion of patients with an incidental finding, % (n/N)** Index test 83.4% (156/187) vs. 0% (0/189) (386 incidental findings were found among 187 CCTA studies) **Most frequently occurring incidental findings on CCTA, %** - Pulmonary findings:63% of exams) - Noncoronary cardiac findings: 37% of exams - Gastrointestinal findings: 26% of exams - Hepatobiliary findings: 22% of exams - Renal findings: 9% of exams	**Radiation exposure (mSv), median (IQR)** Initial diagnostic procedure 9.6 (6.2 to 23) (*n* = 184) vs. 27 (19 to 27) (*n* = 189), p<0.001 All diagnostic procedures at 12 months 12 (6.4 to 26) (*n* = 200) vs. 27 (19 to 27) (*n* = 200), p<0.001 Cardiac imaging over complete follow-up (Median followup 41.7 vs. 39.0 months) 13 (6.9 to 27) (*n* = 200) vs. 27 (19 to 27) (*n* = 200) p<0.001

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
		Potentially serious or life threatening incidental findings, % (n/N exams) - Pneumonia: 1.6% (3/187) - Congestive heart failure: 0.5% (1/187) - Pericardial effusion: 6.4% (12/187) - Aortic dilatation: 3.2% (6/187) - Pulmonary embolism: 2.1 %(4/187) *No significant difference was found between the CCTA and SPECT MPI groups regarding subsequent noncoronary surgical procedures after randomization.*	Noncardiac imaging studies over complete follow-up (Median followup 41.7 vs. 39.0 months) 2.0 (0.003 to 16) (*n* = 200) vs. 2.0 (0.004 to 17) (*n* = 200), p=0.91 All radiation over complete follow-up (Median followup 41.7 vs. 39.0 months) 24 (8.7 to 39) (*n* = 200) vs. 29 (27 to48) (*n* = 200), p<0.001
Nabi, 2016 CCTA vs. SPECT	NR	NR	**Radiation exposure (mSv), Mean (SD)** Index test 12.7 (4.9) vs. 10.9 (4.4), p<0.0001 **Total inpatient diagnostic radiation exposure (mSv) [does not include radiation from ICA], Mean (SD)** Median follow-up of 6.5 (Group A) and 6.4 (Group B) months 13.3 (5.8) vs. 11.0 (4.6), p<0.0001

ACS = acute coronary syndrome, CAD = coronary artery disease, CCTA = coronary computed tomography, ICA = invasive coronary angiogram, IQR = inter-quartile range, MPI = myocardial perfusion imaging, mSv = millisieverts, NA = not applicable, NR = not reported, SD = standard deviation, SPECT = single photon emission computed tomography.

* For patients who underwent angiography and percutaneous coronary angioplasty (PCI) at the same time, the dose of PCI was used for calculating the effective radiation dose. For 24 patients in the CCTA and 16 in the MPI arm, 12-month data were unavailable so effective radiation dose was estimated from 6-month data for these patients.

Appendix Table F13. Data abstraction for CCTA vs. Stress Echo: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
Suspected ACS					
Levsky, 2018 Single-center US Non-profit/Foundation	Population: Suspected ACS; acute chest pain or pressure patients without known coronary artery disease and a negative initial serum troponin level Setting: Emergency department Inclusion: Patients without known coronary artery disease with a pre-test probability of significant coronary stenosis between 10% and 90%, and an initial negative serum troponin level at least 8 hours after symptom onset with subsequent resolution of chest pain Exclusion: 1) elevated serum troponin T; 2) electrocardiogram demonstrating acute ischemia or myocardial infarction; 3) hemodynamic instability; 4) unremitting or crescendo chest pain; 5) contraindications to coronary CCTA, including renal	**A: CCTA (64 slice) (n=201)** - CCTA done: 94.0% (189/201) [7.4% (14/189) of these patients were terminated because of a positive calcium score] - CCTA not done: 6.0% (12/201) Stressor: NA Contrast: Type NR Protocol: Coronary calcium scoring was performed; the presence of heavy calcification was assessed in real time and was grounds for termination of the study at the discretion of the monitoring physician. Clinical management was not dependent on completion of the noninvasive imaging protocol. Definition of positive test: NR **B: Stress Echo (n=199)** - Stress Echo done: 94.4% (188/199) [3% (6/188) of these patients were terminated because a positive test after resting images] - Stress Echo not done: 5.6% (11/199)	A vs. B All patients were at low to intermediate risk Diamond-Forrester pretest probability, Median (IQR) 28% (19% to 55%) vs. 28% (21% to 54%) Thrombolysis In Myocardial Infarction risk score, Median (IQR) 1 (0 to 1) vs. 1 (0 to 1)	A vs. B Subgroup: None N randomized: 400 Mean age (SD): 55 vs. 54 years Female: 43% vs. 42% Race/Ethnicity: - Hispanic: 46% vs. 45% - African-American: 32% vs. 32% - Caucasian: 12% vs. 13% - Asian: 5% vs. 6% - Other: 4% vs. 5% Chest pain: 100% vs. 100% Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: 0% vs. 0% Chest pain frequency: NR Hypertension: 54% vs. 60% Hyperlipidemia: 45% vs. 43% Diabetes: 29% vs. 28% Current smoking: 25% vs. 24%	30 days: 100% (400/400) 12 months: 96.8% (387/400) Median (IQR) follow-up for cardiovascular events: 733 (442 to 1,060) days [2 years]

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	insufficiency, active asthma, recent contrast administration, poor venous access, dysrhythmia that precluded cardiac gating, and intravenous contrast or other serious allergy; 6) contraindications to SE, including known inability to perform treadmill exercise, severe valvular disease, severe hypertension, and recent beta-blocker pharmacotherapy; and 7) coronary CCTA, SE, or cardiac catheterization within the previous 6 months	Stressor: Treadmill (Bruce protocol) (if unable to exercise, patients received dobutamine/atropine infusion (16%)) Contrast: Left ventricular opacification contrast agents Protocol: A full resting echocardiogram was performed; resting wall motion abnormalities or severe valvular disease assessed in real time were grounds for early termination of the study at the discretion of the monitoring physician. Clinical management was not dependent on completion of the noninvasive imaging protocol. Definition of positive test: NR		First-degree relative with CAD: 35% vs. 35% Mean (SD) BMI: 30.4 (6.6) vs. 30.4 (5.8)	
PERFECT trial Uretsky, 2017 Single center US No funding received	Population: Chest pain; suspected acute coronary syndrome Setting: All patients initially presented to the emergency department and were subsequently hospitalized for further examination Inclusion:	**A: CCTA (64 slice) (n=206)** - Underwent CCTA: 90% (185/206) - Underwent a CAC score only: 1% (2/206) - Underwent a stress test: 5% (10/206) - Did not undergo a test: 3.5% (8/206) - Underwent ICA: 0.5% (1/206) Stressor: NA Contrast: iodinated contrast	NR	A vs. B Subgroup: All patients were determined to need hospitalization for further examination N randomized: 411 Mean age (SD): 59 vs. 60 years Female: 54% vs. 53% Race/Ethnicity: - Hispanic: 41% vs. 40%	30 days and subsequently at predefined intervals (6 months and 1 year) % followed at 1 year: 96% (395/411)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	Patients aged 45 years and up, without known coronary artery disease who presented to the emergency department with chest pain and were determined to require hospital admission for further evaluation of chest pain after a negative initial troponin I and an electrocardiogram which was not diagnostic for acute coronary syndrome Exclusion: Patients aged <45 years, known coronary artery disease, a serum creatinine [1.5 mg dL^{-1}, the presence of atrial fibrillation or a markedly irregular heart rhythm, an allergy to iodinated contrast agents, pregnant women, and the inability to give informed consent	Protocol: An initial non-contrast ECG-gated scan was acquired for calcium scoring. Definition of positive test: Mild: ≤50% stenosis Moderate: 50%-70% stenosis or coronary plaques that were densely calcified rendering the coronary stenosis not interpretable Severe: ≥70% stenosis or left main artery stenoses with ≥50% stenosis **B: Stress Echo or Rest/Stress SPECT (n=205)** - Underwent stress echo: 88% (180/205) - Underwent stress SPECT: 4% (9/205) - Underwent CCTA: 2% (3/205) - Did not undergo a test: 6% (13/205) Stressor: - Stress echo: exercise or dobutamine (61%) - SPECT MPI: exercise or regadenason (39%) Contrast: iodinated contrast Protocol: NR Definition of positive test:		- African-American: 39% vs. 33% - Caucasian: 14% vs. 20% - Asian: 3% vs. 3% - Other: 3% vs. 4% Chest pain: 100% vs. 100% Dyspnea: 49% vs. 49% Prior MI: NR Prior revascularization: NR Known CAD: 0% vs. 0% Chest pain frequency: NR Hypertension: 68% vs. 69% Hyperlipidemia: 43% vs. 53%, p=0.04 Diabetes: 24% vs. 33%, p=0.05 Current smoking: 45% vs. 46% Family history of CAD: 18% vs. 25%	

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
		- Stress echo: Myocardial ischemia was defined as (1) a left ventricular wall segment that did not increase in thickening and excursion during stress, (2) a deterioration in left ventricular segment wall thickening and excursion during stress, and (3) a biphasic response to dobutamine stress. Mild ischemia was reported when less than 3 left ventricular segments were abnormal at stress. Moderate ischemia was defined as 3 or more abnormal segments but no high-risk features. Severe ischemia was defined as 3 or more abnormal segments with high-risk features (transient cavity dilation and/or peak wall motion score index ≥1.7). - SPECT MPI: abnormal test consisted of a summed difference score ≥4. Mild ischemia was defined as a summed difference score of 4 to 8. Moderate ischemia was defined as a summed difference score of 9 to 13. Severe ischemia was defined as a summed difference score of ≥13.			

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
Pineiro-Portela, 2021 Single Center Spain Funding NR	Population: Patients admitted to a chest pain unit to detect acute coronary syndrome Setting: Chest pain unit Inclusion: Aged 18 to 80 years, with 1 or more cardiovascular risk factors, and referred to our Chest Pain Unit from the Emergency Department with suspicion of Acute Coronary Syndrome, nondiagnostic ECG, and negative serial tests for markers of myocardial injury. Other requirements were last pain episode at least 12 hours earlier, at least 2 ECGs performed a minimum of 6 to 12 hours apart, and troponin I ≤0.3 mg/dL (2 or more measurements at least 6 hours apart) Exclusion: History of stent implantation, inability to perform a prolonged breath-hold (10-15	**A: CCTA (64 slice) (n=100)** Stressor: A total of 46% of patients were administered intravenous atropine Contrast: Iodinated contrast Protocol: Patients with a positive test were referred for coronary angiography. Suspicion of ACS was confirmed when the coronary angiography showed narrowing > 50% in any coronary arteries or branches in the territory that was positive using the classification technique. Patients were discharged if the triage results were negative. During follow-up, treatment was started or switched as deemed necessary by the attending physician. Definition of positive test: Significant ischemia: Narrowing > 50% in any coronary arteries or branches **B: Stress Echo (n=103)** Stressor: Exercise treadmill (A total of 15% of patients were administered intravenous atropine) Contrast: Echocardiography contrast was not necessary for any patients	NR All patients had at least 1 cardiovascular risk factor. Most patients had a low TIMI score (68% in TIMI I and 32% in TIMI II), with no differences observed between the 2 groups (p=0.37)	A vs. B Subgroup: None N randomized: 203 Mean age (SD): Female: 50% vs. 50% Race: NR Chest pain: - Typical angina: 56% vs. 64% - Atypical/probable angina: 44% vs. 32% - Nonanginal chest pain: 0% vs. 4%, p=0.04 Dyspnea: NR Prior MI: NR Prior revascularization: NR Prior stent: 0% vs. 0% History of CAD: 12% vs. 19% Chest pain frequency: NR Hypertension: 71% vs. 70% Hyperlipidemia: NR Hypercholesterolemia: 74% vs. 76% Diabetes: 27% vs. 29%	Mean (SD) follow-up: 4.7 (2.7) years % Followed: 100% (203/203)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
	seconds), irregular heart rate, contraindication for beta-blockers if heart rate was > 65 bpm or systolic blood pressure was < 100 mmHg, contraindication for atropine, allergy to iodinated contrast material, pregnancy, or creatinine > 1.3 mg/dL	Protocol: Same as above Definition of positive test: Extensive ischemia: involvement of ≥3 segments		Current and former smokers: 39% vs. 34%, p=0.55 Family history of CAD: 6% vs. 4%	

ACS = acute coronary syndrome, BMI = Body Mass Index, CAC = coronary artery calcium, CACS = coronary artery calcium scoring, CAD = coronary artery disease, CCTA = coronary computed tomography, ECG = electrocardiogram, ECHO = echocardiography, f/u = follow-up, ICA = invasive coronary angiogram, mg = milligram, MI = myocardial infarction, MPI = myocardial perfusion imaging, NA = not applicable, NR = not reported, SD = standard deviation, SE = stress echo, SPECT = single photon emission computed tomography, US = United States, vs. = versus.

* p-values non-significant unless reported

Appendix Table F14. Data abstraction for CCTA vs. Stress Echo: Efficacy Outcomes

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Suspected ACS							
Levsky, 2018 CCTA vs. Stress Echo Subgroup analyses: N	**Disposition, % (n/N)** Index visit - Hospitalized: 19.4% (39/201) vs. 11.1% (22/199), difference 8% (95% CI 1% to 15%), p=0.026 **Test results** NR	**All-cause mortality, % (n/N) [component of composite outcome]** Median follow-up of 2 years 1.0% (2/201) vs. 0.5% (1/199), p=1.0 [all 3 had advanced metastatic cancer diagnosed after recruitment] **Cardiac Mortality, % (n/N)** Median follow-up of 2 years	**Nonfatal myocardial infarction, % (n/N)** Median follow-up of 2 years 3.5% (7/201) vs. 2.0% (4/199), p=0.54	**Any revascularization, % (n/N)** Median follow-up of 2 years 5.5% (11/201) vs. 3.5% (7/199), p=0.81* - **CABG**: 2.0% (4/201) vs. 0.0% (0/199), p=0.26 - **PCI**: 3.5% (7/201) vs. 3.5% (7/199), p=1.0	**Cardiac catheterization, % (n/N)** Median follow-up of 2 years 11.0% (23/201) vs. 9.0% (18/199), p=0.51 - Resulting in no revascularization: 6.0% (12/201) vs. 5.5% (11/199), p=0.83 **Proportion of patients requiring additional non-invasive imaging, % (n/N)** Median follow-up of 2 years **- CCTA**: 0% (0/201) vs. 3% (6/199), p=0.01 - **Stress Echo**: 14% (29/201) vs. 7% (14/199), p=0.02	**Major adverse cardiovascular events (consisting of death, myocardial infarction, stroke, and cardiac arrest), % (n/N)** Median follow-up of 2 years 5.5% (11/201) vs. 3.5% (7/199), p=0.47†	**Emergency Department length of stay (hours) for discharged patients, Median (IQR)** Index visit (From randomization to discharge) 5.4 (4.2 to 6.4) vs. 4.7 (3.5 to 6.0), p<0.001 **Hospital length of stay (hours) for admitted patients, Median (IQR)** From hospital admission to discharge 58 (50 to 102) vs. 34 (31 to 54), p=0.002

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
		0% (0/201) vs. 0% (0/199), p=NR			- **MPI**: 6% (12/201) vs. 4% (8/199), p=0.49 **New aspirin prescription, % (n/N)** Median follow-up of 2 years 13% (27/201) vs. 8.0% (15/199), p=0.07 **New or increased lipid prescription, % (n/N)** Median follow-up of 2 years 14% (28/201) vs. 6% (12/199), p=0.01 **New clopidogrel prescription, % (n/N)** Median follow-up of 2 years 4% (8/201) vs. 4% (7/199), p=1.0 **New beta-blocker prescription, % (n/N)**		**Nonfatal stroke, % (n/N) [component of composite outcome]** Median follow-up of 2 years 0.5% (1/201) vs. 2.0% (3/199), p=0.37 **Nonfatal cardiac arrest, % (n/N) [component of composite outcome]** Median follow-up of 2 years 0.5% (1/201) vs. 0% (0/199), p=1.0 **Rehospitalization for any cause, % (n/N)** Median follow-up of 2 years 16.0% (32/201) vs. 14.0 (28/199), p=0.68

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
					Median follow-up of 2 years 9% (18/201) vs. 4% (7/199), p=0.04		**Cardiac-related Rehospitalization, % (n/N)** Median follow-up of 2 years 6.0% (12/201) vs. 4.0 (8/199), p=0.49 **Emergency Department Revisit for any reason, % (n/N)** Median follow-up of 2 years 48.0% (97/201) vs. 41.0% (82/199), p=0.16 **Cardiac-related Emergency Department Revisit, % (n/N)** Median follow-up of 2 years 14.0% (28/201) vs. 14% (27/199), p=1.0

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							Primary care visit, % (n/N) Median follow-up of 2 years 44.0% (89/201) vs. 38.0% (76/199), p=0.22 **Cardiology outpatient visit, % (n/N)** Median follow-up of 2 years 17.0% (35/201) vs. 17.0% (34/199), p=1.0 **Continued chest pain or shortness of breath, % (n/N)** 1 month 28% (54/201) vs. 19% (36/199), p=0.03
PERFECT trial Uretsky, 2017	**Disposition** All patients had already been	**All-cause mortality, % (n/N)**	**Nonfatal myocardial**	**Proportion of patients requiring**	**Proportion of patients receiving additional**	NR	**Time spent in the hospital (hours), mean (SD)**

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
CCTA vs. Stress Echo Subgroup analyses: N	admitted to the hospital at the start of the study **Test results for Group A (CCTA), % (n/N)‡** - No coronary artery disease: 50.5% (95/188) - <50% stenosis: 37.2% (70/188) - 50% to 70% stenosis: 3.2% (6/188) - ≥70% stenosis: 8.5% (16/188) - Uninterpretable due to artifact: 0.5% (1/188) **Test results for Group B (Stress tests), % (n/N)‡** - Normal: 94.5% (188/199) - Abnormal: 5.5% (11/199)	12 months 0% (0/206) vs. 0% (0/205), p=NR	**infarction, % (n/N)** 12 months 1% (2/206) vs. 0.5% (1/205), p=NR	**revascularization, % (n/N)** 12 months Any revascularization: 7% (15/198) vs. 1% (2/197), p=0.002 - **PCI**: 6% (13/198) vs. 0% (0/197), p<0.001 - **CABG**: 1% (2/198) vs. 1% (2/197), p=1.0 **Change in medication use from admission to discharge, % (n/N)** - Aspirin: 24% (50/206) vs. 16% (33/205), p=0.30 - Statin: 18% (37/206) vs. 17% (35/205), p=0.90 - Anti-hypertensive drugs: 10% (20/206) vs. 18% (37/205), p=0.40	**downstream testing, % (n/N)** 12 months Any additional test: 21% (43/198) vs. 15% (30/197), p=0.10 - **Stress tests**: 14% (28/198) vs. 11% (23/197), p=0.60 - **CCTA**: 1% (2/198) vs. 4% (9/197), p=0.40 - **ICA**: 11% (22/198) vs. 2% (5/197), p=0.001		From hospital admission to discharge 48 (40) vs. 49 (48), p=0.80 **Proportion of patients experience a cardiovascular-related repeat hospitalization, %(n/N)** 12 months 14% (28/198) vs. 16% (33/197), p=0.50 **Unstable angina, % (n/N)** 12 months 0.5% (1/206) vs. 0% (0/205), p=NR

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				- Beta-blocker: 8% (18/206) vs. 6% (13/205) - Calcium channel blockers: 5% (11/206) vs. 3% (5/205), p=0.70 - Nitrates: 5% (9/206) vs. 4% (9/205), p=1.0 - Antiplatelet drugs: 3% (6/206) vs. 3% (7/205), p=1.0 - Insulin: 1% (3/206) vs. 1% (2/205), p=0.40 - Oral hypoglycemics: 0% (0/206) vs. 0% (0/205), p=1.0			
Pineiro-Portela, 2021 CCTA vs. Stress Echo	**Disposition, % (n/N)** - Discharged from hospital after index test: 73% (73/100) vs. 67% (69/103), p=NR	**All-cause mortality, % (n/N)** Mean follow-up of 4.7 years 5% (5/100) vs. 2.9% (3/103), p=0.39	**Non-fatal myocardial infarction, % (n/N)** 12 months 1% (1/100) **[STEMI]** vs.	**Revascularization, % (n/N)** 24.1% (49/203) [Not reported by group]	**Proportion of patients receiving ICA, % (n/N)** After index test 27% (27/100) vs. 33% (34/103), p=NR	**Composite outcome (including death, nonfatal myocardial infarction, revascularizations, and readmissions), % (n/N)**	**Chest pain unit revisit, % (n/N)** 12 months 4% (4/100) vs. 2.9% (3/103), p=NR Mean follow-up of 4.7 years

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Subgroup analyses: N	- Hospitalized for further testing after index visit: 27% (27/100) vs. 33% (34/103), p=NR **Test results for Group A (CCTA), % (n/N)** - Positive ischemia: 27% (27/100) - Inconclusive: 6% (6/100) **Test results for Group B (Stress Echo), % (n/N)** <u>Index test</u> - Positive ischemia: 35% (36/103) - Necrosis without associated ischemia: 2% (2/103)	[The cause of death was cardiovascular in 4 patients but group NR	0% (0/103), p=NR <u>Mean follow-up of 4.7 years</u> 2% (2/100) vs. 1.9% (2/103), p=0.51		- ACS confirmed on ICA: 85% (23/27) vs. 88% (30/34), p=NR Proportion of patients receiving additional non-invasive testing during follow-up, % (n/N) - Echocardiogram: 46% (46/100) vs. 30% (31/103), p=0.01 - Stress test: 14% (14/100) vs. 4% (4/103), p=0.01 - Stress echo: 28% (28/100) vs. 25% (26/103), p=0.38 - CCTA: 0% (0/100) vs. 2% (2/103), p=0.25	<u>Mean follow-up of 4.7 years</u> 41% (41/100) vs. 42% (43/100), p=0.91	12% (12/100) vs. 8.7% (9/103), p=NR **Hospital length of stay for patients referred for invasive coronary angiography (days), Median (range)** <u>Index visit</u> 8 (5 to 10.25) vs. 7 (5 to 10), p=0.90

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	- Inconclusive: 4.9% (5/103)						

ACS = acute coronary syndrome, CABG = coronary artery bypass graft, CAD = coronary artery disease, CCTA = coronary computed tomography, CI = confidence interval, ECHO = echocardiography, ICA = invasive coronary angiogram, IQR = inter-quartile range, MPI = myocardial perfusion imaging, N = no, NR = not reported, PCI = percutaneous coronary intervention, SD = standard deviation, STEMI = ST-Segment Elevation Myocardial Infarction, vs. = versus, Y = yes.

* One CCTA patient underwent both CABG and PCI

† 1 Stress Echo patient had both a nonfatal myocardial infarction and a nonfatal stroke; 2 CCTA patients had 2 nonfatal myocardial infarctions

‡ Test results are reported as tested, not as randomized. There were also 3.5% (8/206) of the patients originally randomized to CCTA and 6% (13/205) of the patients originally randomized to stress testing that ultimately did not undergo any testing.

Appendix Table F15. Data abstraction for CCTA vs. Stress Echo: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Suspected ACS			
Levsky, 2018 CCTA vs. Stress Echo	**Serious complications from noninvasive imaging, % (n/N)** Index visit 0% (0/201) vs. 0% (0/199), p=1.0 **Complaints or adverse reactions to imaging, % (n/N)** Index visit 14% (26/189) vs. 6.4% (12/188), p=0.03 **Proportion of patients that complained about examination length or positional discomfort, % (n/N)** Index visit 9% (17/189) vs. 3% (6/188), p=0.03 **Proportion of patients that complained about chest pain or shortness of breath during imaging, % (n/N)** Index visit 0% (0/189) vs. 3% (5/188), p=0.03	NR	**Effective radiation dose (mSv), Median (IQR)** Initial assigned noninvasive imaging 6.4 (5.3 to 7.8) vs. 0 (0 to 0), p<0.001 (n=189 vs. 189) Complete initial work-up 6.5 (5.2 to 8.7) vs. 0 (0 to 0), p<0.001 (n=201 vs. 199)* 12 months (all cardiac imaging) 6.5 (5.3 to 9.7) vs. 0 (0 to 0), p<0.001 (n=201 vs. 199) Median follow-up of 2 years (all cardiac imaging) 6.5 (5.5 to 10) vs. 0 (0 to 0), p<0.001 (n=201 vs. 199)
PERFECT trial Uretsky, 2017 CCTA vs. Stress Echo	NR	NR	NR
Pineiro-Portela, 2021 CCTA vs. Stress Echo	NR	NR	NR

ACS = acute coronary syndrome, AE = adverse events, ECHO = echocardiography, IQR = inter-quartile range, mSv = milliseverts, NR = not reported.

* Although patients in the SE arm underwent subsequent noninvasive imaging and catheterization involving radiation, this involved fewer than one-quarter of patients; thus, the interquartile ranges for radiation exposure remain zero. The mean complete initial work-up dose for SE was 0.96 mSv compared with 7.7 mSv for coronary CCTA.

Appendix Table F16. Data abstraction for Subgroup analyses for efficacy outcomes from CCTA trials

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
CCTA vs. any functional testing								
Chang, 2008	Index visit	**Discharged from ED after index visit**	Low pre-test probability	86% (43/50)	84% (41/49)	NR	0.747	NR
			Intermediate pre-test probability	53% (29/55)	45% (25/56)	NR	0.394	
			High pre-test probability	21% (6/28)	0% (0/28)	NR	NA	
	Index visit	**Admitted to hospital after index visit**	Low pre-test probability	14% (7/50)	16% (8/49)	NR	0.747	NR
			Intermediate pre-test probability	47% (26/55)	55% (31/56)	NR	0.394	
			High pre-test probability	79% (22/28)	100% (28/28)	NR	0.010	
	Index visit	**Revascularization**	Low pre-test probability	6% (3/50)	2% (1/49)	NR	0.617	NR
			Intermediate pre-test probability	20% (11/55)	23% (13/56)	NR	0.681	
			High pre-test probability	43% (12/28)	50% (14/28)	NR	0.592	
	Index visit	**Necessary admission for ACS (for NSTEMI or unstable angina)**	Low pre-test probability	6% (3/50)	6% (3/49)	NR	1.0	NR
			Intermediate pre-test probability	36% (20/55)	32% (18/56)	NR	0.639	
			High pre-test probability	57% (16/28)	64% (18/28)	NR	0.584	
	Index visit	**Necessary admission for ACS (for NSTEMI)**	Low pre-test probability	4% (2/50)	4% (2/49)	NR	NR	NR

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			Intermediate pre-test probability	9% (5/55)	9% (5/56)	NR	NR	
			High pre-test probability	14% (4/28)	29% (8/28)	NR	NR	
	Index visit	**Necessary admission for ACS (for unstable angina)**	Low pre-test probability	2% (1/50)	2% (1/49)	NR	NR	NR
			Intermediate pre-test probability	27% (15/55)	24% (13/56)	NR	NR	
			High pre-test probability	43% (12/28)	36% (10/28)	NR	NR	
	Index visit	**Unnecessary admissions***	Low pre-test probability	0% (0/50)	6% (3/49)	NR	0.117	NR
			Intermediate pre-test probability	4% (2/55)	20% (11/56)	NR	0.015	
			High pre-test probability	18% (4/28)	21% (6/28)	NR	1.0	
	Index visit	**Referral for ICA**	Low pre-test probability	6% (3/50)	10% (5/49)	NR	0.483	NR
			Intermediate pre-test probability	42% (23/55)	46% (26/56)	NR	0.625	
			High pre-test probability	75% (21/28)	93% (26/28)	NR	0.143	
CATCH trial	Median follow-up: 18.7 months	**MACE**	History of CAD	9% (4/44)	14% (5/36)	NR	0.49	NR
			No history of CAD	0.4% (1/241)	4% (9/255)	NR	0.01	
			Low pre-test probability‡	0% (0/59)	0% (0/60)	NR	1.0	NR

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			Intermediate pre-test probability	1% (1/161)	4% (7/173)	NR	0.04	
			High pre-test probability	0% (0/21)	9% (2/22)	NR	0.14	
	Median follow-up: 18.7 months	**MACE + readmission for chest pain**	History of CAD	27% (12/44)	33% (12/36)	NR	0.49	NR
			No history of CAD	7% (18/241)	15% (38/255)	NR	0.02	
			Low pre-test probability§	3% (2/59)	8% (5/60)	NR	0.25	NR
			Intermediate pre-test probability	9% (14/161)	14% (24/173)	NR	0.13	
			High pre-test probability	10% (2/21)	27% (6/22)	NR	0.12	
PROMISE trial	Median follow-up: 25 months	**Primary composite end point (includes death from any cause, nonfatal MI, hospitalization for unstable angina, or major procedural complication)**	Age <65 (N=7111)	NR	NR	HR: 1.10 (95% CI 0.82 to 1.47)**	NR	0.591
			Age ≥65 (N=2892)	NR	NR	HR: 0.97 (95% CI 0.69 to 1.36)**	NR	
			Male (N=4733)	NR	NR	HR: 0.99 (95% CI 0.74 to 1.32)**	NR	0.698
			Female (N=5270)	NR	NR	HR: 1.08 (95% CI 0.76 to 1.51)**	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			White (N=8371)	NR	NR	HR: 0.95 (95% CI 0.74 to 1.20)**	NR	0.100
			Non-white (N=1545)	NR	NR	HR: 1.62 (95% CI 0.89 to 2.92)**	NR	
			Low pre-test risk (≤30%) (N=3755)	NR	NR	HR: 1.33 (95% CI 0.88 to 2.00)**	NR	0.341
			Intermediate pre-test risk (31%-70%) (N=5750)	NR	NR	HR: 0.92 (95% CI 0.69 to 1.23)**	NR	
			High pre-test risk (>70%) (N=481)	NR	NR	HR: 0.94 (95% CI 0.51 to 1.74)**	NR	
			CAD risk equivalent †† (N=2531)	NR	NR	HR: 0.83 (95% CI 0.57 to 1.20)**	NR	0.142
			Not CAD risk equivalent (N=7472)	NR	NR	HR: 1.17 (95% CI 0.89 to 1.54)**	NR	
			Low pre-test probability	NR	NR	HR: 2.30 (95% CI	NR	0.603

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			(N=250)			0.45 to 11.88)**		
			Intermediate pre-test probability (N=9258)	NR	NR	HR: 1.00 (95% CI 0.79 to 1.26)**	NR	
			High pre-test probability (N=495)	NR	NR	HR: 1.08 (95% CI 0.53 to 2.23)**	NR	
			Physician intended functional test of stress nuclear prior to randomization (N=6781)	NR	NR	HR: 0.93 (95% CI 0.72 to 1.21)**	NR	
			Physician intended functional test of stress echo prior to randomization (N=2236)	NR	NR	HR: 1.27 (95% CI 0.78 to 2.05)**	NR	0.293
			Physician intended functional test of exercise ECG prior to randomization (N=986)	NR	NR	HR: 1.80 (95% CI 0.66 to 4.86)**	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
	Median follow-up: 25 months	**Primary composite end point + catheterization without obstructive CAD**	Age <65 (N=7111)	NR	NR	HR: 0.94 (95% CI 0.78 to 1.13)**	NR	0.695
			Age ≥65 (N=2892)	NR	NR	HR: 0.87 (95% CI 0.68 to 1.12)**	NR	
			Male (N=4733)	NR	NR	HR: 0.94 (95% CI 0.76 to 1.15)**	NR	0.633
			Female (N=5270)	NR	NR	HR: 0.87 (95% CI 0.70 to 1.09)**	NR	
			White (N=8371)	NR	NR	HR: 0.88 (95% CI 0.74 to 1.03)**	NR	0.260
			Non-white (N=1545)	NR	NR	HR: 1.12 (95% CI 0.75 to 1.69)**	NR	
			Low pre-test risk (≤30%) (N=3755)	NR	NR	HR: 0.95 (95% CI 0.73 to 1.24)**	NR	0.839

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			Intermediate pre-test risk (31%-70%) (N=5750)	NR	NR	HR: 0.90 (95% CI 0.74 to 1.10)**	NR	
			High pre-test risk (>70%) (N=481)	NR	NR	HR: 0.81 (95% CI 0.50 to 1.30)**	NR	
			CAD risk equivalent (N=2531)	NR	NR	HR: 0.85 (95% CI 0.65 to 1.11)**	NR	0.540
			Not CAD risk equivalent (N=7472)	NR	NR	HR: 0.94 (95% CI 0.79 to 1.13)**	NR	
			Low pre-test probability (N=250)	NR	NR	HR: 0.85 (95% CI 0.33 to 2.20)**	NR	
			Intermediate pre- test probability (N=9258)	NR	NR	HR: 0.90 (95% CI 0.77 to 1.06)**	NR	0.980
			High pre-test probability (N=495)	NR	NR	HR: 0.96 (95% CI 0.57 to 1.61)**	NR	
			Physician intended	NR	NR	HR: 0.87 (95% CI	NR	0.548

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			functional test of stress nuclear prior to randomization (N=6781)			0.73 to 1.03)**		
			Physician intended functional test of stress echo prior to randomization (N=2236)	NR	NR	HR: 1.06 (95% CI 0.76 to 1.49)**	NR	
			Physician intended functional test of exercise ECG prior to randomization (N=986)	NR	NR	HR: 0.99 (95% CI 0.53 to 1.87)**	NR	
	Median follow-up: 25 months	**Proportion of patients with positive invasive coronary angiography (Cath)**	BMI <35	58.8% (255/434)	Nuclear Stress: 47.8% (100/209)	NR	NR	NR
					Stress Echo% 29.5% (23/78)	NR	NR	
					Ex ECG: 56.3%% (9/16)	NR	NR	
			BMI ≥35	51.7% (45/87)	Nuclear Stress: 29.5% (23/78)	NR	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
					Stress Echo: 66.7% (6/9)	NR	NR	
					Ex ECG: 75.0% (3/4)	NR	NR	
	Within 90 days of index test	**Proportion of patients referred for ICA**	With diabetes	15.1% (141/936)	Any functional test: 10.2% (99/972)	Adj. OR 2.12 (95% CI 1.50 to 3.00) §§	<0.001	0.596
			Without diabetes	10.9% (388/3564)	Any functional test: 7.6% (265/3494)	Adj. OR 1.90 (95% CI 1.56 to 2.33) §§	<0.001	
	Within 30 days of ICA	**Proportion of patients referred for revascularization**	With diabetes	55.7% (78/140)	Any functional test: 38.0% (38/100)	Adj. OR 1.51 (95% CI 0.65 to 3.49) §§	0.340	0.372
			Without diabetes	49.2% (191/388)	Any functional test: 38.7% (103/266)	Adj. OR 0.95 (95% CI 0.55 to 1.65) §§	0.861	
	60-day visit	**Medication use to Aspirin**	With diabetes	62.1% (530/854)	Any functional test: 57.3% (504/879)	Adj. OR 1.23 (95% CI 1.01 to 1.50) §§	0.036	0.907
			Without diabetes	52.4% (1658/3167)	Any functional	**Adj. OR 1.25**	<0.001	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
					test: 47.5% (1452/3059)	**(95% CI 1.13 to 1.38) §§**		
	60-day visit	**Medication use to Statin**	With diabetes	71.4% (610/854)	Any functional test: 64.3% (565/879)	Adj. OR 1.40 (95% CI 1.14 to 1.72) §§	0.001	0.783
			Without diabetes	52.9% (1675/3167)	Any functional test: 45.8% (1401/3059)	Adj. OR 1.36 (95% CI 1.23 to 1.50) §§	<0.001	
	60-day visit	**Medication use to Beta Blocker**	With diabetes	35.3% (301/854)	Any functional test: 33.3% (293/879)	Adj. OR 1.10 (95% CI 0.89 to 1.34) §§	0.379	0.941
			Without diabetes	28.7% (909/3167)	Any functional test: 27.3% (835/3059)	Adj. OR 1.10 (95% CI 0.99 to 1.24) §§	0.083	
	60-day visit	**Medication use to angiotensin-converting enzyme inhibitor/angiotensin receptor blocker**	With diabetes	70.6% (603/854)	Any functional test: 68.7% (604/879)	Adj. OR 1.10 (95% CI 0.89 to 1.35) §§	0.382	0.339
			Without diabetes	37.3% (1180/3167)	Any functional	Adj. OR 0.98 (95% CI	0.697	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
					test: 37.8% (1157/3059)	0.88 to 1.09) §§		
	Index test	**Test positive rate (≥70% stenosis in at least one epicardial artery or ≥50% stenosis in the left main)**	Male	16.1% (350/2168)	Any functional test: 14.0% (290/2078)	adj. OR 1.23 (95% CI 1.04 to 1.47) §§	CCTA vs. any functional test: 0.019	CCTA vs. any functional test: <0.001
					Nuclear Stress: 16.9% (230/1362)	adj. OR 1.03 (95% CI 0.85 to 1.25) §§	CCTA vs. Nuclear Stress: 0.75	CCTA vs. Nuclear Stress: NR
					Stress Echo: 7.7% (36/465)	adj. OR 2.10 (95% CI 1.45 to 3.04) §§	CCTA vs. Stress Echo: <0.001	CCTA vs. Stress Echo: NR
					Ex ECG: 9.6% (24/251)	adj. OR 1.79 (95% CI 1.15 to 2.80) §§	CCTA vs. Ex ECG: 0.01	CCTA vs. Ex ECG: NR
			Female	7.9% (184/2332)	Any functional test: 11.5% (274/2388)	adj. OR 0.67 (95% CI 0.55 to 0.82) §§	CCTA vs. any functional test: <0.001	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
					Nuclear Stress: 12.0% (205/1704)	adj. OR 0.66 (95% CI 0.53 to 0.82) §§	CCTA vs. Nuclear Stress: <0.001	
					Stress Echo: 7.7% (39/505)	adj. OR 0.90 (95% CI 0.63 to 1.30) §§	CCTA vs. Stress Echo: 0.58	
					Ex ECG: 16.8% (30/179)	adj. OR 0.39 (95% CI 0.25 to 0.61) §§	CCTA vs. Ex ECG: <0.001	
			BMI <35	12.2% (439/3589)	Nuclear Stress: 13.1% (310/2361)	NR	NR	0.003
					Stress Echo: 7.8% (62/795)	NR	NR	
					Ex ECG: 12.8% (47/368)	NR	NR	
			BMI ≥35	10.3% (90/872)	Nuclear Stress: 18.1% (123/679)	NR	NR	
					Stress Echo: 7.9% (13/165)	NR	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
					Ex ECG: 11.7% (7/60)	NR	NR	
			Age <65 years	10.1% (328/3249)	Any functional test: 11.2% (350/3129)	Adj. OR 1.13 (95% CI 0.96 to 1.33)	p>0.05	
			Age 65-74	15.2% (1553/1008)	Any functional test: 15.6% (164/1054)	Adj. OR 1.04 (95% CI 0.82 to 1.33)	p>0.05	0.20
			Age ≥75	21.8% (53/243)	Any functional test: 17.7% (50/283)	Adj. OR 0.74 (95% CI 0.48 to 1.15)	p>0.05	
			With diabetes	14.9% (139/936)	Nuclear Stress: 17.7% (126/711)	NR	NR	
					Stress Echo: 9.2% (17/185)	NR	NR	
					Ex ECG: 9.2% (7/76)	NR	NR	0.930
			Without diabetes	11.1% (395/3564)	Nuclear Stress: 13.1% (309/2355)	NR	NR	
					Stress Echo: 7.4% (58/785)	NR	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
					Ex ECG: 13.3% (47/354)	NR	NR	
	Median follow-up: 25 months	**Composite outcome of cardiovascular death, myocardial infarction, and unstable angina hospitalization**	With diabetes	3.4% (32/936)	Any functional test: 4.4% (43/972)	Adj. HR 0.74, 95% CI 0.47 to 1.18)***	0.207	0.096
			Without diabetes	3.0% (105/3564)	Any functional test: 2.4% (85/3494)	Adj. HR 1.18, 95% CI 0.88 to 1.57)***	0.269	
	Median follow-up: 25 months	**Composite outcome of cardiovascular death, myocardial infarction**	With diabetes	1.1% (10/936)	Any functional test: 2.6% (25/972)	Adj. HR 0.38, 95% CI 0.18 to 0.79)***	0.01	0.02
			Without diabetes	1.4% (50/3564)	Any functional test: 1.29% (45/3494)	Adj. HR 1.03, 95% CI 0.69 to 1.54)***	0.887	
	6 months from randomization	**Death**	With diabetes	0.2% (2/936)	Any functional test: 0.5% (5/972)	NR	NR	NR
			Without diabetes	0.1% (4/3564)	Any functional test: 0.3% (12/3494)	NR	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
	6 months from randomization	**Cardiovascular death**	With diabetes	0.2% (2/936)	Any functional test: 0.4% (4/972)	NR	NR	NR
			Without diabetes	0.0% (0/3564)	Any functional test: 0.2% (7/3494)	NR	NR	
	6 months from randomization	**Myocardial infarction**	With diabetes	0.1% (1/936)	Any functional test: 0.8% (8/972)	NR	NR	NR
			Without diabetes	0.2% (8/3564)	Any functional test: 0.2% (6/3494)	NR	NR	
	6 months from randomization	**Unstable angina hospitalization**	With diabetes	0.9% (8/936)	Any functional test: 0.5% (5/972)	NR	NR	NR
			Without diabetes	0.6% (23/3564)	Any functional test: 0.6% (21/3494)	NR	NR	
	At end of followup	**Death**	With diabetes	1.7% (16/936)	Any functional test: 2.0% (19/972)	NR	NR	NR
			Without diabetes	1.3% (46/3564)	Any functional test: 1.3% (45/3494)	NR	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
	At end of followup	**Cardiovascular death**	With diabetes	0.9% (8/936)	Any functional test: 1.2% (12/972)	NR	NR	NR
			Without diabetes	0.7% (26/3564)	Any functional test: 0.8% (29/3494)	NR	NR	
	At end of followup	**Myocardial infarction**	With diabetes	0.2% (2/936)	Any functional test: 1.3% (13/972)	NR	NR	NR
			Without diabetes	0.7% (24/3564)	Any functional test: 0.5% (17/3494)	NR	NR	
	At end of followup	**Unstable angina hospitalization**	With diabetes	1.5% (14/936)	Any functional test: 1.1% (11/972)	NR	NR	NR
			Without diabetes	1.1% (38/3564)	Any functional test: 0.8% (29/3494)	NR	NR	
ROMICAT-II trial	Index Visit	**Hospital length of stay (hours)**	Females	17.0 (24.5)	30.7 (24.1)	NR	<0.0001	0.006
			Males	28.8 (44.7)	31.0 (30.9)	NR	0.44	
			With diabetes	32.2 (43.2)	32.0 (20.1)	NR	0.97	0.08
			Without diabetes	21.3 (35.3)	30.6 (29.4)	NR	<0.0001	
	Index Visit	**Direct ED discharge**	Females	55% (132/239)	14% (33/229)	NR	<0.0001	0.22

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			Males	41% (107/262)	12% (33/270)	NR	<0.0001	
			With diabetes	40% (34/86)	14% (12/87)	NR	0.0001	0.27
			Without diabetes	49% (205/415)	13% (54/412)	NR	<0.0001	
			White	46% (153/330)	11% (35/329)	NR	<0.001	0.27
			Black	43% (61/141)	14% (19/140)	NR	<0.001	
	Index Visit	**Hospital admission**	Females	33% (14/239)	25% (57/229)	NR	0.003	0.005
			Males	29% (75/262)	26% (69/270)	NR	0.44	
			With diabetes	35% (30/86)	29% (25/87)	NR	0.41	0.09
			Without diabetes	19% (78/415)	25% (101/412)	NR	0.05	
			White	23% (75/330)	25% (82/329)	NR	0.51	0.31
			Black	18% (25/141)	26% (36/140)	NR	0.11	
	Index Visit	**Downstream testing during index visit**	Females	16% (37/239)	10% (22/229)	NR	0.07	0.08
			Males	30% (79/262)	12% (31/270)	NR	<0.0001	
			With diabetes	38% (33/86)	5% (4/87)	NR	<0.0001	0.001
			Without diabetes	20% (83/415)	12% (49/412)	NR	0.002	
			White	24% (80/330)	13% (42/329)	NR	<0.001	0.16
			Black	22% (/141)	6% (9/140)	NR	<0.001	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
	28 day follow-up	**Downstream testing at any point**	Females	20% (47/239)	24% (11/229)	NR	0.007	0.23
			Males	33% (86/262)	13% (86/270)	NR	<0.0001	
			With diabetes	42% (36/86)	7% (6/87)	NR	<0.0001	0.002
			Without diabetes	23% (97/415)	13% (54/412)	NR	0.0001	
			White	29% (95/330)	15% (48/329)	NR	<0.001	0.18
			Black	23% (32/141)	6% (9/140)	NR	<0.001	
	Index Visit	**ICA at index visit**	Females	5% (12/239)	5% (12/229)	NR	1.0	0.15
			Males	16% (42/262)	9% (24/270)	NR	0.02	
			With diabetes	19% (16/86)	6% (5/87)	NR	0.01	0.06
			Without diabetes	9% (38/415)	8% (31/412)	NR	0.45	
			White	13% (44/330)	9% (30/329)	NR	0.11	0.83
			Black	5% (7/141)	3% (4/140)	NR	0.54	
	28 day follow-up	**ICA at any point**	Females	5% (13/239)	5% (12/229)	NR	1.0	0.24
			Males	18% (46/262)	10% (28/270)	NR	0.02	
			With diabetes	20% (17/86)	7% (6/87)	NR	0.01	0.08
			Without diabetes	10% (42/415)	8% (34/412)	NR	0.40	
			White	15% (48/330)	10% (34/329)	NR	0.12	0.68
			Black	6% (8/141)	3% (4/140)	NR	0.38	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
	Index Visit	**PCI at index visit**	Females	2% (5/239)	1% (2/229)	NR	0.45	0.69
			Males	7% (19/262)	4% (12/270)	NR	0.20	
			With diabetes	7% (6/86)	2% (2/87)	NR	0.17	0.41
			Without diabetes	4% (18/415)	3% (12/412)	NR	0.35	
			White	6% (20/330)	4% (13/329)	NR	0.28	NA
			Black	1% (2/141)	0% (0/140)	NR	0.50	
	28 day follow-up	**PCI at any point**	Females	3% (6/239)	1% (2/229)	NR	0.29	0.45
			Males	8% (21/262)	6% (15/270)	NR	0.30	
			With diabetes	7% (6/86)	2% (2/87)	NR	0.17	0.37
			Without diabetes	5% (21/415)	4% (15/412)	NR	0.40	
			White	7% (22/330)	5% (16/329)	NR	0.40	NA
			Black	5% (16/141)	0% (0/140)	NR	0.25	
	28 day follow-up	**PCI/CABG at 28-day**	Females	3% (7/239)	1% (2/229)	NR	0.18	0.33
			Males	10% (25/262)	7% (18/270)	NR	0.27	
			With diabetes	8% (7/86)	2% (2/87)	NR	0.10	0.26
			Without diabetes	6% (25/415)	4% (18/412)	NR	0.35	
	28 day follow-up	**Repeat ED visit or hospitalizations for chest pain**	Females	3% (6/239)	1% (2/229)	NR	0.50	0.11
			Males	3% (9/262)	6% (17/270)	NR	0.77	
			With diabetes	0% (0/86)	5% (4/87)	NR	0.25	0.97
			Without diabetes	3% (14/415)	4% (15/412)	NR	0.55	
			White	2% (8/330)	5% (16/329)	NR	0.10	0.049

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			Black	4% (6/141)	1% (2/140)	NR	0.28	
	3 day safety follow-up	**Missed acute coronary syndrome**	Females	0% (0/239)	0% (0/229)	NR	NA	NA
			Males	0% (0/262)	0% (0/270)	NR	NA	
			With diabetes	0% (0/86)	0% (0/87)	NR	NA	NA
			Without diabetes	0% (0/415)	0% (0/412)	NR	NA	
			White	0% (0/330)	0% (0/329)	NR	NA	NA
			Black	0% (0/141)	0% (0/140)	NR	NA	
	28 day follow-up	**MACE 28 days**	Females	0.4% (1/239)	0.4% (1/229)	NR	1.0	0.48
			Males	0.4% (1/262)	1.9% (5/270)	NR	0.22	
			With diabetes	0% (0/86)	1% (1/87)	NR	1.0	0.97
			Without diabetes	0.5% (2/415)	1.2% (5/412)	NR	0.29	
	Index Visit	**Normal test result (No CAD) on index test**	Females	58% (130/224)	Any functional test: 86% (147/171)	NR	NR	NR
					ETT: 94% (58/92)	NR	NR	
					Nuclear stress: 44% (48/56)	NR	NR	
					Stress echo: 75% (40/83)	NR	NR	
			Males	37% (97/249)	Any functional test: 84% (147/175)	NR	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
					ETT: 97% (74/76)	NR	NR	
					Nuclear stress: 73% (38/52)	NR	NR	
					Stress echo: 83% (39/47)	NR	NR	
			With diabetes	32% (25/79)	Any functional test: 83% (55/66)	NR	NR	NR
					ETT: 96% (23/66)	NR	NR	
					Nuclear stress: 75% (18/24)	NR	NR	
					Stress echo: 78% (14/18)	NR	NR	
			Without diabetes	50% (198/394)	Any functional test: 85% (239/280)	NR	NR	
					ETT: 93% (106/114)	NR	NR	
					Nuclear stress: 81% (68/84)	NR	NR	
					Stress echo: 795 (65/82)	NR	NR	
CCTA vs. SPECT								
Min, 2012	Index Visit	**Normal test result (No CAD) on index test**	Low pre-test probability	25% (1/4)	13% (1/8)	NR	0.58	NR

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			Intermediate pre-test probability	28% (16/57)	37% (22/60)	NR	0.32	
			High pre-test probability	33% (10/30)	43% (9/21)	NR	0.49	
CCTA vs. Exercise ECG								
SCOT-HEART, 2018	Median 4.8 year follow-up	**Death from Coronary Heart Disease or Nonfatal Myocardial Infarction**	< 65 years	2.1% (32/1538)	3.3% (51/1554)	HR 0.62 (95% CI 0.40 to 0.96)	NR	0.68
			>65 years	3.0% (16/535)	5.8% (30/519)	HR 0.53 (95% CI 0.29 to 0.98)	NR	
			Female	1.2% (11/911)	22/910 (2.4)	HR 0.50 (95% CI 0.24 to 1.04)	NR	0.57
			Male	3.2% (37/1162)	5.1% (59/1163)	HR 0.63 (95% CI 0.42 to 0.95)	NR	
			10 year cardiovascular risk <15%	1.5% (15/969)	2.0% (21/1067)	HR 0.78 (95% CI 0.40 to 1.51)	NR	0.21
			10 year cardiovascular risk ≥15%	3.0% (33/1104)	6.0% (60/1006)	HR 0.50 (95% CI 0.33 to 0.77)	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			No previous coronary heart disease	1.9% (35/1887)	3.3% (62/1887)	HR 0.57 (95% CI 0.37 to 0.86)	NR	0.68
			Previous coronary heart disease	7.0% (13/187)	10.1% (19/189)	HR 0.65 (95% CI 0.32 to 1.32)	NR	
			Diabetes	2.2% (41/1850)	3.5% (64/1852)	HR 0.63 (95% CI 0.43 to 0.94)	NR	0.40
			No diabetes	3.1% (7/223)	7.7% (17/221)	HR 0.36 (95% CI 0.15 to 0.87)	NR	
			NICE classification of non-anginal chest pain	1.1% (8/712)	2.4% (18/735)	HR 0.45 (95% CI 0.19 to 1.03)	NR	0.58
			NICE classification anginal chest pain	2.3% (27/1174)	3.8% (44/1149)	HR 0.60 (95% CI 0.37 to 0.96)	NR	
	Median 4.8 year follow-up	**Non-fatal MI**	NICE classification of non-anginal chest pain	1.1% (8/712)	2.2% (16/735)	HR 0.50 (95% CI 0.21 to 1.17)	NR	NR
			NICE classification of	2.0% (24/1174)	3.6% (41/1149)	HR 0.57 (95% CI	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			possible anginal chest pain			0.34 to 0.94)		
			Previous coronary heart disease	6.5% (12/187)	8.6% (19/189)	HR 0.71 (95% CI 0.33 to 1.50)	NR	
	Median 4.8 year follow-up	**Non-fatal stroke**	NICE classification of non-anginal chest pain	0.4% (3/712)	1.0% (7/735)	HR 0.45 (95% CI 0.12 to 1.75)	NR	NR
			NICE classification of possible anginal chest pain	0.8% (9/1174)	1.0% (12/1149)	HR 0.72 (95% CI 0.30 to 1.70)	NR	
			Previous coronary heart disease	1.6% (3/187)	0.5% (1/189)	HR 2.87 (95% CI 0.29 to 28.22)	NR	
	Median 4.8 year follow-up	**Coronary Heart Disease Death**	NICE classification of non-anginal chest pain	0% (0/712)	0.3% (2/735)	HR 0.00 (95% CI 0.00 to Inf)	NR	NR
			NICE classification of possible anginal chest pain	0.3% (3/1174)	0.3% (4/1149)	HR 0.74 (95% CI 0.17 to 3.34)	NR	
			Previous coronary heart disease	0.5% (1/187)	1.6% (3/189)	HR 0.34 (95% CI 0.04 to 3.33)	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
	Median 4.8 year follow-up	**Cardiovascular Disease Death**	NICE classification of non-anginal chest pain	0% (0/712)	0.4% (3/735)	HR 0.00 (95% CI 0.00 to Inf)	NR	NR
			NICE classification of possible anginal chest pain	0.3% (4/1174)	0.5% (6/1149)	HR 0.67 (95% CI 0.19 to 2.38)	NR	
			Previous coronary heart disease	0.5% (1/187)	1.6% (3/189)	HR 0.34 (95% CI 0.04 to 3.33)	NR	
	Median 4.8 year follow-up	**Non-coronary heart disease death**	NICE classification of non-anginal chest pain	1.1% (8/712)	0.5% (4/735)	HR 2.06 (95% CI 0.62 to 6.85)	NR	NR
			NICE classification of possible anginal chest pain	1.8% (21/1174)	1.8% (21/1149)	HR 0.99 (95% CI 0.54 to 1.82)	NR	
			Previous coronary heart disease	4.8% (9/187)	3.2% (6/189)	HR 1.51 (95% CI 0.54 to 4.24)	NR	
	Median 4.8 year follow-up	**All-cause death**	NICE classification of non-anginal chest pain	1.1% (8/712)	1.0% (7/735)	HR 1.18 (95% CI 0.43 to 3.26)	NR	NR
			NICE classification of	2.1% (25/1174)	2.3% (27/1149)	HR 0.92 (95% CI	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			possible anginal chest pain			0.53 to 1.59)		
			Previous coronary heart disease	5.4% (10/187)	4.8% (9/189)	HR 1.12 (95% CI 0.45 to 2.75)	NR	
	Median 4.8 year follow-up	**Invasive Coronary Angiography**	NICE classification of non-anginal chest pain	6.9% (49/712)	4.9% (36/735)	HR 1.42 (95% CI 0.93 to 2.19)	NR	NR
			NICE classification of possible anginal chest pain	30.7% (361/1174)	33.8% (388/1149)	HR 0.93 (95% CI 0.80 to 1.07)	NR	
			Previous coronary heart disease	43.5% (81/187)	41.9% (78/189)	HR 1.05 (95% CI 0.77 to 1.44)	NR	
	Median 4.8 year follow-up	**Any coronary revascularization**	NICE classification of non-anginal chest pain	2.5% (18/712)	2.9% (21/735)	HR 0.89 (95% CI 0.47 to 1.67)	NR	NR
			NICE classification of possible anginal chest pain	18.7% (220/1174)	17.4% (200/1149)	HR 1.10 (95% CI 0.91 to 1.34)	NR	
			Previous coronary heart disease	22% (41/187)	24.7% (46/189)	HR 0.90 (95% CI 0.59 to 1.37)	NR	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
	Median 4.8 year follow-up	**Percutaneous coronary intervention**	NICE classification of non-anginal chest pain	2.2% (16/712)	2.7% (20/735)	HR 0.83 (95% CI 0.43 to 1.60)	NR	NR
			NICE classification of possible anginal chest pain	14.2% (167/1174)	13.8% (159/1149)	HR 1.04 (95% CI 0.84 to 1.30)	NR	
			Previous coronary heart disease	19.4% (36/187)	17.7% (33/189)	HR 1.12 (95% CI 0.70 to 1.79)	NR	
	Median 4.8 year follow-up	**Coronary artery bypass graft**	NICE classification of non-anginal chest pain	0.3% (2/712)	0.1% (1/735)	HR 1.85 (95% CI 0.16 to 20.92)	NR	NR
			NICE classification of possible anginal chest pain	5.0% (59/1174)	4.0% (46/1149)	HR 1.27 (95% CI 0.86 to 1.8)	NR	
			Previous coronary heart disease	4.3% (8/187)	8.1% (15/189)	HR 0.51 (95% CI 0.22 to 1.21)	NR	
	Median 3.2 year follow-up	**Fatal and non-fatal MI**	NICE classification of non-anginal chest pain	1.0% (7/712)	1.5% (11/735)	HR 0.65 (95% CI 0.25 to 1.69)	0.379	0.836
			NICE classification of	1.9% (22/1174)	3.2% (37/1149)	HR 0.58 (95% CI	0.045	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			possible anginal chest pain			0.34 to 0.99)		
	Median 3.2 year follow-up	**Fatal MI, non-fatal MI and stroke**	NICE classification of non-anginal chest pain	1.1% (8/712)	2.2% (16/735)	HR 0.51 (95% CI0.22 to 1.2)	0.123	0.554
			NICE classification of possible anginal chest pain	2.4% (28/1174)	3.5% (40/1149)	0.69 (0.42 to 1.11)	0.128	
	Median 3.2 year follow-up	**Non-fatal MI**	NICE classification of non-anginal chest pain	1.2% (9/712)	1.0% (7/735)	0.8 (0.3 to 2.14)	0.654	0.509
			NICE classification of possible anginal chest pain	1.6% (19/1174)	3.0% (34/1149)	0.54 (0.31 to 0.96)	0.034	
	Median 3.2 year follow-up	**Non-fatal stroke**	NICE classification of non-anginal chest pain	0.1% (2/712)	0.7% (5/735)	0.21 (0.02 to 1.8)	0.155	0.200
			NICE classification of possible anginal chest pain	0.5% (6/1174)	0.5% (6/1149)	1.01 (0.32 to 3.12)	0.991	
	Median 3.2 year follow-up	**All-cause death**	NICE classification of non-anginal chest pain	1.0% (7/712)	0.5% (4/735)	1.81 (0.53 to 6.18)	0.346	0.200

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			NICE classification of possible anginal chest pain	1.5% (18/1174)	1.9% (22/1149)	0.82 (0.44 to 1.53)	0.536	
	Median 3.2 year follow-up	**Coronary Heart Disease Death**	NICE classification of non-anginal chest pain	0% (0/712)	0.3% (2/735)	0 (0 to Infinity)	0.99	0.998
			NICE classification of possible anginal chest pain	0.3% (3/1174)	0.3% (4/1149)	0.78 (0.17 to 3.48)	0.742	
	Median 3.2 year follow-up	**Non-coronary Heart Disease Death**	NICE classification of non-anginal chest pain	1.0% (7/712)	0.3% (2/735)	3.64 (0.75 to 17.57)	0.108	0.096
			NICE classification of possible anginal chest pain	1.3% (15/1174)	1.6% (18/1149)	0.83 (0.42 to 1.65)	0.598	
	Median 3.2 year follow-up	**Any coronary revascularization**	NICE classification of non-anginal chest pain	2.2% (16/712)	1.0% (14/735)	1.2 (95% CI 0.59 to 2.46)	0.619	0.938
			NICE classification of possible anginal chest pain	18.7% (220/1174)	16.5% (170/1149)	1.16 (0.95 to 1.41)	0.140	
	Median 3.2 year follow-up	**PCI**	NICE classification of non-anginal chest pain	2.0% (14/712)	1.8% (13/735)	1.13 (0.53 to 2.40)	0.753	0.978

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
			NICE classification of possible anginal chest pain	14.5% (170/1174)	13.1% (170/1149)	1.11 (95% CI 0.89 to 1.38)	0.349	
	Median 3.2 year follow-up	**CABG**	NICE classification of non-anginal chest pain	0.3% (2/712)	0.1% (1/735)	1.85 (95% CI 0.16 to 20.92)	0.620	0.704
			NICE classification of possible anginal chest pain	4.8% (56/1174)	3.7% (43/1149)	1.3 (0.87 to 1.94)	0.198	
	Median 3.2 year follow-up	**Invasive Coronary Angiogram**	NICE classification of non-anginal chest pain	6.6% (47/712)	3.7% (27/735)	HR 1.82 (95% CI 1.13 to 2.92)	0.014	NR
			NICE classification of possible anginal chest pain	30.2% (355/1174)	32.1% (369/1149)	HR 0.95 (95% CI 0.82 to 1.10)	0.481	
	Median 3.2 year follow-up	**ICA revealing normal coronary arteries**	NICE classification of non-anginal chest pain	NR	NR	RR 0.78 (95% CI 0.30 to 2.05)	0.622	NR
			NICE classification of possible anginal chest pain	NR	NR	RR 0.32 (95% CI 0.19 to 0.52)	<0.001	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Comparator % (n/N) or Mean (SD)	Author reported effect estimate (95% CI)	Author reported p-value for effect estimate	Author reported Interaction p-value
	Median 3.2 year follow-up	**ICA revealing obstructive coronary arteries**	NICE classification of non-anginal chest pain	NR	NR	RR 0.82 (95% CI 0.50 to 1.34)	0.422	NR
			NICE classification of possible anginal chest pain	NR	NR	RR 1.18 (95% CI 1.07 to 1.32)	0.002	
	Median 3.2 year follow-up	**Proportion of patients experiencing a prescription change**	NICE classification of non-anginal chest pain	19% (135/712) †††	5% (37/735) †††	NR	NR	NR
			NICE classification of possible anginal chest pain	27% (317/1174) †††	7% (80/1149) †††	NR	NR	

* Unnecessary admission: Admission for a medical condition that should not have led to hospitalization, which was ultimately confirmed to be neither ACS nor any medical conditions requiring hospitalization (determined by consensus of the outcome panel).
† MACE includes cardiac death, myocardial infarction, unstable angina pectoris, and revascularization.
‡ Patients with a history of CAD were excluded from subgroup analysis of differentiated pre-test probabilities
§ Patients with a history of CAD were excluded from subgroup analysis of differentiated pre-test probabilities
** HRs <0 favor CCTA, while HRs >0 favor functional imaging
†† CAD risk equivalent was defined as diabetes, peripheral vascular disease, or cerebrovascular disease.
‡‡ CAD risk equivalent was defined as diabetes, peripheral vascular disease, or cerebrovascular disease.
§§ Adjusted model controls for noninvasive testing results (positive vs. negative), sex, and age
*** Author's do not state what they adjusted for.
††† Estimated from figure 2a in Admonson 2018.

ACS = acute coronary syndrome, adj. = adjusted, BMI = body mass index, CABG = coronary artery bypass graft, CAD = coronary artery disease, CCTA = coronary computed tomography, CI = confidence interval, ECG = electrocardiogram, ECHO = echocardiography, ED = emergency department, ETT = exercise treadmill test, HR = hazard ratio, ICA = invasive coronary angiogram, MACE = major adverse cardiovascular events, MI = myocardial infarction, NICE = National Institute for Health and Care Excellence, NR = not reported, NSTEMI = Non-ST-Segment Elevation Myocardial Infarction, OR = odds ratio, PCI = percutaneous coronary intervention, RR = risk ratio, SD = standard deviation.

Appendix Table F17. Data abstraction for Subgroup analyses for safety outcomes from CCTA trials

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Functional Test % (n/N) or Mean (SD)	Difference within groups p-value	Interaction p-value
CCTA vs. any functional testing							
PROMISE trial	≤90 days	**Cumulative radiation effective dose among those patients intended for nuclear stress testing**	<65 years	12.2 (8.1) (N=2178)	15.3 (6.9) (N=2159)	NR	0.072
			≥65 years	12.6 (8.9) (N=968)	15.0 (6.7) (N=1044)	NR	
			Male	13.7 (9.0) (N=1452)	160 (7.4) (N=1694)	NR	0.82
			Female	11.2 (7.5) (N=1694)	14.6 (6.3) (N=1786)	NR	
			Not Obese (<30 kg/m2)	11.1 (8.0) (N=1556)	14.9 (6.9) (N=1537)	NR	0.10
			Obese (≥30 kg/m2)	13.6 (8.5) (N=1570)	15.5 (6.7) (N=1638)	NR	
			Heart rate <75 bpm*	11.9 (8.4)	15.3 (6.9)	NR	0.042
			Heart rate ≥75 bpm*	13.0 (8.3)	15.0 (6.6)	NR	
ROMICATT-II	Index test only	**Radiation Dose During the Index Visit**	Female	10.8 (8.7)	4.7 (8.1)	<0.0001	0.003
			Male	14.2 (11.2)	4.7 (8.7)	<0.0001	
	28 days	**Mean (SD) cumulative radiation dose (mSv)**	Female	11.0 (8.9)	6.0 (8.2)	<0.0001	0.002
			Male	14.7 (12.0)	5.6 (10.7)	<0.0001	
			With diabetes	18.4 (14.7)	6.6 (10.4)	<0.0001	0.04
			Without diabetes	13.4 (9.8)	5.1 (9.5)	<0.0001	
			White	Median (IQR) 12.0 (7.9 to 17.2)	Median (IQR) 0.0 (0.0 to 12.4)	<0.001	0.60
			Black	Median (IQR)	Median (IQR)	<0.001	

Trial name Author, year	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Functional Test % (n/N) or Mean (SD)	Difference within groups p-value	Interaction p-value
				11.7 (8.6 to 16)	0.0 (0.0 to 0.0)		

bpm = beats per minute, CCTA = coronary computed tomography angiography, IQR = interquartile range, kg = kilograms, mSv = millisieverts, NR = not reported, SD = standard deviation.

* Baseline resting heart rate was recorded at the enrollment physical examination.

APPENDIX G. Data Abstraction of Included Studies Evaluating Stress Echo

Appendix Table G1. Data abstraction for Stress Echo vs. Exercise ECG: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
Jeetley, 2006 RCT (Single Center) UK Funding NR	Population: Mixed suspected and known CAD Setting: Hospital admission Inclusion: - Patients presenting to hospital with a history of acute chest pain - Normal or non-diagnostic ECG - Two or more risk factors CAD Exclusion: - ST-segment elevation >1 mm in 2 leads or significant planer ST-segment depression suggestive of acute infarction or ischemia on the presenting ECG - Any significant rise in cardiac troponin - Patients with known coronary artery disease awaiting revascularization	**A. Stress Echo (n=148 randomized, n=142 available for follow-up)** Stressor: Treadmill exercise or dobutamine. Contrast: Optison Protocol: 2D echocardiogram performed in the left lateral decubitus position using harmonic imaging. Digitized images of the left ventricle obtained in the parasternal long-axis, short-axis and apical 4-, 2-, and 3-chamber views. Those with a high post-test likelihood of CAD had ICA performed for confirmation. Definition of positive test: Evidence of inducible ischemia at stress, or a resting wall motion abnormality in at least one segment (except isolated basal inferior or basal inferior septal segment) without prior history of myocardial infarction were considered to have high probability of significant CAD. **B. Exercise ECG (n=154 randomized, n=151 available for followup)** Patients underwent limited Bruce (or modified Bruce) protocol exercise testing using a treadmill with continuous monitoring of a 12-lead ECG and regular blood pressure measurements.	**A vs. B** Low: 20% vs. 21% Intermediate: 72% vs. 65% High: 9% vs. 14%	**A vs. B** Subgroup: None N randomized: 302 Mean age (SD): 61 (12.8) vs. 60 (12.5) Female: 43% vs. 44% Race: Caucasian: 51% vs. 45% South Asian: 41% vs. 47% Chest pain: NR - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: 12% vs. 18% Prior revascularization: 17.6% vs. 31.8% Known CAD: NR Chest pain frequency:	8.5 (±4.9) month: 97% Crossover: 0% **A vs. B** Patients that didn't receive their randomized test, % (n/N): 3.9% (6/154) vs. 2% (3/148)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
	- Patients in whom history and clinical examination suggested a non-cardiac source of chest pain - Patients with absolute contraindications for exercise testing			Hypertension: 70% vs 62% Hyperlipidemia: 55% vs. 65% Diabetes: 23% vs 25% Current smoking: 15% vs 15% Medication: Aspirin: 76% (112/148) vs. 87% (134/154) Clopidogrel: 40% (59/148) vs. 43% (66/154) Beta-blocker: 42% (62/148) vs. 40% (62/154) Calcium antagonist: 22% (33/148) vs. 23% (36/154) Statin: 51% (76/148) vs. 53% (81/154) ACE inhibitor/ARB: 28% (42/148) vs. 36% (56/154)	
Desideri, 2005 RCT (Multi Center)	Population: Mixed suspected and known CAD	**A. Stress Echo (n=132)** Stressor: Dipyridamole (dobutamine in case of contraindication) Contrast: NR	NR	**A vs. B** Subgroup: None N randomized: 262	12 months: 100% (262/262) Crossover: 0%

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
Italy/Spain/Poland Funding NR	Setting: Inpatient Inclusion: - Presented with uncomplicated AMI admitted within 24 hours of the onset of symptoms Exclusion: - Age >75 years; serious arrhythmias - Left bundle branch block - Pericarditis - Insufficient acoustic window - Poor short term prognosis because of concomitant disease	Protocol: Patients instructed to avoid coffee, tea, or caffeine within eight hours of tests. Early (days 3 to 5) use of pharmacologic stress and discharge on days 7 to 9 in case of a negative result. For dipyridamole test, two dimensional echocardiogram was recorded without withdrawing medical treatment at rest and in combination with dipyridamole infusion; for dobutamine test, stress was administered in three minute dose increments and stopped as soon as positive criteria was reached. Definition of positive test: Detection of a transient wall motion abnormality that was absent at baseline or worsened during the test. **B. Exercise ECG (n=130)** Maximum, symptom limited test on days 7 to 9 followed by discharge in case of a negative test result, otherwise positive test was followed by coronary angiography followed by ischemia guided revascularization		Mean age (SD): 58 (10) vs. 59 (11) Female: 12% vs. 15% Race: NR Chest pain: NR - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: 6% vs. 11% Prior revascularization: 4% vs. 5% Known CAD: NR Chest pain frequency: NR Hypertension: 43% vs. 41% Hyperlipidemia: NR Diabetes: 17% vs. 16% Current smoking: 65% vs. 61%	
Badano, 1999; Nucifora, 2009 RCT	Population: Suspected ACS Setting:	**A. Stress Echo (n=110 randomized, n=77 analyzed)** Stressor: Dobutamine-atropine Contrast:	NR	**A vs. B** Subgroup: None N randomized: 180*	2 months: 84.4% (152/180) Crossover: 0%

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
(Multi Center) Italy Funding NR	ED Inclusion: - ACP within previous 24 hours in absence of local trauma and abnormalities on chest X-ray - Non-diagnostic electrocardiogram at admission - Negative myocardial injury biomarkers - Ability to perform electrocardiogram exercise testing Exclusion: - Age <30 years - Prehospital or emergency department complication of acute ischemia or MI - Premature ventricular beats >6 per minute - Atrial fibrillation - Dilated or hypertrophic cardiomyopathy - Complex congenital heart disease - Significant valvular disease - Known aortic aneurism >50 mm	Protocol: Dobutamine was administered intravenously for 3 minutes, increasing every 3 minutes, atropine was added for those not achieving 85% of their age and gender-predicted maximal heart rate and without symptoms or signs of myocardial ischemia. During test, symptoms and ECG were monitored each minute. Definition of positive test: NR **B. Exercise ECG (n=89 randomized, n=75 analyzed)** Twelve-lead ECGs were recorded at admission, before randomization, and during each episode of chest pain during hospital stay. discharge after several hours or days.		Mean age (SD): 52 (10) vs. 50 (10) Female: 47% vs. 32% Race: NR Chest pain: NR - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: 3% vs. 3% Prior revascularization: Known CAD: NR Chest pain frequency: NR Hypertension: 38% vs. 35% Hyperlipidemia: NR Diabetes: 12% vs. 7% Current smoking: 48% vs. 44%	

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
	- Uncontrolled proven hypertension >180/100 mmHg - Complete left branch bundle block.				
Zacharias, 2017; Gurunathan, 2018 RCT (Single Center) UK Funding NR	Population: Suspected CAD Setting: Outpatient (rapid access chest pain clinic) Inclusion: - Referred for evaluation of possible CAD - Normal resting ECG - Intermediate pre-test probability of CAD - Moderate physical functioning - No known history of CAD Exclusion: - Unstable angina - Prior history of CAD - Very low pre-test probability	**A. Stress Echo (n=191 randomized, n=188 analyzed)** Stressor: Treadmill exercise Contrast: Ultrasound contrast agent Sonovue Protocol: Parasternal long axis, short axis, and apical 4-chamber, 2-chamber, and 3-chamber images were obtained at rest and peak stress. Definition of positive test: Patients with evidence of wall motion abnormalities at rest or who developed regional wall motion abnormalities at peak stress. **B. Exercise ECG (n=194 randomized, n=190 analyzed)** Treadmill exercise using the standard Bruce protocol. Patients had a positive test if they developed significant chest pain, hypotension, an arrhythmia, or ≥1 mm planar or down sloping ST depression in two or more leads of the same territory, during exercise or in recovery.	**A vs. B** Low: 41.3% vs. 40.2% Intermediate: 30.9% vs. 37.6% High: 27.7% vs. 22.2%	**A vs. B** Subgroup: None N randomized: 385 Mean age (SD): 55 (11) vs. 54 (11) Female: 30% vs. 34% Race: NR Chest pain: 100% vs. 100% - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: 0% Prior revascularization: 0% Known CAD: 0% Chest pain frequency: NR Hypertension: 12% vs. 14% Hyperlipidemia: NR	36 months (via postal questionnaire or telephone): 98.1% Crossover: 0%

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
				Diabetes: 14% vs. 17% Current smoking: 14% vs 18%	
Sanfilippo, 2005 RCT (Single Center) Canada Funding American Society of Echocardiography	Population: Suspected CAD or ACS Setting: Mixed – referred from OP MD (72%), ED (23%), Inpatient (4%) Inclusion: - Women experiencing chest pain with no established diagnosis - No known CAD - At least two cardiac risk factors - The ability to undergo all of the study investigations Exclusion: - Known CAD	**A. Stress ECHO (n=104)** Stressor: Treadmill exercise or dobutamine (plus atropine if target heart rate not achieved) Contrast: NR Protocol: "Carried out according to standard protocol" - 45.2% (47/104) received dobutamine stress testing - 54.8% (57/104) received exercise stress testing Definition of positive test: A new regional abnormality of systolic function was noted with exercise or global systolic function worsened with exercise. **B. Exercise ECG (n=54)** Carried out according to standard protocol. A positive result was defined as development of at least 1 mm of horizontal or down sloping ST depression in two adjacent leads.	NR	**A vs. B** Subgroup: None N randomized: 158 Mean age (SD): 54.5 (10.8) Female: 100% Race: Caucasian: 97.1% vs. 100% Chest pain: NR - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: NR Chest pain frequency: Hypertension: 53.8% vs. 38.9	24 months: 100% Crossover: 0%

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
				Hyperlipidemia: 41.4% vs. 42.6 Diabetes: 10.6% vs. 7.4% Current smoking: 18.2% vs 25.9%	

2D = two-dimensional, ACE = Angiotensin-converting enzyme, ACP = acute chest pain, ACS = acute coronary syndrome, AMI = acute myocardial infarction, ARB = Angiotensin II Receptor Blockers, CAD = coronary artery disease, ECG = electrocardiogram, ECHO = echocardiography, ED = emergency department, f/u = follow-up, MI = myocardial infarction, mm = millimeter, NR = not reported, OP = outpatient, RCT = randomized control trial, SD = standard deviation, vs. = versus.

* An additional 110 patients were randomized to a stress echo arm of this trial. The data for these patients are abstracted elsewhere (Appendix table XXX).

Appendix Table G2. Data abstraction for Stress Echo vs. Exercise ECG: Efficacy Outcomes

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Jeetley, 2006 Stress Echo (A) vs. Exercise ECG (B)	**A vs. B** **Disposition, % (n/N)** Hospitalized 100% (302/302) **Test result, % (n/N)** Positive test result 14.9% (22/148) vs. 18.2% (28/154) Negative test result 80.4% (119/148) vs. 26% (40/154) Inconclusive test result 2.7% (4/148) vs. 51.9% (80/154)	**A vs. B** **All-cause mortality, % (n/N)** Mean 8.5 months 0.7% (1/142) vs. 0.7% (1/151)	**A vs. B** **MI (NOS), % (n/N)** Mean 8.5 months 0.7% (1/142) vs. 1.3% (2/151)	**A vs. B** **Revascularization, % (n/N)** Mean 8.5 months 11.3% (16/142) vs. 15.6% (22/151)	**A vs. B** **Invasive Coronary Angiography, % (n/N)** Mean 8.5 months 14.2% (21/148) vs. 23.4% (36/154) **Significant CAD on angiography** Mean 8.5 months 76.2% (16/21) vs. 55.6% (20/36)	NR **Death or MI, % (n/N)** Mean 8.5 months 1.4% (2/142) vs. 2.0% (3/151) **Death, MI or revascularization % (n/N)** Mean 8.5 months 12.7% (18/142) vs. 16.6% (25/151)	NR
Desideri, 2005	**A vs. B**	**A vs. B**	**A vs. B**	**A vs. B**	**A vs. B**	**A vs. B**	**A vs. B**

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Stress Echo (A) vs. Exercise ECG (B)	**Test result, % (n/N)**‡ Positive for ischemia 36.4% (48/132) vs. 40.8% (53/130) Negative for ischemia 63.6% (84/132) vs. 56.2% (73/130)	**All-cause mortality** 12 months 0.75% (1/132) vs. 0% (0/130)	**Nonfatal MI (reinfarction)** 12 months 3.8% (5/132) vs. 1.5% (2/130)	**Revascularization (any), % (n/N)** 12 months 34.8% (46/132) vs. 33.8% (44/130) **Revascularization (PCI), % (n/N)** 12 months 22% (29/132) vs. 21.5% (28/130) **Revascularization (CABG), % (n/N)** 12 months 12.9% (17/132) vs. 12.3% (16/130)	**Invasive Coronary Angiography, % (n/N)** 12 months 50% (66/132) vs. 49.2% (63/130)	**MACE (including death, non-fatal MI, unstable angina) %, (n/N)** 12 months 19.7% (26/132) vs. 13.8% (18/130)	**Hospital length of stay [including index MI and subsequent events] (days), mean (95% CI)** 9 (8 to 14) vs. 10 (8 to 14) **Unstable angina (requiring admission), % (n/N)** 15.2% (20/132) vs. 12.3% (16/130)
Badano, 1999; Nucifora, 2009 Stress Echo (A) vs. Exercise ECG (B)	**A vs. B** **Diagnosis of ischemic chest pain, % (n/N)** 17% (13/77) vs. 23% (17/75) **Diagnosis of nonischemic chest pain, % (n/N)**	**A vs. B** **All-cause mortality, % (n/N)** Index/in-hospital 0% (0/77) vs. 0% (0/75) 2 months 0% (0/77) vs. 0% (0/75)	**A vs. B** **Nonfatal MI, % (n/N)** Index/in-hospital 0% (0/77) vs. 0% (0/75) 2 months 0% (0/77) vs. 0% (0/75)	**A vs. B** **Revascularization (any), % (n/N)** 2 months 6.5% (5/77) vs. 7% 8.0% (6/75) **Revascularization (PCI), % (n/N)** 2 months 5% (4/77) vs. 7% (5/75)	**A vs. B** **Invasive Coronary Angiography, % (n/N)** 2 months 0% (0/77) vs. 4% (3/75) **Stress echocardiography, % (n/N)** 2 months	NR	**A vs. B** **Hospital length of stay (hours), mean (SD)** Index 40 (42) vs. 39 (35) **Rehospitalization for acute chest pain, % (n/N)** 2 months 3% (2/77) vs. 7% (5/75)

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	83% (64/77) vs. 77% (58/75)			**Revascularization (CABG), % (n/N)** 2 months 1% (1/77) vs. 1% (1/75) **Medications prescribed at discharge, % (n/N)** Nitrates 13% (10/77) vs. 16% (12/75) Antiplatelet drugs 30% (23/77) vs. 33% (25/75) Beta-blockers 21% (16/77) vs. 23% (17/75) Calcium channel blockers 21% (16/77) vs 19% (14/75)	0% (0/77) vs. 0% (0/75) **Transthoracic echocardiography, % (n/N)** 2 months 1% (1/77) vs.4% (3/75), p=NR **Electrocardiogram, % (n/N)** 2 months 9% (7/77) vs. 5% (4/75)		**Nottingham Health Profile score, mean (SD)** **Physical mobility** Index 26 (23) vs. 24 (27) 2 months 15 (16) vs. 14 (16) **Pain** Index 25 (26) vs. 20 (30) 2 months 7 (10) vs. 6 (14) **Social isolation** Index 19 (30) vs. 18 (32) 2 months 4 (9) vs. 6 (17) **Emotional reactions** Index 27 (26) vs. 26 (30) 2 months 21 (25) vs. 14 (23) **Energy level** Index 38 (39) vs. 31 (38) 2 months

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							14 (14) vs. 11 (16) **Sleep** Index 41 (31) vs. 35 (30) 2 months 22 (17) vs. 23 (22)
Zacharias, 2017; Gurunathan, 2018 Stress Echo (A) vs Exercise ECG (B)	**A vs. B** **Test result, % (n/N)**[§] Positive test result 4.7% (9/191) vs. 7.2% (14/194) Negative test result 94.8% (181/191) vs. 55.7% (108/194) Inconclusive test result 0.5% (1/191) vs. 37.1% (72/194)[*]	**A vs. B** **All-cause mortality, % (n/N)** Mean 21 months 0.5% (1/191) vs. 0% (0/194), p=NR Mean 36 months (not including rates at 21 months) 0% (0/191) vs. 2.1% (4/194), p=0.18 **Cardiac death % (n/N)**	**A vs. B** **Nonfatal MI, % (n/N)** Mean 21 months 0% (0/191) vs. 0% (0/194), p= Mean 36 months (not including rates at 21 months) 0.5% 1/191) vs. 0.5% (1/194), p=0.99	**A vs. B** **Revascularization (any), % (n/N)** Mean 36 months 5.8% (11/191) vs. 6.2% (12/194), p=0.86 **Late revascularization (any revascularization occurring after 6 months), % (n/N)** Mean 36 months 1.6% (3/191) vs. 1.0% (2/194), p=0.64	**A vs. B** **Invasive Coronary Angiography, % (n/N)** Mean 21 months 4.7% (9/191) vs. 9.8% (19/194), p=0.05 (within 4 months) 36 months (not including rates at 21 months) 1.6% (3/188) vs. 3.7% (7/190), p= 0.21 Total across entire study period 6.3% (12/191) vs. 13.7% (26/190), p=0.02 **Any additional test after index evaluation** 36 months 5% (10/191) vs. 44% (85/194), p<0.01	**A vs. B** **Combined endpoint (death, nonfatal MI, later revascularization, and hospitalization for chest pain)** 10.5% (20/191) vs. 13.4% (26/194); HR 1.15 (95% CI 0.39 to 3.43) for ECG vs. Echo, p=0.38	**A vs. B** **Hospitalized for chest pain, % (n/N)** Mean 21 months 0.5% (1/191) vs. 0% (0/194), p=0.5 (1 additional patient in echo group admitted for urgent non cardiac surgery) Mean 36 months 7.9% (15/191) vs. 9.8% (19/194), p=0.5 **Total number of clinic visits** 36 months 31 vs 59, p<0.01 **Total number of emergency visits** 36 months 14 vs 30, p=0.01; (8 vs. 29 overnight stays)

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
		Mean 21 months 0.5% (1/191) vs. 0% (0/194), p=NR			**Stress echocardiography** At index evaluation 0.5% (1/191) vs. 37.1% (72/194) Following diagnosis (36 months) 6.3% (12/191) vs. 7.7% (13/194), p=0.87 **CMR** Following diagnosis (36 months) 0.5% (1/191) vs. 0.5% (1/194), p= 0.99 **SPECT** Following diagnosis (36 months) 0% (0/191) vs. 1% (2/194), p=NR **Exercise ECG** 0.5% (1/191) vs. 2.6% (5/194), p=0.10		
Sanfilippo, 2005 Stress Echo (A) vs. Exercise ECG (B)	**A vs. B** **Patient disposition** NR	NR	**A vs. B** **Nonfatal MI, % (n/N)** Mean 28 months 1.3% (2/158)†	NR	**A vs. B** **Requirement for additional cardiac diagnostic testing (including cardiac**	NR **Clinical events (NOS) (definitive diagnosis of CAD by subsequent**	**A vs. B** **Unstable angina, % (n/N)‡‡** Mean 28 months 1.3% (2/158)†

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	Test result, % (n/N)** <u>Positive</u> 15.4% (16/104) vs. 14.8% (8/54) <u>Negative</u> 82.7% (86/104) vs. 61.1% (33/54) <u>Inconclusive</u> 1.9% (2/104) vs. 24.1% (13/54)				**catheterization), % (n/N)** <u>Mean 28 months</u> 1.9% (2/104) vs. 24.1% (13/54)	**angiography), % (n/N):** <u>Mean 28 months</u> 7.8% (8/104) vs. 7.4% (4/54),	**Acceleration of chest pain syndrome (did not fulfill criteria for MI or UA but resulted in frequent presentation to clinic and ED), % (n/N)** <u>Mean 28 months</u> 9.5% (15/158) [all got ICA; 8/15 had significant CAD] **Final diagnosis, % (n/N)** <u>Mean 28 months</u> - Cardiac chest pain (definitive diagnosis of CAD supported by angiography): 7.8% (8/104) vs. 7.4% (4/54), p=NR - Noncardiac chest pain: 79.8% (83/104) vs. 83.3% (45/54), p=NR - Indeterminate§§ clinical outcome: 12.5% (13/104) vs. 9.3% (5/54), p=NR

CABG = coronary artery bypass graft, CAD = coronary artery disease, CI = confidence interval, CMR = cardiac magnetic resonance, ECG = electrocardiogram, ECHO = echocardiography, MACE = major adverse cardiovascular events, MI = myocardial infarction, NOS = not otherwise specified, NR = not reported, PCI = percutaneous coronary intervention, SD = standard deviation, SPECT = single photon emission computed tomography, UA = unstable angina.

* All inconclusive tests underwent further/repeat SE. Group A 1 repeat SE was negative; Group B: 67 tests were negative, 5 were positive and later referred for angiography.

† Only summary data available
‡ Positive = wall motion score increased by one or more points in two or more adjacent segments relative to the resting echocardiogram; negative = NR
§ Positive = significant chest pain, hypotension, arrhythmia, or ≥1 mm planar or down sloping ST depression in two or more leads of the same territory, during exercise or in recovery ;Negative = work-load of ≥9 METS or achieved 85% of target heart rate, without any symptoms, hemodynamic compromise, or ECG changes.
** Electrocardiographic: Positive = development of at least 1mm of horizontal or down sloping ST depression in two adjacent leads; Negative = absence of ST depression changes at 90% predicted maximal heart rate. Exercise echocardiographic: Positive = new regional abnormality of systolic function noted with exercise or global systolic function worsened with exercise; Negative = absence of positive criteria and augmentation of all segments with exercise. Dobutamine: Positive = NR; Negative = NR; abnormal = worsening of systolic function in at least one segment.
‡‡ Defined as prolonged or accelerating chest pain with EKG changes but no enzyme rises diagnostic of MI.
§§ Patients who continued to experience their presenting chest pain syndrome without clinical confirmatory events were considered to remain indeterminate.

Appendix Table G3. Data abstraction for Stress Echo vs. Exercise ECG: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Jeetley, 2006 Stress Echo (A) vs. Exercise ECG (B)	NR	NR	N/A
Badano, 1999; Nucifora, 2009 Stress Echo (A) vs. Exercise ECG (B)	NR	NR	N/A
Desideri, 2005 Stress Echo (A) vs. Exercise ECG (B)	No complication occurred during either stress echocardiography or exercise ECG.	NR	NR
Zacharias, 2017; Gurunathan 2018 Stress Echo (A) vs. Exercise ECG (B)	NR	NR	N/A
Sanfilippo, 2005 Stress Echo (A) vs. Exercise ECG (B)	NR	NR	N/A

AE = adverse events, ECG = electrocardiogram, Echo = echocardiography, N/A = not applicable, NR = not reported.

Appendix Table G4. Data abstraction for Stress Echo vs. ICA: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
Sharples, 2007; Thom 2014 RCT (single Center) UK Funding National Institute for Health Research	Population: Mixed suspected CAD or known CAD Setting: Outpatient, nonemergent Inclusion: - Established or suspected chronic stable angina referred for angiography - An EET result which merited referral for angiography Exclusion: - Recent MI or revascularization - admission with chest pain - urgent revascularization - contraindication to pharmacological stress testing on MRI - incapable of performing modified Bruce exercise test - not available by phone	**A. Stress echocardiography (n=226)** Stressor: dobutamine (atropine if necessary) Contrast: intravenous ultrasound contrast medium Protocol: Performed using a standard staged protocol of increasing doses of dobutamine infusion in stages of 3 minutes duration. Imaging performed with standard views acquired using tissue harmonic imaging on a 3.5-MHz ultrasound prone in the last 1 minute of each 3-minute stage. Intravenous ultrasound contrast medium was used to delineate the left ventricular endocardial border. Positive diagnoses for ischemia showed stress-related deterioration in contractility in functional or hibernating myocardial segments. Definition of positive test: Studies were positive for ischemia if stress-induced deterioration in contractility was observed **B. ICA (n=222)** This group acted as the control group. ICA was performed and reported per	**A vs. B** 1: 2% (4/226)vs. 1% (3/222) 2: 12% (26/226) vs. 10% (21/222) 3: 17% (39/226) vs. 19% (42/222) 4: 35% (79/226) vs. 32% (70/222) 5: 34% (76/226) vs. 38% (85/222)*	**A vs. B** Subgroup: None N randomized: 898† Mean age (SD): 61.9 (9.9) vs. 60.7 (9.1) Female: 29% vs. 33% Race: NR Chest pain: NR - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: 26% vs. 28% Prior revascularization: NR Known CAD: NR Chest pain frequency: NR Treated Hypertension: 57% vs. 53% Treated Hyperlipidemia: 79% vs. 74% Diabetes: 12% vs. 12% Current smoking: 43% vs. 47% Medications: Anti-platelets: 81% vs. 76% Statins: 69% vs. 64% Beta-blockers: 64% vs. 57% ACE inhibitors: 31% vs. 35% Calcium-channel blockers: 28% vs. 27% Nicorandil/potassium-channel activators: 24% vs. 19% Nitrates: 17% vs. 16%	18 months: 84% 36 months: 84% Crossover: Received allocated test, % (n/N): 96.5% (218/226) vs. 98.2% (218/222)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
		standard techniques from the right femoral artery approach using the Seldinger technique. Positive diagnoses was defined as having 50% stenosis in the left main stem or 70% stenosis in any other major vessel.		Diuretics: 15% vs. 17% Angiotensin-II receptor antagonists: 7% vs. 7%	

ACE = Angiotensin-converting-enzyme; CAD = coronary artery disease; ECHO = echocardiography; ICA = invasive coronary angiography; MI = myocardial; RCT = randomized control trial; SPECT = single-photon emission computerized tomography

* Baseline risk of CAD was assessed by a clinician on a scale of 1 (lowest) to 5 (highest).

† Study also includes MRI. 898 patients were randomized to angiography (n=222), SPECT (n=224), MRI (226), or stress echo (226)

Appendix Table G5. Data abstraction for Stress Echo vs. ICA: Efficacy Outcomes

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Sharples, 2007; Thom, 2014 Stress Echo (A) vs. ICA (B)	**A vs. B** **Test result (Stress ECHO only), % (n/N)**[*†] Positive 45.6% (103/226) Negative 44.3% (100/226) Equivocal 3.1% (7/226) Not done 3.5% (8/226) Test failed 3.5% (8/226)	**A vs. B** **All-cause mortality, % (n/N)** Index 0% (0/226) vs. 0.4% (1/222), p=NR 18 months 2.7% (6/226) vs. 1.8% (4/222), p=NR 72 months 2.2% (5/226) vs. 0.9% (2/222) Cumulative 4.9% (11/226) vs. 3.2% (7/222) **Cardiac mortality, % (n/N)** 18 months: 0.4% (1/226) vs. 1.4% (3/222), p=NR	**A vs. B** **Admission for acute MI, % (n/N)** 2.76% (6/226) vs. 0% (0/222), p=NR	**A vs. B** **Revascularization (CABG) , % (n/N)** Index 12.9% (29/226) vs. 9.5% (21/222), p=NR 18 months 1.8.% (4/226) vs. 1.4% (3/222)§, p=NR **Revascularization (PCI), % (n/N)** Index 22.7% (51/226) vs. 24.8% (55/222), p=NR 18 months 2.2% (5/226) vs. 1.8% (4/222), p=NR Cumulative % of any revascularization post-index: 53.5% (121/226) vs. 53.2% (118/222)	**A vs. B** **Proportion of patients requiring additional testing, % (n/N)** Index Any additional testing: 74.8% (169/226) vs. 3.6% (8/222), p=NR - *ICA*: 74.8% (169/226) vs. 0% (0/222), p=NR - *SPECT*: 0% (0/226) vs. 3.2% (7/222), p=NR - *MRI*: 0% (0/226) vs. 0.5% (1/222), p=NR	**A vs. B** **Total nonfatal events (admission for chest pain or acute MI, unplanned PCI or CABG, other)‡** 18 months 13.7% (31/226) vs. 8.6% (19/222) **Total nonfatal plus fatal events** 18 months 16.4% (37/226) vs. 10.8% (24/222)	**A vs. B** **Angina, % (n/N)** 18 months 1.3% (3/226) vs. 3.2% (7/222), p=NR **Admission for chest pain, % (n/N)** 18 months 10.6% (24/226) vs. 6.3% (14/222), p=NR **SAQ, mean (SD)** Exertional capacity Index 73.2 (21.5) vs. 75.1 (20.4), p=NR 6 months 81 (20.5) vs. 80.2 (19.3), p=NR 18 months

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							81.5 (20) vs. 81.7 (19.2), p=NR Anginal stability <u>Index</u> 50 (20.4) vs. 52.5 (21.8), p=NR <u>6 months</u> 65.2 (26.6) vs. 66.6 (24.7), p=NR <u>18 months</u> 64.4 (20) vs. 64.6 (25.1), p=NR Anginal frequency <u>Index</u> 65.4 (25.8) vs. 67.4 (24.1), p=NR <u>6 months</u> 84 (23.1) vs. 83.8 (21.1), p=NR <u>18 months</u> 86.8 (21.8) vs. 84.2 (21.4), p=NR

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							Treatment satisfaction index 87.5 (25.4) vs. 88.9 (14.7), p=NR 6 months 91.6 (14.8) vs. 90.4 (15.1), p=NR 18 months 91.9 (16.1) vs. 91.8 (15.0), p=NR Disease perception Index 57.1 (25.4) vs. 60.5 (23.1), p=NR 6 months 75.6 (22.2) vs. 73.1 (22.5), p=NR 18 months 78.4 (22) vs. 77.4 (21.2), p=NR

CABG = coronary artery bypass graft; CAD = coronary artery disease; ECHO = echocardiography; ICA = invasive coronary angiography; MACE = major adverse cardiovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention; SAQ = Seattle Angina Questionnaire; SPECT = single-photon emission computerized tomography

* Positive = showed stress-related deterioration in contractility in functional or hibernating myocardial segments; Negative = NR

† Studies do not report test results for ICA group.

‡ Stress Echo: transient ischemic attack (1). ICA group: CVA post-ICA, observed overnight (1)
§ In ICA group, three patients subsequently required CABG; all had positive tests but were initially managed with PCI (2) or medically (1). Three patients with positive echoes were initially managed with PCI and subsequently required bypass surgery.

Appendix Table G6. Data abstraction for Stress Echo vs. ICA: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Sharples, 2007; Thom, 2014 Stress Echo (A) vs. ICA (B)	NR	NR	NR

AE = adverse events; ECHO = echocardiography; ICA = invasive coronary angiography, NR = not reported.

Appendix Table G7. Data abstraction for Stress Echo vs. Usual care: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
Badano, 1999; Nucifora, 2009 RCT (Multi Center) Italy Funding NR	Population: Suspected ACS Setting: ED Inclusion: - ACP within previous 24 hours in absence of local trauma and abnormalities on chest X-ray - Non-diagnostic electrocardiogram at admission - Negative myocardial injury biomarkers - Ability to perform electrocardiogram exercise testing Exclusion: - Age <30 years - Prehospital or emergency department complication of acute ischemia or MI - Premature ventricular beats >6 per minute - Atrial fibrillation	**A. Stress Echo (n=110 randomized, n=77 analyzed)** Stressor: Dobutamine-atropine Protocol: Dobutamine was administered intravenously for 3 minutes, increasing every 3 minutes, atropine was added for those not achieving 85% of their age and gender-predicted maximal heart rate and without symptoms or signs of myocardial ischemia. During test, symptoms and ECG were monitored each minute. Definition of positive test: NR **B. Standard Care (n=91 randomized, n=55 analyzed)** Current clinical protocols, prescribing an in-hospital observation period and discharge after several hours or days.	NR	**A vs. B** Subgroup: None N randomized: 201* Mean age (SD): 52 (10) vs. 56 (14) Female: 47% vs. 45% Race: NR Chest pain: NR - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: 3% vs. 2% Prior revascularization: NR Known CAD: NR Chest pain frequency: NR Hypertension: 38% vs. 49% Hyperlipidemia: NR Diabetes: 12% vs. 11%	2 months: 65.7% (132/201) Crossover: 0%

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
	- Dilated or hypertrophic cardiomyopathy - Complex congenital heart disease - Significant valvular disease - Known aortic aneurism >50 mm - Uncontrolled proven hypertension >180/100 mmHg - Complete left branch bundle block.			Current smoking: 48% vs. 49%	

ACP = acute chest pain; ACS = acute coronary syndrome; CAD = coronary artery disease; ECG = electrocardiogram; ED = emergency department; f/u = follow-up; MI = myocardial infarction; mm = millimeter; NR = not reported; RCT = randomized control trial.

* An additional 89 patients were randomized to an ETT arm of this trial. The data for these patients are abstracted elsewhere (Appendix table XXX)

Appendix Table G8. Data abstraction for Stress Echo vs. Usual care: Efficacy Outcomes

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Badano, 1999; Nucifora, 2009 Stress Echo (A) vs. Usual care (B)	**A vs. B** **Diagnosis of ischemic chest pain, % (n/N)** 17% (13/77) vs. 49% (27/55), p=NR **Diagnosis of nonischemic chest pain, % (n/N)** 83% (64/77) vs. 51% (28/55), p=NR	**A vs. B** **All-cause mortality, % (n/N)** Index/in-hospital 0% (0/77) vs. 0% (0/55), p=NR 2 months 0% (0/77) vs. 0% (0/55), p=NR	**A vs. B** **Nonfatal MI, % (n/N)** Inde/in-hospital 0% (0/77) vs. 0% (0/55), p=NR 2 months 0% (0/77) vs. 0% (0/55), p=NR	**A vs. B** **Revascularization (any), % (n/N)** 2 months 6.5% (5/77) vs. 2% 3.6% (2/55), p=NR **Revascularization (PCI), % (n/N)** 2 months 5% (4/77) vs. 2% (1/55), p=NR **Revascularization (CABG), % (n/N)** 2 months 1% (1/77) vs. 2% (1/55), p=NR **Medications prescribed at discharge, % (n/N)** Nitrates 13% (10/77) vs. 22% (12/55), p=NR Antiplatelet drugs 30% (23/77) vs. 44% (24/55), p=NR Beta-blockers	**A vs. B** **Invasive Coronary Angiography, % (n/N)** 2 months 0% (0/77) vs. 11% (6/55), p=NR **Stress echocardiography, % (n/N)** 2 months 0% (0/77) vs. 4% (2/55), p=NR **Transthoracic echocardiography, % (n/N)** 2 months 1% (1/77) vs. 22% (12/55), p=NR **Electrocardiogram, % (n/N)** 2 months 9% (7/77) vs. 24% (13/55), p=NR	NR	**A vs. B** **Rehospitalization for acute chest pain, % (n/N)** 2 months 3% (2/77) vs. 15% (8/55), p=NR **Hospital length of stay (hours), mean (SD)** Index 40 (42) vs. 95 (74), p=NR **Nottingham Health Profile score, mean (SD)** **Physical mobility** Index 26 (23) vs. 37 (32), p=NR 2 months, p=NR 15 (16) vs. 22 (19) **Pain** Index 25 (26) vs. 35 (33), p=NR 2 months 7 (10) vs. 15 (19), p=NR

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				21% (16/77) vs. 29% (16/55), p=NR <u>Calcium channel blockers</u> 21% (16/77) vs 24% (13/55), p=NR			**Social isolation** <u>Index</u> 19 (30) vs. 29 (36), p=NR <u>2 months</u> 4 (9) vs. 11 (16), p=NR **Emotional reactions** <u>Index</u> 27 (26) vs. 34 (31), p=NR <u>2 months</u> 21 (25) vs. 29 (30), p=NR **Energy level** <u>Index</u> 38 (39) vs. 47 (41), p=NR <u>2 months</u> 14 (14) vs. 21 (21) , p=NR **Sleep** <u>Index</u> 41 (31) vs. 38 (31), p=NR <u>2 months</u> 22 (17) vs. 20 (15), p=NR

CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention

Appendix Table G9. Data abstraction for Stress Echo vs. Usual care: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Badano, 1999; Nucifora, 2009 Stress Echo (A) vs. Usual care (B)	NR	NR	NR

AE = adverse events, Echo = echocardiogram, NR = not reported.

APPENDIX H. Data Abstraction of Included Studies Evaluating PET

Appendix Table H1. Data abstraction for PET vs. SPECT: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
Mullani, 2000 RCT (single center) United States Partial funding (Bracco Diagnostics, Positron Corporation)	Population: Mixed, suspected (70%) and known history (30%) of CAD Setting: Outpatient Inclusion: Prior history of heart disease documented by coronary angiography; patients with no prior history of CAD were clinically evaluated and required to have symptoms of chest pain, shortness of breath, or resting ECG changes before recommending a nuclear cardiology scan; age > 18 years. Exclusion: medical reasons that would preclude randomization to one modality or the other	**A. PET (n=105)** Stressor: 0.56 mg/kg dipyridamol Contrast: 1480 MBq 82Rb chloride Protocol: 20-minutesute attenuation scan to correct for radiation absorption in the body, before rest scan with infusion of 1480 MBq 82Rb chloride. Stress induced with a dipyridamole for 4 minutes, then stress scan obtained with another infusion of 1480 MBq 82Rb-chloride. Data acquisition times for both rest and stress scans were 6 minutes. Definition of positive test: NR **B. SPECT (n=105)** Stressor: dipyridamole (except n=6 underwent dobutamine stress) Contrast: 74-111MBq Tl-chloride Protocol: dual isotope technique; a rest scan with 74-111MBq Tl-chloride was carried with a 180°-arc data collection. Dipyridamole infused at the rate of 0.56 mg/kg for 4 minutes. At 4 minutes post infusion, injection of 740 MBq Tc-labeled sestamibi made at peak exercise. After 30 minutes wait time, a 180° arc data acquisition performed for the stress scan. Definition of positive test: NR	A vs. B NR	A vs. B Subgroup: None N randomized: 210 Mean age (SD): 63 (12) vs. 65 (11) years Female: 41% vs. 60%; p=0.006 Race: NR Chest pain: NR - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: 30% vs. 30% Chest pain frequency: NR Hypertension: NR Hyperlipidemia: NR Diabetes: NR Current smoking: NR *Women vs. Men*	9 month (mean; range 6-12 months): 87% (182/210) Crossover: NR

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
				Mean age (SD): 66 (12) vs. 62 (11) years; p = 0.004 Race: NR Chest pain: 44% vs.30% - Atypical angina: 19% vs.12% - Exertional: 8% vs.6% - Stress: 3% vs.3% - Rest: 10% vs. 8% Dyspnea: 19% vs.13% Prior MI: 12% vs.10% Prior revascularization: NR Known CAD: 30% vs. 30% Chest pain frequency: NR Hypertension: 52% vs.45% Hyperlipidemia (defined as >240): 16% vs.11% Diabetes: NR Current smoking: NR Family history of CAD: 20% vs.18% Coronary angiography: 11% vs.14% Irregular heart beat: 10% vs.9% CHD: 4% vs.3%	

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
				Prior history of CAD (documented by coronary angiography or MI) vs. no prior history of CAD Mean age (SD): 65 (10) vs. 64 (11) p-values non-significant unless reported	
Patel, 2019 RCT (single center) United States Funding: Blue Cross Blue Shield of Kansas City	Population: Symptomatic, prior history of CAD Setting: Outpatient Inclusion: Age 30-90 years with known stable CAD presenting with new/worsening symptoms (chest pain and/or dyspnea) in either the office or hospital and clinically indicated pharmacologic MPI Exclusion: Renal dysfunction (serum creatinine greater than 2.5 mg/dl), MI or coronary revascularization within past 6 months, significant valvular	**A. PET (n=161)** Stressor: regadenoson (n=36; 0.4 mg rapid IV push) or weight-based dose of dipyridamole (n=286; 0.56 mg/kg IV over 4 minutes) Contrast: weight-based dose of Tc-99m sestamibi (7.8-11.0 mCi) Protocol: all patients received iv injection of Rb-82 [mean rest dose 42.9 +/− 9.0 mCi (23.7-60.1 mCi)] followed by list mode ECG-gated rest emission image acquisition for 7 minutes for PET/CT systems and a 5 minutes ECG gated perfusion. Then stress testing conducted. At peak stress, dose of Rb-82 [mean stress dose 42.4 +/− 9.1 mCi (21.1-64.9 mCi)] injected, and stress PET images acquired in a similar manner to rest PET images. Stress dose of IV Tc-99m sestamibi (19.2-38.1 mCi) injected at peak stress, prior to stress dose of Rb-82. Definition of positive test:	A vs. B NR	A vs. B Subgroup: None N randomized: 330 (322 with evaluable scans) Mean age (SD): 66 (9) vs. 66(10) years Female: 37% vs. 33% Race: NR Chest pain: - Typical angina: 44% vs. 36% - Atypical angina: 29% vs. 38% - Nonspecific chest pain: 27% vs. 26% Dyspnea: 66% vs. 71% Syncope: 3% vs. 3% Prior MI: NR Prior revascularization: NR	3 month: 98% (322/330) 6 month: 95% (314/330) 12 month: 95% (314/330) Crossover: NR

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
	disease, prior transplant, morbid obesity (BMI ≥ 38 kg/m2), LVEF < 40%, pregnant patients and patients unwilling to undergo angiography if indicated.	High risk MPI findings defined as presence of moderate or severe ischemia on MPI, a TID ratio of >1.2. Patients without any high risk MPI findings classified as low risk MPI. **B. SPECT (n=161)** Stressor: regadenoson (n=36; 0.4 mg rapid IV push) or weight-based dose of dipyridamole (n=286; 0.56 mg/kg IV over 4 minutes) Contrast: weight-based dose of Tc-99m sestamibi (7.8-11.0 mCi) Protocol: ECG-gated rest SPECT image acquisition started approximately 60 minutes post-radioisotope injection. Stress SPECT images were acquired approximately 60 minutes post-stress Tc-99m injection in similar fashion to rest SPECT image acquisition. Definition of positive test: High risk MPI findings defined as the presence of moderate or severe ischemia on MPI, a TID ratio of >1.2, or a LVEF reserve of <0%. Patients without any high risk MPI findings classified as low risk MPI.		Known CAD: 100% vs. 100% Chest pain frequency: NR Hypertension: 86% vs. 93%, p=0.04 Hyperlipidemia: 99% vs. 99% Diabetes: 27% vs. 29% Current smoking: 17% vs. 20% BMI: 28.8 (4.5) vs. 29.2 (5.2) Family history of CVD: 41% vs. 46% CVA: 15% vs. 16% PVD: 27% vs. 27% Atrial Fibrillation: 20% vs. 12% Hospital status at time of MPI: Inpatient: 1% vs. 2% Outpatient: 99% vs. 98% Abnormal Baseline ECG: 45% vs. 39% Mean SAQ – physical limitation: 84.86 vs. 81.84 Mean SAQ – angina frequency: 78.07 vs. 78.82	

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
				Mean SAQ – quality of life: 70.65 vs. 69.62 p-values non-significant unless reported	

ACS = acute coronary syndrome, CAD = coronary artery disease, CHD = coronary heart disease, CVA = cerebrovascular accident, CVD = cardiovascular disease, ECG = electrocardiogram, f/u = follow-up, LVEF = left ventricular ejection fraction, MI = myocardial infarction, MPI = myocardial perfusion imaging, NR = not reported, PET = positron emission tomography, RCT = randomized control trial, SAQ = Seattle Angina Questionnaire, SD = standard deviation, SPECT = single photon emission computed tomography, TID = Transient ischemic dilatation.

* A total of n=330 patients were randomized. However, only patients with an evaluable scan at baseline were followed for up to 1 year and included in the analytic cohort. Eight patients (n=4 in each group A and group B) did not have an evaluable scan at baseline. Patient characteristics and patient outcomes are described out of persons with an evaluable scan at baseline (n=322). Patient follow-up is described out of the persons randomized (n=330).

Appendix Table H2. Data abstraction for PET vs. SPECT: Efficacy Outcomes

Author/trial Interventions	Patient disposition Test result	Mortality (All – cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Mullani, 2000 PET vs. SPECT	**Disposition** Discharged from ED: NR Admitted to hospital: NR **Test result** Positive scan: 38% (40/105) vs. 29% (30/105), p=0.143 *With history of CAD:* 49% (15/31) vs. 59% (19/32), p=0.382 - no significant association of positive scans with age, sex, or modality of imaging (multivariate regression) *Without history of CAD:* 34% (25/74) vs. 15%	**All-cause mortality** NR **Cardiac (CAD-related) mortality** 9 months (mean; range 6-12 months): 3% (3/105) vs. 4% (4/105), p=NR* *With history of CAD:* 3% (1/31) vs. 3% (1/32), *Without history of CAD:* 3% (2/74) vs. 4% (3/73) p=NR	NR	NR	NR	NR	NA

Author/trial Interventions	Patient disposition Test result	Mortality (All – cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	(11/73), p=0.008 - significant association of positive scans with sex (males = OR 3.9, 95% CI 1.7 to 9.2) and modality of imaging (PET = OR 2.5 (95 CI 1.1 to 5.7) (multivariate regression) Diagnosed with ACS: NR Perfusion abnormality without significant stenosis: NR						
Patel, 2019 PET vs. SPECT	**Disposition** Discharged from ED**:** NR Admitted to hospital: NR	**All-cause mortality** 12 months 1% (1/161) vs. 1% (2/161), p=1.0 **Cardiac mortality**	**MI** 12 months 0% (0/161) vs. 1% (2/161), p=0.50	**Revascularization (PCI/CABG)** 3 months *Overall*: 11% (18/161) vs. 10% (16/161), p=0.72 *Low risk MPI*: 0% (0/96) vs. 4.5% (3/67), p=0.07	**Diagnostic failure†** 60 days 2% (3/161) vs. 3% (4/161), p=0.70 **Invasive Coronary Angiography** 3 months	NR	**Obstructive disease on angiography** 3 months 16% (25/161) vs. 11% (17/161), p=0.19

Author/trial Interventions	Patient disposition Test result	Mortality (All – cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	Test result Low risk MPI: 60%(96/161) vs.42% (67/161),p=NR High risk MPI§: 40% (65/161) vs. 58% (94/161), p=NR **Ischemia findings** No ischemia 58% (94/161) vs. 59% (95/161) Mild ischemia 7% (11/161) vs. 9% (14/161) Moderate ischemia 14% (23/161) vs. 19% (31/161) Severe ischemia 20% (32/161) vs. 11% (17/161) Non-diagnostic 1% (1/161) vs. 3% (4/161)	NR		*High risk MPI*: 27.7% (18/65) vs. 13.8% (13/94), p=0.03 6 months *Overall*: 12% (20/161) vs. 12% (19/161), p=0.86 *Low risk MPI*: 0% (0/96) vs. 6.0% (4/67), p=0.03 *High risk MPI*: 30.8% (20/65) vs. 16.0% (15/94), p=0.03 12 months 16% (25/161) vs. 15% (24/161), p=0.88 *Low risk MPI*: 4.2% (4/96) vs. 7.5% (5/67), p=0.01 *High risk MPI*: 32.3% (21/65) vs. 19.1% (18/94), p=0.06 **Late revascularization after 3 months**** 4% (7/161) vs. 5% (8/161), p= 0.70	*Overall*: 21% (33/161) vs. 16% (25/161), p=0.25 *Low risk MPI*: 2.1% (2/96) vs. 9.0% (6/67), p=0.07 *High risk MPI*: 47.7% (31/65) vs. 20.2% (19/94), p<0.01 6 months *Overall*: 22% (36/161) vs. 19% (30/161), p=0.41 *Low risk MPI*: 3.1% (3/96) vs. 10.4% (7/67), p=0.09 *High risk MPI*: 50.8% (33/65) vs. 24.5% (23/94), p<0.01 12 months *Overall*: 29% (46/161) vs. 28% (45/161), p=0.90 *Low risk MPI*: 8.3% (8/96) vs. 19.4% (13/67), p=0.04 *High risk MPI*: 56.9% (37/65) vs. 34.1% (32/94), p<0.01 **Stress testing** NR		**Longitudinal health status outcomes‡** *Mean SAQ – physical limitation:* 1 month 90.27 vs. 90.14 3 month 92.98 vs. 90.42 6 month 92.32 vs. 90.38 12 month 92.09 vs. 88.74 p = 0.07 *Mean SAQ – angina frequency:* 1 month 88.21 vs. 89.31 3 month 89.42 vs. 89.17 6 month 90.26 vs. 88.01 12 month 91.35 vs. 89.79 p =0.70 *Mean SAQ – quality of life:* 1 month

Author/trial Interventions	Patient disposition Test result	Mortality (All – cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	p value across all groups = 0.09 <u>Diagnosed with ACS</u>: NR <u>Perfusion abnormality without significant stenosis:</u> NR			**Escalation in anti-anginal therapy††** <u>3 months</u> 26% (41/161) vs. 23% (37/161), p=0.60 **Hospitalization/ED visit**: NR			81.30 vs. 78.18 <u>3 month</u> 83.87 vs. 81.63 <u>6 month</u> 83.72 vs. 81.07 <u>12 month</u> 83.39 vs. 81.21 p=0.20 *Median RDS:* <u>1 month</u> 1 vs. 1 <u>3 month</u> 1 vs. 1 <u>6 month</u> 1 vs. 1 <u>12 month</u> 1 vs. 1 p=0.53

ACS = acute coronary syndrome, CAD = coronary artery disease, CHD = coronary heart disease, CVA = cerebrovascular accident, CVD = cardiovascular disease, ECG = electrocardiogram, f/u = follow-up, LVEF = left ventricular ejection fraction, MI = myocardial infarction, MPI = myocardial perfusion imaging, NR = not reported, PET = positron emission tomography, RCT = randomized control trial, SAQ = Seattle Angina Questionnaire, SD = standard deviation, SPECT = single photon emission computed tomography, TID = Transient ischemic dilatation.

* Scan results were as follows for those who suffered cardiac death: PET (2 positive, 1 negative) vs. SPECT (2 positive, 2 negative)

† Defined as unnecessary coronary angiography (absence of ≥ 50% stenosis in ≥ 1 vessels) or additional non-invasive testing.

‡ p values represent between group differences over time.

§ High Risk MPI was defined as patients with moderate or severe ischemia or transient ischemic dilation (TID >1.20) or LVEF Reserve <0%. Patients not meeting these criteria wer5e considered having low-risk MPI in both PET and SPECT.

** Defined as the cumulative number of patients that had revascularization after 3 months.

†† Defined as addition of another anti-anginal medication class or increase in dose or frequency of one or more of existing anti-anginal medications within 3 months post baseline. Antianginal medication = the following drug classes: aspirin/other anti-platelets, beta-blockers, statins, calcium channel blockers, nitrates, and ranolazine.

Appendix Table H3. Data abstraction for PET vs. SPECT: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Mullani, 2000 PET vs. SPECT	NR	NR	NR
Patel, 2019 PET vs. SPECT	NR	NR	NR

AEs= adverse events, NR = not reported, PET = positron emission tomography, SPECT = single photon emission computed tomography.

APPENDIX I. Data Abstraction of Included Studies Evaluating SPECT

Appendix Table I1. Data abstraction for SPECT vs. Exercise ECG: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
Mieres, 2009, Mieres 2011, Shaw 2011 RCT (Multi Center) USA Funding GE Healthcare	Population: Women with stable angina (known CAD excluded) Setting: Outpatient, non-emergent (cardiology practices) Inclusion: - Chest pain or anginal equivalent symptoms at intermediate to high pretest risk for CAD - Capable of performing >5 metabolic equivalents of exercise - ≥50 years of age or ≥30 years of age with surgical menopause - Diabetic women of any age presenting for evaluation of chest pain symptoms - Women of any age with metabolic syndrome presenting	**A. SPECT (MPI) (n=412 randomized, n=384 analyzed)** Stressor: Exercise Contrast: Tc-99 m tetrofosmin Protocol: All testing was performed in accordance with the most recent ACC/AHA guidelines stipulating that continuous ECG monitoring be employed. Definition of positive test: Summed stress score ≥4 **B. Exercise ECG (n=412 randomized, n=388 analyzed)** Negative result defined as <1.0 mm of horizontal or downsloping ST segment depression.	Intermediate: 100% (inclusion criteria)	**A vs. B** Subgroup: Women N randomized: 824 Median age (IQR): 62 (58 to 68) vs. 63 (60 to 69) Female: 100% Race: Black: 6.6% Hispanic: 2.9% Asian: 2% Caucasian: 87.3% Chest pain: 89.4% vs 90% - Typical angina: 59.8% VS. 61.2% - Atypical angina: 9.3% VS. 9.1% - Nonspecific chest pain: 27.8% vs. 27% Dyspnea: 48.3% Vs. 52.5% Prior MI: 0%* Prior revascularization: 0% Known CAD: 0%	24 months: 93.7% Crossover: 0%

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
	with chest pain symptoms Exclusion: - Known CAD, MI, or catheterization results revealing a >50% lesion in one or more coronary arteries - Scoring ≤5 metabolic equivalents on the DASI - Women that are nursing or pregnant - Nuclear medicine study within preceding 10 days - Significant valvular heart disease - Uncontrolled hypertension - History of heart failure - Left ventricular ejection fraction - Inability or unwillingness to complete long-term followup			Chest pain frequency: <1 per week: 65.8% vs. 70.9% 1 to 3 times: 40.9% vs. 39.1% 1 to 3 times per week: 24.9% vs. 31.8% Almost everyday: 10.7% vs. 9% 1 to 3 times per day: 7.4% vs. 4.7% ≥4 times per day: 2% vs. 2.7% Hypertension: 52% vs. 55.2% Hyperlipidemia: 53.7% vs. 55.2% Diabetes: 14.2 vs. 12.6% Current smoking: 42.4% vs. 48.8% Medications: ACE inhibitor: 18.4% vs. 15.6% Angiotensin receptor blocker: 10.9% vs. 10.9% Beta-blocker: 19.7% vs. 18.3%	

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
				Calcium channel blocker: 11.2% vs. 9.9% Aspirin: 37.1% vs. 33.2% Gastrointestinal: 28.4% vs. 25.5% Antidepressant: 18.7% vs. 16.6% Anxiolytic: 6.4% vs. 5.2% Nitrates: 2.5% vs. 3.5% Statins: 33.1% vs. 31.7% NSAIDS: 16.9% vs. 14.9%	
Sabharwal, 2007 RCT Single Center UK Funding Bristol-Myers Squibb Medical Imaging, Northwick Park	Population: Suspected CAD Setting: Outpatient, chest pain clinic Inclusion: - ≥25 years old - chest pain suspicious of CAD. Exclusion:	**A. SPECT (MPI) (n=250)** Stressor: Exercise treadmill, dipyridamole or dobutamine. Contrast: Sestamibi Protocol: All patients asked to abstain from all caffeine intake 12 hours before the clinic appointment and to stop taking beta-blockers, diliazem, or verapamil 48 hours before stress testing. After randomization, patients underwent stress gated myocardial perfusion SPECT infusion. Rest scans were taken 24 to 48 hours later if stress scan was abnormal and ambiguous. - 62% (154/250) had treadmill stress testing alone. - 38% (96/250) underwent pharmacologic stress testing	**A vs. B** Low: 10.8% (27/250) vs. 21.2%% (44/207) Intermediate: 71.2% (178/250) vs. 49.3% (102/207)	**A vs. B** Subgroup: None N randomized: 457[†] Mean age (SD): 59.7 (12.2) vs. 58.9 (11.4) Female: 44.4% vs. 42.5% Race: White: 55.6% vs. 46.9%	24 months (96.9% followed) Crossover: 0%

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
Cardiac Research Fund, personal grant from Mr. Michael Tabor	- Acute coronary syndromes - known CAD - pregnant or lactating women	Definition of positive test: NR **B. Exercise ECG (n=207)** Treadmill electrocardiography. After randomization, underwent symptom-limited Bruce or modified Bruce protocol exercise treatment test by use of a Marquette CASE 8000 system. Result classified as normal (ability to reach an adequate workload and heart rate without significant ECG changed or symptoms suggestive of CAD), inconclusive/indeterminate, or positive for CAD. Abnormal response was defined according to symptoms and standard ECG criteria (≥1 mm of horizontal or donwsloping ST-segment depression during exercise or persisting into recovery in ≥1 lead or exertional hypotension >20 mm Hg) - 98.5% (204/207) underwent exercise test - 1.4% (3/207) did not undergo treadmill exercise due to suspected hypertrophic cardiomyopathy, atrioventricular block on the resting electrocardiogram, or chest pain at rest immediately before ETT. - 58.8% (147/250) underwent rest scans due to abnormal scans.	High: 18% (45/250) vs. 29.5% (61/207)	Chest pain: NR - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: 0% Chest pain frequency: NR Hypertension: 53.2%% vs 46.3% Hyperlipidemia: NR Diabetes: 19.2% vs 14.5% Current smoking: 12.8% vs 16.4%	

ACC = American College of Cardiology; ACE = Angiotensin-converting-enzyme; AHA = American Heart Association; CAD = coronary artery disease; DASI = Duke Activity Status Index; ECG = electrocardiogram; ETT = exercise tolerance test; NSAIDS = non-steroidal anti-inflammatory drugs; MI = myocardial infarction; MPI = myocardial perfusion imaging; RCT = randomized control trial; SPECT = single-photon emission computerized tomography

* Prior MI and CAD was an exclusion criteria

† Patients with an abnormal resting electrocardiogram were assessed in the clinic but excluded from the analysis.

Appendix Table I2. Data abstraction for SPECT vs. Exercise ECG: Efficacy Outcomes

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Mieres, 2009, Mieres 2011, Shaw 2011 (WOMEN trial) SPECT (A) vs. Exercise ECG (B)	**A vs. B** **Test result, % (n/N)**[*] **Exercise ECG interpretation**[‡] Normal 69.8% (268/384) vs. 64.1% (249/388) Indeterminate 14% (54/384) vs. 15.8% (61/388) Abnormal 16.1% (62/384) vs. 20.2% (78/388) *p=0.22 for all* **SPECT MPI interpretation subsets**[§] Normal 90.5% (347/384) Mildly abnormal 3.3% (13/384) Moderately to severely abnormal 6.2% (24/384)	**A vs. B** **Non-cardiac-related mortality, % (n/N)**[*] 24 months 1.0% (4/384) vs. 0.5% (2/388), p=0.39 **Sudden cardiac death, % (n/N)**[*†] 24 months 0.1% (1/772)	**Nonfatal MI, % (n/N)**[†] 24 months 0.4% (3/772)	**A vs. B** **Revascularization (any), % (n/N)**[*] 24 months 2.2% (8/384) vs. 1.0% (4/388), p=0.16 **Changes in medication therapy**[**] 24 months Similar rates of new use or discontinuation of nitrates, beta-blockers, statins and antidepressants between groups, p=0.20	**A vs. B** **Invasive Coronary Angiography, % (n/N)**[*] 24 months 5.5% (21/384) vs. 6.7% (26/388), p=0.98 (almost half occurred within 2 months) - Normal: 4% (14/347) vs. 3% (7/249) - Indeterminant/Mildly Abnormal: 0% (0/13) vs. 7% (4/61) - Abnormal: 29% (7/24) vs. 18% (14/78) **Any Stress testing, % (n/N)** [*] 24 months 9.4% (36/384) vs. 18.6% (72/388), p=NR **Additional exercise SPECT MPI, % (n/N)**[*] 6 months 1.2% (5/384) vs. 10.4% (40/388), p=NR 12 months 3.4% (13/384) vs. 12.4% (48/388), p=NR 24 months	**A vs. B** **MACE (composite of cardiac death, nonfatal MI, or hospital admission for an ACS or heart failure), % (n/N)**[*] 24 months *Overall*: 2.3% (9/384) vs. 1.7% (8/388), relative HR 1.3 (95% CI 0.5 to 3.5), p=0.59 *Normal test results:* 1.2% (4/347) vs. 0.4% (1/249), p=0.4 *Abnormal test results:* 13.1% (5/37) vs. 5.1% (7/139), p=0.19	**A vs. B** **Hospitalization for chest pain symptoms, % (n/N)**[*] 24 months 4% (15/384) vs. 3% (12/388), p=0.39 **Hospitalization for heart failure, % (n/N)**[†] 24 months 0.1% (1/772) **Hospitalization for ACS, % (n/N)**[†] 24 months 1.6% (12/772) **SAQ, median % (IQR)** All subscales similar between groups during follow-up (data not provided) *Overall*

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
					9.1% (35/384) vs. 17.8% (69/388), p=NR **Additional exercise ECG, % (n/N)**[*] 24 months 0.3% (1/384) vs. 0.5% (2/388), p=NR **Proportion of patients receiving no additional diagnostic testing after index test, % (n/N)** 24 months 89% (385/384) vs. 81% (314/388), p<0.0001		**Angina Free, % (n/N)**[*††] 6 months 51% (196/384) vs. 50.6% (196/388), p=0.92 12 months 49.5% (190/384) vs. 48.9% (190/388), p=0.88 24 months 64.9% (249/384) vs. 60.4% (234/388), p=0.25 **Asymptomatic, % (n/N)** 24 months 65% vs. 60%, p=0.25
Sabharwal, 2007 SPECT (A) vs. Exercise ECG (B)	**A vs. B** **Test result, % (n/N)**[*] **Treadmill result, % (n/N)**[‡‡] Normal: 30.0% (75/155) vs. 26.1% (54/204)	**A vs. B** **All-cause mortality, % (n/N)**[*] Mean 19.6 months 0.8% (2/250) vs. 1.0%	**A vs. B** **Fatal MI, % (n/N)**[*] Mean 19.6 months 0% (0/250) vs. 0.5% (1/207)[***], p=NS	**A vs. B** **Revascularization (any), % (n/N)**[*] Index visit 10.8% (27/250) vs. 17.9% (37/207), p=NR **Proportion of patients subsequently referred for revascularization,**	**A vs. B** **Referred for ICA, % (n/N)**[*] Index visit 16.4% (41/250) vs. 47.3% (98/207), p<0.0001 **Proportion of patients who underwent ICA and**	NR	NR

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	Inconclusive: 14.4% (36/155) vs. 38.6% (80/204) Positive: 17.6% (44/155) vs. 33.8% (70/204) **MPI results, % (n/N)**§§ Normal: 74% (186/250) Mildly abnormal: 6% (15/250) Moderately abnormal: 8% (19/250) Severely abnormal: 12% (30/250)	(2/207), p=NS **Cardiac mortality (i.e., fatal MI) , % (n/N)*** Mean 19.6 months 0% (0/250) vs. 0.5% (1/207), p=NS		**as a function of the number of ICAs obtained, % (n/N)*** Index visit 65.9% (27/41) vs 37.8% (37/98), p=0.005 **Aggressive medical therapy, % (n/N)*** Index 83.6% (209/250) vs. 30.4% (63/207), p=NR	**had a normal test result, % (n/N)*** 17.1% (7/41) vs. 36.7% (36/98), p=0.03 **Stress (pharmacological) Echocardiography, % (n/N)*** Index visit 0% (0/250) vs. 23.2% (48/207), p<0.0001 **Any further investigations (to include ICA) for diagnosis of CAD, % (n/N)*** Index visit 16.4% (41/250) vs. 70.5% (146/207), p<0.0001		

CAD = coronary artery disease; ECG = electrocardiogram; ETT = exercise tolerance test; ICA = invasive coronary angiography; MACE = major adverse cardiovascular events; MI = myocardial infarction; MPI = myocardial perfusion imaging; SAQ = Seattle Angina Questionnaire SPECT = single-photon emission computerized tomography; SSS = summed stress score

* n's calculated from % and denominator provided

† not reported by treatment arm

‡ Normal ETT = no significant ST-segment changes with adequate exercise tolerance; Indeterminate ETT = 0.5 to 1.0 mm of ST-segment changes, exertional chest pain, and/or submaximal exercise tolerance; Abnormal ETT = ≥1 mm of ST-segment changes generally occurring in ≥2 leads.

§ Normal = summed stress score (SSS) of <4; Mildly abnormal = SSS of 4 to 8; Moderate to severely abnormal = SSS of >8

** data not provided

†† Cumulative data available only

‡‡ Only patients who ended up undergoing treadmill stress were included. 155 of 250 MPI patients had treadmill (95 had pharmacological) and 204 of 207 ECG had treadmill (3 did not undergo treadmill stress for various reasons).

§§ Normal (SSS of 0), mildly abnormal (SSS of 1-3), moderately abnormal (SSS of 4-8), and severely abnormal (SSS of >8)

*** Same patient as included under cardiac mortality

Appendix Table I3. Data abstraction for SPECT vs. Exercise ECG: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Mieres, 2009, Mieres 2011, Shaw 2011 SPECT (A) vs. Exercise ECG (B)	NR	NR	**SPECT MPI only (index test):** Mean ionizing radiation exposure: 14 mSv
Sabharwal, 2007 SPECT (A) vs. Exercise ECG (B)	NR	NR	NR

AEs = adverse events; ECG = electrocardiogram; MPI = myocardial perfusion imaging; mSv = millisievert; SPECT = single-photon emission computerized tomography

Appendix Table I4. Data abstraction for SPECT vs. ICA: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
Sharples, 2007; Thom 2014 RCT (single Center) UK Funding National Institute for Health Research	Population: Mixed suspected CAD or known CAD Setting: Outpatient, nonemergent Inclusion: - Established or suspected chronic stable angina referred for angiography - An EET result which merited referral for angiography Exclusion: - Recent MI or revascularization - admission with chest pain - urgent revascularization - contraindication to pharmacological stress testing on MRI - incapable of performing modified Bruce exercise test	**A. SPECT (n=224 randomized)** Stressor: Adenosine (dobutamine if contraindications) Contrast: 99mTc Sestamibi Protocol: Patients abstained from all caffeinated food and drink for 24 hours prior to test, fasted for 6 hours pre-injection and took a fatty meal post injection. Pharmacological stress consisted of 6-minute adenosine infusion, 130 µg/kg/minute with tracer injected at 3 minutes. 400-MBq 99mTc MIBI administered at 3 minutes after infusion of adenosine, with imaging performed at 60 to 90 minutes after injection. Definition of positive test: positive diagnoses showed reversible ischemia in at least one segment of a 20-segment model. **B. ICA (n=222 randomized)** This group acted as the control group. ICA was performed and reported per standard techniques from the right femoral artery approach using the Seldinger technique. Positive diagnoses was defined as having 50% stenosis in the left main stem or 70% stenosis in any other major vessel.	**A vs. B** 1: 1% (1/224) vs. 1% (3/222) 2: 12% (27/224) vs. 10% (21/222) 3: 19% (41/224) vs. 19% (42/222) 4: 37% (81/224) vs. 32% (70/222) 5: 31% (69/224) vs. 38% (85/222)*	**A vs. B** Subgroup: None N randomized: 898† Mean age (SD): 62.1 (9.5) vs. 60.7 (9.1) Female: 30% vs. 33% Race: NR Chest pain: NR - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: 23% vs. 28% Prior revascularization: NR Known CAD: NR Chest pain frequency: NR Treated hypertension: 59% vs. 53% Treated hyperlipidemia: 76% vs. 74% Diabetes: 11.6% vs. 12.6% Current smoking: 41.9% vs. 46.8% Medications: Anti-platelets: 75% vs. 76%	18 months: 84% 36 months: 84% Crossover: **A vs. B** Received allocated test, % (n/N) 98.2% (220/224) vs. 98.2% (218/222)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
	- not available by phone			Statins: 67% vs. 64% Beta-blockers: 50% vs. 57% ACE inhibitors: 32% vs. 35% Calcium-channel blockers: 31% vs. 27% Nicorandil/potassium-channel activators: 18% vs. 19% Nitrates: 16% vs. 16% Diuretics: 13% vs. 17% Angiotensin-II receptor antagonists: 4% vs. 7%	

ACE = Angiotensin-converting-enzyme; CAD = coronary artery disease; EET = exercise ECG test; ECG = electrocardiogram; ICA = invasive coronary angiography; MI = myocardial; RCT = randomized control trial; SPECT = single photon emission computerized tomography

* Baseline risk of CAD was assessed by a clinician on a scale of 1 (lowest) to 5 (highest).

† Study also includes MRI. 898 patients were randomized to angiography (n=222), SPECT (n=224), MRI (226), or stress echo (226)

Appendix Table I5. Data abstraction for SPECT vs. ICA: Efficacy Outcomes

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Sharples, 2007; Thom 2014 (CECaT trial) SPECT (A) vs ICA (B)	**A vs. B** **Test result (SPECT only), % (n/N)**[*†] Positive 54% (121/224) Negative 40.2% (90/224) Equivocal 4% (9/224) Not done 1.8% (4/224)	**A vs. B** **All-cause mortality, % (n/N)** Index 0.4% (1/224) vs. 0.4% (1/222) , p=NR 18 months 1.8% (4/220) vs. 1.8% (4/218), p=NR **Cardiac mortality, % (n/N)** 18 months: 2.2% (5/224) vs. 1.4% (3/222), p=NR	**A vs. B** **Admission for acute MI, % (n/N)** 18 months 0.9% (2/224) vs. 0% (0/222), p=NR	**A vs. B** **Revascularization (CABG), % (n/N)** Index 12.9% (29/224) vs. 9.5% (21/222), p=NR 18 months 0.5% (1/224) vs. 1.4% (3/222), p=NR **Revascularization (PCI) , % (n/N)** Index 17.4% (39/224) vs. 24.8% (55/222), p=NR 18 months 0.5% (1/224) vs. 1.8% (4/222), p=NR	**A vs. B** **Proportion of patients requiring additional testing, % (n/N)** Index Any additional testing: 78.6% (176/224) vs. 3.6% (8/222), p=NR - *ICA*: 78.1% (175/224) vs. 0% (0/222), p=NR - *SPECT*: 0.5% (1/224) vs. 3.2% (7/222), p=NR - *MRI*: 0% (0/224) vs. 0.5% (1/222), p=NR	**A vs. B** **Total nonfatal events (admission for chest pain or acute MI, unplanned PCI or CABG, other)** 18 months 10.7% (24/224) vs. 8.6% (19/222), p=NR	**A vs. B** **Angina, % (n/N)** 18 months 14.7% (33/224) vs. 12.6% (28/222), p=NR **Admission for chest pain, % (n/N)** 18 months 8.5% (19/224) vs. 6.3% (14/222), p=NR **SAQ, mean (SD)** Exertional capacity Index 72.6 (21.2) vs. 75.1 (20.4), p=NR 6 months 77.5 (21.3) vs. 80.2 (19.3) 18 months 78.5 (23) vs. 81.7 (19.2), p=NR

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							Anginal stability Index 52.2 (22.5) vs. 52.5 (21.8), p=NR 6 months 61.9 (24.1) vs. 66.6 (24.7), p=NR 18 months 62.6 (25.1) vs. 64.6 (25.1), p=NR Anginal frequency Index 67.8 (23.9) vs. 67.4 (24.1), p=NR 6 months 83.5 (21.7) vs. 83.8 (21.1) 18 months 86.9 (19.4) vs. 84.2 (21.4), p=NR Treatment satisfaction index

Author/trial Interventions	Patient disposition Test result	Mortality (All –cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							88.8 (15.2) vs. 88.9 (14.7), p=NR 6 months 92 (12.7) vs. 90.4 (15.1), p=NR 18 months 91.2 (14.6) vs. 91.8 (15.0), p=NR Disease perception Index 59.8 (22.5) vs. 60.5 (23.1), p=NR 6 months 74.8 (20.1) vs. 73.1 (22.5), p=NR 18 months 77 (21.9) vs. 77.4 (21.2), p=NR

CABG = coronary artery bypass graft; CAD = coronary artery disease; ICA = invasive coronary angiography; MACE = major adverse cardiovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention; SAQ = Seattle Angina Questionnaire; SPECT = single-photon emission computerized tomography

* Positive result = shows reversible ischemia in at least one segment of a 20-segment model, negative = NR, equivocal = NR

† Studies do not report test results for ICA group

Appendix Table I6. Data abstraction for SPECT vs. ICA: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Sharples, 2007; Thom 2014 SPECT (A) vs ICA (B)	No patient experienced adverse events at the time of test.	NR	

AE = adverse events; ICA = invasive coronary angiography; SPECT = single-photon emission computerized tomography.

Appendix Table I7. Data abstraction for SPECT vs. Any functional test: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
Greenwood, 2016 RCT (multicenter) UK Funding British Heart Foundation, the Leeds Teaching Hospital Charitable Foundations and the National Institute for Health Research (NIHR)	Population: Suspected CAD Setting: Outpatient, non-emergent Inclusion: - Patients with suspected angina pectoris - ≥30 years old - CHD pretest likelihood of 10% to 90% - Suitable for revascularization Exclusion: - Known CAD - Nonanginal chest pain - Normal MPS or cardiac computed tomography result within previous 2 years - Clinically unstable; previous MI - Previous coronary revascularization; contraindication to any study noninvasive imagine test.	**A. SPECT (MPS) (n=481) †** - SPECT: 92.7% (446/481) - CMR: 0.8% (4/481) - CCTA: 0.2% (1/481) - ETT or stress echo: 1.0% (5/481) - Immediate ICA: 1.0% (5/481) - No test: 4.4% (21/481) Stressor: treadmill or bicycle exercise, or pharmacologic vasodilator stress with adenosine or regadenoson, or a combination. Contrast: Tc-tetrofosmin or Tc-Sestamibi Protocol: Patients underwent a 1 or 2 day scanning protocol. Definition of positive test: Summed stress score ≥4, unless believed by the reporting clinician to represent attenuation artifact, will by protocol necessitate referral for ICA+FFR. **B. NICE guidelines (n=240)†** Patients were scheduled for CCTA if they had a pretest likelihood of 10% to 29%, MPS if they had a pretest likelihood of 30% to 60%, or coronary angiography if they had a pretest likelihood of 61% to 90%. - CCTA: 23.3% (56/240) - SPECT: 35.8% (86/240)	A vs. B Low: 26% (125/481) vs. 25.4% (61/240) Intermediate: 38% (183/481) vs. 36.7% (88/240) High: 36% (173/481) vs. 37.9% (91/240)	A vs. B Subgroup: None N randomized: 721* Mean age (SD): 55.9 (8.87) vs. 56.5 (9.21) Female: 46.8% vs. 46.7% Race: NR Nonwhite: 7.9% vs. 7.9% Chest pain: - Typical angina: 32.4% vs. 34.2% - Atypical angina: 67.6% vs. 65.8% - Nonspecific chest pain: NR Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: NR Chest pain frequency: NR Hypertension: 37.8% vs 41.3% Hyperlipidemia: NR Diabetes: 15.2% vs 10% Former or Current smoking: 56.3% vs. 61.3% Medications: Antiplatelet therapy: 55.7% vs. 62.5% Beta-blockers: 32.6% vs. 30.8% Statin or other lipid-lowering therapy: 41.8% vs. 45%	Median (IQR): 15.8 (12.1 to 24.2) months: 97.4% (702/721) Received allocated test: 92.7% (446/481) vs. 100% (240/240)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
		- Stress echo: 0.4% (1/240) - CMR: 0.4% (1/240) - Immediate ICA: 35.4% (85/240)		Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker: 25.4% vs. 27.5% Other antianginal medication: 57.4% vs. 59.2%	

CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; CHD = coronary heart disease; CMR = cardiac magnetic resonance; FFR = fractional flow reserve; ICA = invasive coronary angiography; MI = myocardial infarction; MPS = myocardial perfusion scintigraphy; NICE = National Institute for Health and Care Excellence; RCT = randomized control trial; SPECT = single photon emission computed tomography

* An additional 481 patients were randomized into a CMR arm in this trial. Data for these patients are not included here as CMR is not an included intervention in this HTA.

† Patients may have received more than 1 test, in addition to or as an alternative to their strategy.

Appendix Table I8. Data abstraction for SPECT vs. Any functional test: Efficacy Outcomes

Author/trial Interventions	Patient disposition Test result	Mortality (All – cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Greenwood, 2016 SPECT (A) vs. NICE guidelines (B)	**A vs. B** **Test result, % (n/N)** Positive for CHD on Index test 18.2% (81/446) vs. 13.4% (19/142), p=NR	**A vs. B** **All-cause mortality, % (n/N)** Median 16 month follow-up 0.6% (3/481) vs. 1.5% (3/240), p=NR **Cardiovascular mortality, % (n/N)** Median 16 month follow-up 0.6% (3/481) vs. 0.4% (1/240), p=NR	**A vs. B** **Nonfatal MI, % (n/N)** Median 16 month follow-up 0.4% (2/481) vs. 0.8% (2/240), p=NR	**A vs. B** **Revascularization (PCI), % (n/N)** 12 months 5.7% (27/477) vs. 5.8% (14/238), p=NR **Revascularization (CABG), % (n/N)** 12 months 2.7% (13/481) vs. 2.9% (7/240), p=NR Unplanned PCI, % (n/N) Median 16 month follow-up 0.8% (4/481) vs. 0.8% (2/240) Unplanned CABG, % (n/N) Median 16 month follow-up 0% vs. 0%	**A vs. B** **Invasive Coronary Angiography, % (n/N)** Index visit 10.4% (5/481) vs. 35.4% (85/240), p=NR 12 months 16.4% (73/481) vs. 7.1% (17/240), p=NR [Total ICAs in each group across entire study period: 16.2% (78/481) vs. 42.5% (102/240)], p=NR **Unnecessary ICA, % (n/N)** 12 months 7.1% (34/481) vs. 28.8% (69/240), p=NR	**A vs. B** **MACE (composite of cardiovascular death, myocardial infarction, unplanned coronary revascularization, and hospital admission for cardiovascular cause), % (n/N)** Median 16 month follow-up 3% (15/481) vs. 2.5% (6/240), p=NR	**A vs. B** **Arrhythmia, % (n/N)** Median 16 month follow-up 0.6% (3/481) vs. 0.8% (2/240), p=NR **Heart failure, % (n/N)** Median 16 month follow-up 0.8% (4/481) vs. 0% (0/240), p=NR **Stroke or TIA, % (n/N)** Median 16 month follow-up 0.2% (1/481) vs. 0% (0/240), p=NR

CABG = coronary artery bypass graft; CCT = coronary computed tomography; CHD = coronary heart disease; CMR = cardiac magnetic resonance; ICA = invasive coronary angiography; MI = myocardial infarction; MPS = myocardial perfusion scan; NICE = National Institute for Health and Care Excellence; PCI = percutaneous coronary intervention; RCT = randomized control trial; SPECT = single photon emission computed tomography; TIA = transient ischemic attack.

* Data are only reported for those that received their initial randomized test. In the NICE-guidelines group, only data for those that underwent CCTA or SPECT as their initial test have data reported here.

† Components of this outcome include receiving a false positive on a non-invasive test, being directed straight to ICA based on treatment strategy, having a negative noninvasive test (not per-protocol), and having an inconclusive noninvasive test or result.

Appendix Table I9. Data abstraction for SPECT vs. Any functional test: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Greenwood, 2016 SPECT (A) vs. NICE guidelines (B)	In the study, 5 test-related medical complications were reported: CMR (1 case: mild urticarial reaction), MPS (0 cases), CCT (1 case: vasovagal episode), and angiography (3 cases: ventricular tachycardia, pseudo-aneurysm and popliteal deep venous thrombosis, right coronary artery spasm and transient ST elevation).*	NR	NR

AE = adverse events; MPS = myocardial perfusion scan; NICE = National Institute for Health and Care Excellence; SPECT = single photon emission computed tomography

* Events were not reported by randomized group and therefore these events could have occurred among patients randomized to CMR, which was not abstracted here as this intervention was not of interest for the purposes of this HTA.

Appendix Table I10. Data abstraction for SPECT vs. Usual care: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
Lim, 2013 RCT (single Center) Singapore Funding Singapore Research Institute, Ministry of Health Holdins	Population: Suspected ACS Setting: ED Inclusion: - Aged ≥25 years - Presenting at Singapore General Hospital ED with acute chest pain - Initial 12-lead ECG was non-diagnostic for myocardial ischemia or AMI - No lower age limit for patients with coronary risk factors or family history of AMI Exclusion: - Congestive cardiac failure or hypotension associated with chest pain - Unequivocal non-cardiac chest pian based on clinical assessment	**A. SPECT (SMPI) (n=1126 randomized, n=1004 analyzed)** Stressor: symptom-limited physical exercise testing Bruce Protocol, dipyridamole or dobutamine. Contrast: Tc-99m tetrofosmin Protocol: following randomization, patients received in the first 6 hours a continuous ECG monitoring, a 12-lead ECG, and sampling of 10 mL of blood at 0, 3, and 6 hours after arrival for analysis of creatine kinase-MB (CKMB) isoenzyme and troponin T. Any patients that developed recurring chest pain or positive CKMB or troponin T were admitted to the Department of Cardiology. After this, they underwent a stress nuclear MPI scan within 24 hours of presentation with exercise as preference, those unable to received intravenous pharmacologic testing. Tc-99m tetrofosmin was injected at peak stress, and SPECT was performed 30 (exercise) or 60 (pharmacologic) minutes later. Definition of positive test: Participants with abnormal stress scans (defect size ≥5% of left ventricle or LVEF <50% with regional wall motion	NR	**A vs. B** Subgroup: Participants with negative observation following 6-hours N randomized: 1690* Mean age (SD): 52 (12.4) vs. 51.8 (12.8) Female: 40.3% vs. 43.4% Race: Chinese: 70% vs. 68.3% Malay: 10.5% vs. 12.7% Indian: 17.8% vs. 17.3% Others: 1.6% vs. 1.8% Chest pain: NR - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: 1% vs. 1.6% Prior revascularization: NR Known CAD: 4.1% vs 4.4% Chest pain frequency: NR Hypertension: 43.2% vs. 39.3% Hyperlipidemia: NR Diabetes: 17.9% vs. 17.9% Current smoking: 33% vs. 30.7%	12 months: **A vs. B** Crossover: 9.7% (109/1126) vs. 9.8% (55/564) admitted before 6 hours 1.2% (13/1126) vs. 0.9% (5/564) self-discharged without receiving intervention

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
	- Clinical syndrome of persistent chest pain consistent with unstable angina - Previous angiogram or SMPI/echo test within 18 months - Concomitant illnesses requiring admission; pregnant	abnormalities) were admitted for further management, while those with equivocal stress scans (mild defects with defect size <5% with normal left ventricle function and no regional wall motion abnormalities) were scheduled for rest imaging, which may go on to be reported as ischemia. **B. Usual care (n=564 randomized, n=504 analyzed)** Following 6 hours of observation, control group were assessed for likelihood of ACS based on age, sex, characteristics of chest discomfort, known history of CAD or MI, present of other coronary risk factors and non-diagnostic ECG changed <1 mm of ST segment depression or the presence of T-wave inversion with symptoms. Patients were admitted if physician felt participant had high or intermediate risk for ACS.			

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; CKMB = creatine kinase-MB isoenzyme; ECG = electrocardiogram; ED = emergency department; MI = myocardial infarction; mL = milliliter; RCT = randomized control trial; SMPI = stress myocardial perfusion imaging; SPECT = single photon emission computed tomography

* 1690 patients were randomized, but 162 were excluded within 6 hours due to cardiac events or significant coronary artery disease and admitted to further testing, and another 18 were self-discharged without undergoing intervention.

Appendix Table I11. Data abstraction for SPECT vs. Usual care: Efficacy Outcomes

Author/trial Interventions	Patient disposition Test result	Mortality (All – cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Lim, 2013 SPECT (A) vs Usual care (B)	**A vs. B** **Disposition, % (n/N)** Discharged from ED: 89.8% (902/1004) vs 81.5% (411/504) [of these, self-discharged: 0.9% (9/1004) vs. 0.4% (2/504)] Admitted to hospital: 10.2% (102/1004) vs. 18.5% (93/504) **Test result, % (n/N)***† SMPI normal 78.3% (786/1004) vs. NR SMPI probably normal with attenuation 13.4% (135/1004) vs. NR SMPI abnormal 8.2% (82/1004) vs. NR	**A vs. B** **Cardiac mortality, % (n/N)** 30 days 0% (0/1004) vs. 0% (0/504) 12 months 0.3% (3/1004) vs. 0% (0/504) Risk Difference (95% CI) = 0.003 (-0.0004 to 0.006)	**A vs. B** **NR**	**A vs. B** **Revascularization (any PCI, CABG), % (n/N)** 12 months 4.8% (48/1004) vs. 6.2% (31/504) Risk difference (95% CI) = -1.4% (-3.9% to 1.1%) **Necessary admission for ACS, % (n/N)** Index visit 7.6% (77/1004) vs. 17.3% (89/504)	**A vs. B** **Invasive Coronary Angiography, % (n/N)** 12 months 7.3% (73/1004) vs. 11% (56/504) Risk difference (95% CI) = -3.8% (-7.0% to -0.07%) **Stress testing, % (n/N)** 12 months 3.6% (36/1004) vs. 57.3% (289/504) Risk difference (95% CI) = -53.8% (-58.2% to 49.3%) -stress echocardiogram, 1.0% (10/1004) vs. 8.5% (43/504) -stress MPI, 16.0% (16/1004) vs. 23.8% (120/504) -stress ECG, 10.0% (10/1004) vs. 25.0% (126/504) **Resting echocardiogram, % (n/N)** 12 months 85.0% (85/1004) vs. 10.9% (55/504)	**A vs. B** **Cardiac event (including cardiac death, ventricular fibrillation, MI, cardiogenic shock or acute pulmonary edema requiring intubation), % (n/N)** 30 days 0.4% (4/1004) vs. 0.8% (4/504) RR (95% CI) = 0.5 (0.13 to 2.0) 12 months 0.7% (7/1004) vs. 1% (5/504) RR (95% CI) = 0.70 (95% CI 0.22 to 2.20)	**A vs. B** **Diagnosis of SCAD, % (n/N)** 30 days 3.6% (36/1004) vs. 3% (15/504) RR (95% CI) = 1.2 (0.61 to 2.17) 12 months 5.1% (51/1004) vs. 5.8% (29/504) RR (95% CI) = 0.88 (0.57 to 1.37)

ACS = acute coronary syndrome; MI = myocardial infarction; SMPI = stress myocardial perfusion imaging; SCAD = severe coronary artery disease, SPECT = single photon emission computed tomography.

* Usual care group did not report any type of test results.

† Normal = no perfusion defect, defect size of 0%, left ventricular ejection fraction ≥50%, normal regional wall motion; abnormal = defect size ≥5% of the left ventricle or left ventricular ejection fraction <50% with regional wall motion abnormalities.

‡ All reported cardiac events were due to nonfatal myocardial infarction.

Appendix Table I12. Data abstraction for SPECT vs. Usual care: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Lim, 2013 SPECT (A) vs Usual care (B)	NR	NR	NR

AE = adverse events, NR = not reported, SPECT = single photon emission tomography.

Appendix Table I13. Data abstraction for SPECT vs. Stress Echo: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
Salame, 2018 RCT (single Center) USA Funding AHRQ	Population: Mixed suspected CAD or known CAD Setting: ED Inclusion: - Atraumatic chest pain or possible angina equivalent - Age > 18 years - Patients referred for stress imaging from 6am to 6pm Monday to Friday Exclusion: - Referral for standard exercise electrocardiography without imaging - ACS defined by positive troponin-I levels - Severe left ventricular systolic dysfunction; - Severe valvular disease - Left bundle branch block - Paced ventricular rhythm - Concurrent conditions that might	**A. Stress MPI (MDCT) (n=120 randomized, n=116 analyzed)** Stressor: Exercise treadmill, persantine or dobutamine (at provider's discretion) - 27% received exercise testing. - 73% received dipyridamole. Contrast: Ultrasound Protocol: NR Definition of positive test: Adequate image quality to exclude ischemia and achievement of >85% of age-predicted maximal heart rate in the case of exercise or dobutamine stress studies. **B. Stress Echo (n=120 randomized, n=113 analyzed)** Stress ECHO was introduced to the hospital in the previous five years. It used exercise or dobutamine stressors at the discretion of the healthcare provider. - 42% received exercise testing. - 58% received dobutamine.	NR	A vs. B Subgroup: None N randomized: 240 Mean age (SD): 57.9 (10.0) vs. 54.6 (8.6) Female: 55.2% vs. 53.1% Race: Black/African-American: 19% vs. 21.2% White: 75.9% vs. 71.7% Other: 5.2% vs. 7.1% Chest pain: 100% vs 100% - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: 14.7% vs. 15.9% Prior revascularization: NR Known CAD: 26.7% vs 21.2% Chest pain frequency: NR Hypertension: 76.7% vs 75.2% Hyperlipidemia: 47.4% vs 48.7% Diabetes: 38.8% vs 38.9% Current smoking: NR Medications: Beta-blockers: 31% vs. 26.6 Other antihypertensives: 62.2 vs. 58.4%	1 month: 100% Crossover: 0% **A vs. B** Completed allocated test: 96.7% (116/120) vs. 94.2% (113/120)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
	compromise patient safety if they underwent stress testing.			Diabetes medication: 25.9% vs. 25.7% Aspirin: 44% vs. 40.7% Clopidogrel: 1.7% vs. 0.9% Lipid-lowering medication: 42.2% vs. 43.4% Warfarin: 4.3% vs. 8.9%	
Sharples, 2007; Thom 2014 RCT (single Center) UK Funding National Institute for Health Research	Population: Mixed suspected CAD or known CAD Setting: Outpatient, nonemergent Inclusion: - Established or suspected chronic stable angina referred for angiography - An EET result which merited referral for angiography Exclusion:	**A. SPECT (n=224 randomized) PAGE 24** Stressor: Adenosine (dobutamine if contraindications) Contrast: 99mTc Sestamibi Protocol: Patients abstained from all caffeinated food and drink for 24 hours prior to test, fasted for 6 hours pre-injection and took a fatty meal post injection. Pharmacological stress consisted of 6-minute adenosine infusion, 130 µg/kg/minute with tracer injected at 3 minutes. 400-MBq 99mTc MIBI administered at 3 minutes after infusion of adenosine, with imaging performed at 60 to 90 minutes after injection.	**A vs. B** 1: 1% (1/224) vs. 2% (4/226) 2: 12% (27/224) vs. 12% (26/226) 3: 19% (41/224) vs. 17% (39/226) 4: 37% (81/224) vs. 35% (79/226) 5: 31% (69/224) vs. 34% (76/226)*	**A vs. B** Subgroup: None N randomized: 898† Mean age (SD): 62.1 (9.5) vs. 61.9 (9.9) Female: 30% vs. 29% Race: NR Chest pain: NR - Typical angina: NR - Atypical angina: NR - Nonspecific chest pain: NR Dyspnea: NR Prior MI: 23% vs. 31% Prior revascularization: NR Known CAD: NR Chest pain frequency: NR Treated hypertension: 59% vs. 57%	18 months: 84% 36 months: 84% Crossover: 0% **A vs. B** Crossover: Received allocated test, % (n/N): 98.2% (220/224) vs. 96.5% (218/226)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD	Patient characteristics	Length f/u (% followed) Cross-over, % (n/N)
	- Recent MI or revascularization - admission with chest pain - urgent revascularization - contraindication to pharmacological stress testing on MRI - incapable of performing modified Bruce exercise test - not available by phone	Definition of positive test: positive diagnoses showed reversible ischemia in at least one segment of a 20-segment model. **B. Stress echocardiography (n=226 randomized)** Performed using a standard staged protocol of increasing doses of dobutamine infusion in stages of 3 minutes duration. Imaging performed with standard views acquired using tissue harmonic imaging on a 3.5-MHz ultrasound prone in the last 1 minute of each 3-minute stage. Intravenous ultrasound contrast medium was used to delineate the left ventricular endocardial border. Positive diagnoses for ischemia showed stress-related deterioration in contractility in functional or hibernating myocardial segments.		Treated hyperlipidemia: 76% vs. 79% Diabetes: 11.6% vs. 11.9% Current smoking: 41.9% vs. 43.8% Medications: Anti-platelets: 75% vs. 81% Statins: 67% vs. 69% Beta-blockers: 50% vs. 64% ACE inhibitors: 32% vs. 31% Calcium-channel blockers: 31% vs. 28% Nicorandil/potassium-channel activators: 18% vs. 24% Nitrates: 16% vs. 17% Diuretics: 13% vs. 15% Angiotensin-II receptor antagonists: 4% vs. 7%	

ACE = Angiotensin-converting-enzyme; CAD = coronary artery disease; ECHO = echocardiography; ICA = invasive coronary angiography; MI = myocardial; RCT = randomized control trial; SPECT = single-photon emission computerized tomography

* Baseline risk of CAD was assessed by a clinician on a scale of 1 (lowest) to 5 (highest).

† Study also includes MRI. 898 patients were randomized to angiography (n=222), SPECT (n=224), MRI (226), or stress echo (n=226)

Appendix Table I14. Data abstraction for SPECT vs. Stress Echo: Efficacy Outcomes

Author/trial Interventions	Patient disposition Test result	Mortality (All – cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
Salame, 2018 SPECT (A) vs. Stress Echo (B)	**A vs. B** **Test result, % (n/N) (95% CI)**[*‡] <u>Diagnostic test rates:</u> *Overall*: 94.8% (110/116) (89.1% to 98.1%,) vs. 89.4% (101/113) (82.2% to 94.4%), p=0.13 *After excluding patients who failed to achieve target heart rate*: 94.8% (110/116) (95% CI, 89.1% to 98.1%) vs. 100% (101/101), p=0.03 <u>Negative test (for ischemia)</u> 89.1% (103/116) (95% CI NR) vs. 94.1%	**All-cause mortality, % (n/N)** <u>30 days</u> 0.8% (1/116) vs. 0% (0/113)	MI 0% (0/116) vs. 0% (0/113)	**PCI, % (n/N)** <u>30 days</u> 0% (0/116) vs. 0.9% (1/113)	**A vs. B** **Invasive Coronary Angiography, % (n/N)** <u>30 days</u> 1.7% (2/116) vs. 4.4% (5/113)	NR	**A vs. B** **ED revisit (for chest pain), % (n/N)** <u>30 days</u> 2.6% (3/116) vs. 2.7% (3/113) **Rehospitalization (for chest pain), % (n/N)** <u>30 days</u> 2.6% (3/116) vs. 0.9% (1/113) **Hospital Length of stay, (hours) median, IQR**: 25.5 (19.4 to 42.5) vs. 26 (20.3 to 40.6) **Duration of imaging (hours), median, IQR:** 4.1 (3.2 to 5.2) vs. 1.8 (1.3 to 2.6)

Author/trial Interventions	Patient disposition Test result	Mortality (All – cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
	(106/113) (95 CI NR), p=0.2						
Sharples, 2007; Thom 2014 SPECT (A) vs stress Echo (B)	**A vs. B** **Test result, % (n/N)**[†] Positive 54% (121/224) vs. 45.6% (103/226) Negative 40.2% (90/224) vs. 44.3% (100/226) Equivocal 4% (9/224) vs. 3.1% (7/226) Not done 1.8% (4/224) vs. 3.5% (8/226) Test failed NR vs. 3.5% (8/226)	**A vs B.** **All-cause mortality, % (n/N)** Index 0.4% (1/224) vs. 0% (0/226) 18 months 1.8% (4/224) vs. 2.7% (6/226) 72 months 0.9% (2/224) vs. 2.2% (5/226) Cumulative 3.1% (7/224) vs. 4.9% (11/226) **Cardiac mortality, % (n/N)** 18 months: 2.2% (5/224) vs. 0.4% (1/226)	**A vs. B** **Admission for acute MI, % (n/N** 18 months 0.9% (2/224) vs. 2.76% (6/226)	**A vs. B** **Revascularization (CABG), % (n/N)** Index 12.9% (29/224) vs. 12.9% (29/226) 18 months 0.5% (1/224) vs. 1.8.% (4/226), p=NR **Revascularization (PCI), % (n/N)** Index 17.4% (39/224) vs. 22.7% (51/226) 18 months 0.5% (1/224) vs. 2.2% (5/226), p=NR Cumulative % of any revascularization post-index: 43.8% (98/224) vs. 53.5% (121/226)	**A vs. B** **Invasive Coronary Angiography, % (n/N)** Index 78.1% (175/224) vs. 74.8% (169/226) **SPECT, % (n/N)** Index: 0.4 (1/224) vs. 0% (0/226) **Proportion of patients requiring additional testing, % (n/N)** Index Any additional testing: 78.6% (176/224) vs. 74.8% (169/226), p=NR - *ICA*: 78.1% (175/224) vs. 74.8% (169/226), p=NR - *SPECT*: 0.5% (1/224) vs. 0% (0/226), p=NR - *MRI*: 0% (0/224) vs. 0% (0/226), p=NR	**A vs. B** **Total nonfatal events (admission for chest pain or acute MI, unplanned PCI or CABG, other§)** 18 months 10.7% (24/224) vs. 13.7% (31/226) **Total nonfatal plus fatal events** 18 months 12.9% (29/224) vs. 16.4% (37/226)	**A vs. B** **Angina, % (n/N)** 18 months 14.7% (33/224) vs. 14.6% (34/226) **Admission for chest pain, % (n/N** 18 months 8.5% (19/224) vs. 10.6% (24/226) **Admission for chest pain or MI** **18 months** **9.4% (21/224) vs. 13.3% (30/226)** **SAQ, mean (SD)** Exertional capacity Index 72.6 (21.2) vs. 73.2 (21.5) 6 months 77.5 (21.3) vs. 81 (20.5) 18 months

Author/trial Interventions	Patient disposition Test result	Mortality (All – cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							78.5 (23) vs. 81.5 (20) Anginal stability <u>Index</u> 52.2 (22.5) vs. 50 (20.4) <u>6 months</u> 61.9 (24.1) vs. 65.2 (26.6) <u>18 months</u> 62.6 (25.1) vs. 64.4 (20) Anginal frequency <u>Index</u> 67.8 (23.9) vs. 65.4 (25.8) <u>6 months</u> 83.5 (21.7) vs. 84 (23.1) <u>18 months</u> 86.9 (19.4) vs. 86.8 (21.8) Treatment satisfaction <u>index</u> 88.8 (15.2) vs. 87.5 (25.4) <u>6 months</u>

Author/trial Interventions	Patient disposition Test result	Mortality (All – cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
							92 (12.7) vs. 91.6 (14.8) <u>18 months</u> 91.2 (14.6) vs. 91.9 (16.1) Disease perception <u>Index</u> 59.8 (22.5) vs. 57.1 (25.4) <u>6 months</u> 74.8 (20.1) vs. 75.6 (22.2) <u>18 months</u> 77 (21.9) vs. 78.4 (22)

CABG = coronary artery bypass graft; CAD = coronary artery disease; ECHO = echocardiography; MACE = major adverse cardiovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention; SAQ = Seattle Angina Questionnaire; SPECT = single-photon emission computerized tomography

* Study considered diagnostic if image quality was adequate to exclude ischemia and achievement of >85% of age-predicted maximal heart rate; non-diagnostic if final interpretation stated that MI could not be excluded.

† positive result = shows reversible ischemia in at least one segment of a 20-segment model, negative = NR, equivocal = NR

‡ Findings did not differ after multivariable adjustment accounting for age, gender, BMI, and study group.

§ Post-CABG wound infection, admission for breathlessness, admission for ICD implant, admission for suspected MI found to be muscular pain, seen in A&E with chest pain (5 in SPECT); transient ischemic attack (stress echo).

Appendix Table I15. Data abstraction for SPECT vs. Stress Echo: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
Salome, 2018 SPECT vs. Stress Echo	NR	NR	NR
Sharples, 2007; Thom 2014 SPECT (A) vs. stress Echo (B)	NR	NR	NR

AE = adverse events; ECHO = echocardiography; NR = not reported; SPECT = single-photon emission computerized tomography.

APPENDIX J. Data Abstraction of Included Studies Evaluating CCTA + FFR

Appendix Table J1. CCTA FFR vs. any functional test: Study and Patient Characteristics

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
PLATFORM study Douglas, 2015 & 2016 Prospective Cohort; Multicenter (11 sites) Europe	Population: Suspected CAD Setting: Outpatient; non-emergent Inclusion: symptomatic outpatients ≥18 years old, without known CAD, but with an intermediate likelihood of obstructive CAD, whose physician had planned non-emergent, non-invasive, or invasive cardiovascular testing to evaluate suspected CAD Exclusion: acute coronary syndrome or clinical instability, previously documented CAD, contraindications to CCTA, needed emergent or urgent procedure, and recent cardiovascular testing (<90 days)	Each cohort was subdivided into two groups based on the evaluation plan decided upon before enrolment in the study: non-invasive testing (any form of stress testing or CTA without FFRCT) or invasive coronary angiography (ICA) **Originally planned for NIT (N=204); received:** - **A: CCTA FFR (≥64 slice) (n=104)** [CCTA was performed in 100% (104/104) of patients, submitted for FFR in 64.4% (67/104), and analyzed in 57.7% (60/104)] Tests completed before enrollment into study Exercise ECG: 4% Stress echo: 0% SPECT: 1% CMR: 0% CTA: 0% Other test: 0% - **C: NIT (n=100)** Tests completed before enrollment into study No test: 100% **Originally planned for ICA (N=380); received:** - **B: CCTA FFR (≥64 slice) (n=193)** [CCTA was performed in 100% (193/193) of patients, submitted for FFR in 69%	Mean pre-test probability of obstructive CAD (SD) calculated by updated Diamond and Forrester score **Originally planned for non-invasive testing (A vs. C)** 45.3% (16.8%) vs. 44.5% (15.3%) **Originally planned for ICA (B vs. D)** 49.4% (17.2%) vs. 51.7% (16.7%)	**Originally planned for non-invasive testing (A vs. C)** Subgroup: None N enrolled: 204 Mean age (SD): 59.5 (9.3) vs. 57.9 (10.7) Female: 34% vs. 42.3% Racial/ethnic minority: 0% vs. 5% Chest pain: - Typical angina: 17.3% vs. 8% - Atypical angina: 76.9% vs. 91.0% - Non-cardiac chest pain: 5.8% vs. 1.0% p=0.018 Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: 0% vs. 0%	90 days, 6 months, and 12 months % followed at 90 days: 96.4% (563/584) % followed at 12 months: 99.5% (581/584)

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
		(134/193) of cases, and analyzed in 60% (117/193)] Tests completed before enrollment into study Exercise ECG: 40% Stress echo: 6% SPECT: 8% CMR: 0% CTA: 0% Other test: 0% Stressor: NA Contrast: Iodinated contrast Protocol: Fractional flow reserve by CCTA analyses were performed centrally when requested by the site (recommended if the CCTA revealed ≥30% stenosis or if the patient was referred to ICA). Optimal medical therapy was encouraged, and local physicians made all subsequent clinical decisions following standard practice, including cancelling, or ordering additional testing or procedures Definition of positive test: ≥50% stenosis - **D: ICA (n=187)** Tests completed before enrollment into study Exercise ECG: 61% Stress echo: 7% SPECT: 20% CMR: 3% CTA: 21% Other test: 0%		Chest pain frequency: NR Hypertension: 54.8% vs. 38%, p=0.02 Hyperlipidemia: 26.9% vs. 22.0% Diabetes: 5.8% vs. 8.0% Current or past tabaco use: 56.7% vs. 52.0% **Originally planned for ICA (B vs. D)** Subgroup: None N enrolled: 380 Mean age (SD): 60.7 (10.2) vs. 63.4 (10.9), p=0.02 Female: 38.3% vs. 42.2% Racial/ethnic minority: 0.5% vs. 1.1% Chest pain: - Typical angina: 23.3% vs. 27.8% - Atypical angina: 73.6% vs. 65.2% - Non-cardiac chest pain: 2.6% vs. 7.0%	

Trial Author, year Study Design Country Funding	Population Setting Inclusion and Exclusion Criteria	Tests evaluated	Baseline risk for CAD*	Patient characteristics*	Length f/u (% followed) Cross-over, % (n/N)
		No NI test: 48% Stressor: Pharmacologic or exercise Contrast: Iodinated contrast Protocol: Optimal medical therapy was encouraged, and local physicians made all subsequent clinical decisions following standard practice, including cancelling, or ordering additional testing or procedures Definition of positive test: NR		Dyspnea: NR Prior MI: NR Prior revascularization: NR Known CAD: 0% vs. 0% Chest pain frequency: NR Hypertension: 57.5% vs. 59.4% Hyperlipidemia: 39.9% vs. 40.6% Diabetes: 5.8% vs. 8.0% Current or past tabaco use: 52.3% vs. 55.1%	

CAD = coronary artery disease, CCTA = coronary computed tomography, CMR = cardiac magnetic resonance, CT = computed tomography, ECG = electrocardiogram, ECHO = echocardiography, f/u = follow-up, FFR = fractional flow reserve, ICA = invasive coronary angiogram, MI = myocardial infarction, NA = not applicable, NI = non-invasive, NIT = non-invasive testing, NR = not reported, SD = standard deviation, vs. = versus.
* p-values non-significant unless reported

Appendix Table J2. CCTA FFR vs. any functional test: Efficacy Outcomes

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
PLATFORM study Douglas, 2015 & 2016 Originally planned NIT A: CCTA FFR C: NIT Originally planned ICA: B: CCTA FFR D: ICA Subgroup Analyses: Y Test for interaction: Y	**Patient Disposition** NR **Test Results for CCTA FFR, % (n/N)** <u>Stenosis ≥50%</u> A: 37.5% (39/104) of all patients in group A B: 61% (118/193) of all patients in group B*	**All-cause mortality (part of composite outcome), % (n/N)** <u>90 days</u> - A vs. C: 0% (0/104) vs. 0% (0/100),p=NR - B vs. D: 0% (0/193) vs. 0% (0/187), p=NR <u>Between 90 days (3 months) and 12 months</u> - A vs. C: 0% (0/104) vs. 0% (0/100),p=NR - B vs. D: 0% (0/193) vs. 0.5% (1/187), p=NR	**Non-fatal MI (part of composite outcome), % (n/N)** <u>90 days</u> - A vs. C: 0% (0/104) vs. 0% (0/100),p=NR - B vs. D: 0.5% (1/193) vs. 0% (0/187), p=NR <u>Between 90 days (3 months) and 12 months</u> - A vs. C: 0% (0/104) vs. 1% (1/100),p=NR - B vs. D: 0% (0/193) vs. 0.5% (1/187), p=NR	**Proportion of patients experiencing revascularization, % (n/N)** <u>90 days</u> <u>90 days</u> **PCI** - A vs. C: 8.7% (9/104) vs. 3% (3/100),p=NR - B vs. D: 23.3% (45/193) vs. 22.5% (42/187), p=NR **CABG** - A vs. C: 1% (1/104) vs. 2% (2/100),p=NR - B vs. D: 5.2% (10/193) vs. 9.1% (17/187), p=NR <u>12 months</u> **PCI** - A vs. C: 8.7% (9/104) vs. 4% (5/100),p=NR	**Proportion receiving ICA** **90 days:** - A vs. C: 18.3% (19/104) vs. 12.0% (12/100) - B vs. D: 12.4% 39.4% (76/193) vs. 100% (187/187), **ICA without obstructive CAD by core lab quantitative coronary angiography, % (n/N)** <u>90 days</u> - A vs. C: 12.5% (13/104) vs. 6.0% (6/100), RD -6.5% (95% CI -14.4% to 1.4%), p=0.95 - B vs. D: 12.4% (24/193) vs. 73.3% (137/187), RD	**MACE (including death, non-fatal MI, and hospitalization with urgent revascularization), % (n/N)** <u>90 days</u> - A vs. C: 0% (0/104) vs. 0% (0/100),p=NR - B vs. D: 1.0% (2/193) vs. 0% (0/187), p=NR <u>Between 90 days (3 months) and 12 months</u> - A vs. C: 0% (0/104) vs. 1% (1/100),p=NR - B vs. D: 0% (0/193) vs. 1% (2/187), p=NR **MACE or vascular complication, % (n/N)** <u>90 days</u> - A vs. C: 1% (1/104) vs. 0% (0/100),p=NR	**Hospitalization with urgent revascularization (part of composite outcome), % (n/N)** <u>90 days</u> - A vs. C: 0% (0/104) vs. 0% (0/100),p=NR - B vs. D: 0.5% (1/193) vs. 0% (0/187), p=NR <u>Between 90 days (3 months) and 12 months</u> - A vs. C: 0% (0/104) vs. 0% (0/100),p=NR - B vs. D: 0% (0/193) vs. 0% (0/187), p=NR **Total number of hospital days** <u>12 months</u> - A vs. C: 57 vs. 43, p=NR - B vs. D: 283 vs. 514, p=NR

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
				- B vs. D: 28.5% (55/193) vs. 26.2% (49/187), p=NR **CABG** - A vs. C: 1% (1/104) vs. 2% (2/100),p=NR - B vs. D: 5.2% (10/193) vs. 9.6% (18/187), p=NR **Changes in medication use** From enrollment to 12 months - B vs. D Aspirin: p=0.56 Statins: p=0.76 $P2Y_{12}$ inhibitors: p=0.006 (higher use in group B)	60.8% (53.0% to 68.7%), p<0.0001 **Rate of ICA documenting no obstructive CAD among propensity matched planned ICA groups (B vs. D) (n=148 vs. 148)** <u>90 days</u> 11.5% (17/148) vs. 72.3% (107/148), RD 60.8% (95% CI 52.0% to 69.7%), p<0.0001 **Invasive catheterization without obstructive CAD by site interpretation, % (n/N)** <u>90 days</u> - A vs. C: 7.7% (8/104) vs. 5.0% (5/100), RD -2.7% (95% CI -9.4% to 4.0%), p=0.0.79	- B vs. D: 3.6% (7/193) vs. 1.1% (2/187), p=NR <u>Between 90 days (3 months) and 12 months</u> - A vs. C: 0% (0/104) vs. 1% (1/100), RD -0.04% (90% CI -11.7% to 11.62%), p=NR - B vs. D: 0% (0/193) vs. 1.1% (2/187), RD 1.49% (90% CI -7.05% to 9.95%), p=NR *RDs are for the comparison in the reverse direction*	**Total number of clinic visits** <u>12 months</u> - A vs. C: 48 vs. 56, p=NR - B vs. D: 111 vs. 162, p=NR

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
					- B vs. D: 9.3% (18/193) vs. 56.7% (106/187), RD 47.4% (39.2% to 55.6%), p<0.0001 *RDs are for the comparison in the reverse direction* **Testing performed after enrollment (including index test), % (n/N)** <u>12 months</u> - A vs. C Exercise ECG: 8.7% (9/104) vs. 11% (11/100), p=NR Stress echo: 1.9% (2/104) vs. 29% (29/100), p=NR SPECT: 7.7% (8/104) vs. 17% (17/100), p=NR MRI: 2.9% (3/104) vs. 3% (3/100), p=NR		

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
					CCTA: 100% (104/104) vs. 62% (62/100), p=NR FFR-CT: 57.7%% (60/104) vs. 0% (0/100), p=NR Diagnostic ICA: 12.5% (13/104) vs. 11% (11/100), p=NR ICA with PCI: 5.6% (9/104) vs. 5% (5/100), p=NR FFR determined by ICA: 4.8% (5/104) vs. 0% (0/100), p=NR Intravascular ultrasound: 1.9% (2/104) vs. 3% (3/100), p=NR Optical coherence tomography: 0% (0/104) vs. 0% (0/100), p=NR - B vs. D Exercise ECG: 9.8% (19/193) vs. 9.1% (17/187), p=NR		

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
					Stress echo: 3.1% (6/193) vs. 2.7% (5/187), p=NR SPECT: 1.6% (3/193) vs. 3.2% (6/187), p=NR MRI: 1.6% (3/193) vs. 3.2% (6/187), p=NR CCTA: 100% (194/193) vs. 0.5% (1/187), p=NR FFR-CT: 60.6% (117/193) vs. 0% (0/187), p=NR Diagnostic ICA: 22.8% (44/193) vs. 85.0% (159/187), p=NR ICA with PCI: 28.5% (55/193) vs. 23.5% (44/187), p=NR FFR determined by ICA: 15.0% (29/193) vs. 6.4% (12/187), p=NR Intravascular ultrasound: 2.6%		

Author/trial Interventions Subgroup analyses? Formal test for interaction?	Patient disposition Test result	Mortality (All-cause, cardiac)	Myocardial infarction	Referral for treatment	Referral for additional testing	Composite outcomes	Other
					(5/193) vs. 4.3% (8/187), p=NR Optical coherence tomography: 0.5% (1/193) vs. 1.6% (3/187), p=NR		

CABG = coronary artery bypass graft, CAD = coronary artery disease, CCTA = coronary computed tomography, CI = confidence interval, CMR = cardiac magnetic resonance, ECG = electrocardiogram, ECHO = echocardiography, FFR = fractional flow reserve, ICA = invasive coronary angiogram, MACE = major adverse cardiovascular event, MI = myocardial infarction, MRI = magnetic resonance imaging, NI = non-invasive, NIT = non-invasive testing, NR = not reported, PCI = percutaneous coronary intervention, RD = risk difference, SD = standard deviation, SPECT = single photon emission computed tomography, vs. = versus.

* Only 67.7% (201/297) of all patients allocated to one of the CCTA-FFR groups actually had an FFR study submitted. The data were measurable in 88% (177/201) of studies. Motion and misalignment accounted for 75% of failures, heavy calcification 13%, and missing data 13%.

Appendix Table J3. CCTA FFR vs. any functional test: Safety Outcomes

Author/trial Interventions	Imaging-related AEs	Incidental findings	Radiation
PLATFORM study Douglas, 2015 & 2016	Overall, there was one reported adverse event from CCTA testing, a mild contrast reaction (group NR)	NR	**Cumulative radiation exposure (mSv), Mean (SD)** <u>90 days</u> - A vs. C: 8.8 (9.9) vs. 5.8 (7.1), p=0.0002 - B vs. D: 9.9 (8.7) vs. 9.4 (4.9), p=0.20 <u>12 months</u> - A vs. C: 9.55 (10.56) vs. 6.42 (7.47), p<0.001 - B vs. D: 10.72 (9.62) vs. 10.36 (6.69), p=0.21

AE = adverse event, CCTA = coronary computed tomography, mSv = millisieverts, NR = not reported, SD = standard deviation.

Appendix Table J4. CCTA FFR vs. any functional test: Subgroup analyses for efficacy outcomes

Trial name Author, year	Timing	Outcome	Subgroup	CCTA FFR % (n/N)	NIT or ICA % (n/N)	Author reported Interaction p-value
Cohort originally planned to receive NIT						
PLATFORM study Douglas 2015, 2016	90 days	Invasive catheterization without obstructive coronary artery disease	Age < 65 years	12.3% (9/73)	4.2% (3/72)	0.37
			Age ≥ 65 years	12.9% (4/31)	10.7% (3/28)	
			Male	13.3% (8/60)	7.6% (5/66)	0.53
			Female	11.4% (5/44)	2.9% (1/34)	
			Non-racial minority	12.5% (12/96)	5.4% (5/92)	NA
			Racial minority	20% (1/5)	NA (no racial minorities)	
			No diabetes	13.3% (13/98)	5.5% (5/91)	0.96
			Diabetes	12.5% (1/8)	0.0% (0/6)	
			Pre-test probability of CAD <50%	11.6% (8/69)	1.4% (1/71)	0.06
			Pre-test probability of CAD ≥50%	14.3% (5/35)	17.2% (5/29)	
Cohort originally planned to receive ICA						
PLATFORM study Douglas 2015, 2016	90 days	Invasive catheterization without obstructive coronary artery disease	Age < 65 years	10.5% (12/114)	74.7% (74/99)	0.29
			Age ≥ 65 years	15.2% (12/79)	71.6% (63/88)	
			Male	13.4% (16/119)	68.5% (74/108)	0.15
			Female	10.8% (8/74)	79.7% (63/79)	
			Non-racial minority	74.1% (123/166)	11.7% (22/188)	0.93
			Racial minority	100% (2/2)	0.0% (0/1)	
			No diabetes	11.0% (18/163)	74.7% (112/150)	0.10
			Diabetes	20.0% (6/30)	66.7% (24/36)	
			Pre-test probability of CAD <50%	8.7% (9/104)	80.2% (77/96)	0.01
			Pre-test probability of CAD ≥50%	16.9% (15/89)	65.9% (60/91)	

CAD = coronary artery disease, CCTA = coronary computed tomography, CI = confidence interval, FFR = fractional flow reserve, ICA = invasive coronary angiogram, NA = not applicable, NR = not reported, SD = standard deviation.

APPENDIX K. Data Abstraction of Economic Studies

Table K1. Stable outpatients with suspected CAD (U.S. studies)

		Min 2017[56]	Karady 2020[35]
Study Design	**Synopsis**	A well conducted study of stable CP patients that explored numerous testing pathways and reported results assuming multiple levels of CAD prevalence. While the authors found a sequence of imaging tests to be the most cost-effective, they further found that at 20%, 50% and 80% pretest likelihood of CAD an ICER that favored CCTA, ECHO and MPS over ICA given a WTP of $100,000 per QALY.	A high-quality study of low risk, stable CP patients that compared anatomical tests with functional tests. Authors found CCTA and CCTA FFR to be cost-effective with an ICER of $2743/QALY for CCTA and functional tests to be both more costly and less effective than CCTA FFR. Generally, anatomical approaches led to 6 additional months of patient in good health over a lifetime. Grouping of various functional tests makes it difficult to make direct comparisons between specific tests.
	Population	Stable CP Intermediate risk No prior CAD 20% pretest likelihood 55-year-old male	Stable CP Low risk 53.3% pretest likelihood Mean age 60, 52.7% Female, 77.7% White
	Intervention(s)	CCTA ECHO MPS (others)	Anatomical tests (CCTA, CCTA with FFR)
	Comparator(s)	ETT ICA (others)	Functional tests (67.5%SPECT, 22.4%ECHO,10.2%ETT)
	Country	USA	USA
	Funding	Unclear; authors list GE Healthcare. Dalio Institute; clinical data from National Heart, Lung and Blood Institute funded study	HeartFlow PROMISE trial funded by National Heart, Lung and Blood Institute;
	Perspective	Payer Perspective	Stated as Societal
	Time horizon	Lifetime	Lifetime
	Analytic model	Markov Simulations	Markov Simulations
	Costing year	NR	2014
	Currency	USD	USD
	Discounting	3%	3%

		Min 2017[56]	Karady 2020[35]
	Key Assumptions	Sensitivity: ETT=68.0% CCTA = 93.7% ECHO = 86.7% Specificity: ETT =77.0% CCTA = 84.7% ECHO = 80.7%% Indeterminate: ETT=62.0% CCTA = 7.0% ECHO = 7.0%	Sensitivity: ETT =45-50% CCTA = 95-99% SPECT = 73-83% Specificity: ETT =85-90% CCTA = 64-83% SPECT = 63-87%
	Limitations	All positive diagnostic tests resulted in ICA which was assumed to have perfect sensitivity and specificity Difficult to interpret many results due to how similar the effectiveness measures were. Sensitivity analysis was limited in scope and authors did not fully explore potential biases.	Uncertainty around diagnostic accuracy Offers limited insight for comparing CCTA with specific functional test as all functional test have been grouped together Two years of results from the PROMISE trial were available; the model extrapolates to a lifetime High pre-test likelihood of obstructive CAD of 53.3% is not consistent with original objective of authors to study patients of low risk of CAD
	QHES	94/100	90/100
Results and Conclusions	**Cost / QALY of intervention**	With 20% pretest likelihood: CCTA: $12274/16.1283 QALY ECHO: $11356/16.1097 QALY MPS $11798/16.1073 QALY	CCTA: $8683/25.16 QALY CCTA with FFRct: $7222/25.14 QALY
	Cost / QALY of comparator(s)	ICA: $14003/16.1205 QALY	Functional: $7989/24.68 QALY
	ICER or C-E Measure	With 20% pretest likelihood: CCTA vs ICA: CCTA Dominates ICA ECHO vs ICA: ICA costs additional $245093/QALY	1. CCTA costs additional $2743/QALY

		Min 2017[56]	Karady 2020[35]
		MPS vs ICA: ICA costs additional $167046/QALY	($1912/QALY for women and $3,559/QALY for men) 2. CCTA with FFRct dominates functional tests
	Sensitivity Analysis Results	Varying CAD prevalence up to 80%: CCTA vs ICA: ICA costs $3857303/QALY ECHO vs ICA: ICA costs $1300236/QALY MPS vs ICA: ICA costs $906222/QALY Varying post-test treatment approach showed cost-effectiveness contingent on follow-up care posttest.	CCTA remained cost effective across genders and with declining adherence to statin therapy. All interventions were cost effective compared to "Do Nothing Strategy" where patients only received medication according to their risk factor profile Quasi-probabilistic allowing incremental changes show the CCTA to be dominant approach 38.6% and cost effective 69.4% with a WTP of $100,000
	Author's Conclusion	CCTA, ECHO and MPS are all cost-effective alternatives to ICA. Increasing the pretest likelihood of CAD both reduces their costs and increases their effectiveness.	Relatively robust evidence suggesting anatomic approaches are cost-effective compared with functional testing.

Table K2. Stable outpatients with suspected CAD (European studies)

		Agus 2016[4]	Gurunathan 2018[26]	Lorenzoni 2019[48]
Study Design	**Synopsis**	An RCT conducted in Northern Ireland with several potential limitations that investigated the cost effectiveness of CCTA vs ETT. CCTA was found to be the dominate strategy for patients when a pretest likelihood of less than 30% was	A relatively poor-quality study that evaluated the predictive value and costs of stress ECHO and ETT. Authors found ECHO to have 20% reduction in cost and fewer downstream testing, hospital visits. ETT yielded a 64% positive predictive value in determining a flow-	A moderately well conducted European study that looked at several testing strategies. The primary results showed that CCTA to be cost saving and more effective versus no imaging with a negative ICER of -€796.85/diagnosis. ECHO and SPECT approaches were both

		assumed. As the pretest likelihood increased to 30%-60% and then above 60% the ICER increased to £2820 and £24106 respectively still suggesting CCTA to be a cost-effective approach with a willingness to pay of $50,000.	limiting disease on angiography. Meanwhile, ECHO achieved 100% positive predictions.	found to be less expensive alternative but yielded less correct diagnoses. Therefore, no imaging would save €3316.41 and €2110.95 per diagnosis for ECHO and SPECT respectively.
	Population	Patients without known CAD Stable CP Pretest likelihood: CCTA group 48%; ETT group 45% >50% had nonanginal CP	Stable CP Intermediate risk (excluded patients with "very low risk") pretest likelihood) averaged 34% probability	Stable CP Intermediate risk (excluded patients with low risk and high risk based on initial ETT) 28% CAD prevalence
	Intervention(s)	CCTA	Stress ECHO	CCTA ECHO PET SPECT
	Comparator(s)	ETT	ETT	No imaging
	Country	UK	UK	Italy (European data)
	Funding	South Eastern Health and Social Care Trust	NR	EU grant, Centre of Excellence in Cardiovascular Disease
	Perspective	National Health Service	Payer perspective	Payer perspective
	Time horizon	12 months	3 year mean F/U	NR
	Analytic model	Regression model	Means and Survival Analysis	Mean comparisons
	Costing year	2015	2014	2012
	Currency	British Pounds	British Pounds	Euro
	Discounting	None	None	NR
	Key Assumptions	Risk of CAD: <30% CCTA = 41% ETT = 44% 30-60% CCTA = 22% ETT = 25% >60% CCTA = 36% ETT = 31%	Positive Predictive Value calculated: ECHO = 100% ETT = 64%	False Negative Rate: CCTA = NR ECHO = 0 to 2.1% PET = 3.4 to 9.1% SPECT = 8.5 to 13.4 Obstructive CAD defined as > 50% stenosis at quantitative ICA in the left main or at least one major coronary vessel.

	Limitations	Missing data issues Outcome assessment was not fully blinded from investigators Sample population exclude BMI >35% and included low number of diabetic patients Relatively short follow up time Imbalanced CAD prevalence across groups	Underpowered to detect most clinical outcomes Overly simplistic analytic model No model validation, subgroup or sensitivity analysis Narrow application	Lots of heterogeneity in data (sourcing from multiple countries with variation in practices) Assumed perfect accuracy of ICA Anyone not receiving ICA was assumed to be a true negative test result
	QHES	64/100	50/100	84/100
Results and Conclusions	**Cost / QALY of intervention**	£2008/0.81QALY	£631	CCTA: €512.05/73% ECHO: €426.12/55% PET: €1177.22/71% SPECT: €901.25/68%
	Cost / QALY of comparator(s)	£20580.79QALY	£796	No imaging: €989.91/72%
	ICER or C-E Measure	3. CCTA dominant strategy 4. (-£50.45/0.02QALY) 5. With a WTP of £20 000 per QALY the probability of CCTA being cost-effective was 83% 6.	ECHO = £631/100% 7. ETT = £796/ 64% 8. 9. With no statistically significant difference in death, MI, unplanned revascularization or hospitalization for CP	CCTA: -€796.85/diagnosis (cost savings) ECHO: €3316.41/diagnosis (ECHO found cheaper but less effective) PET: Dominated by no imaging 10. SPECT: €2110.95/diagnosis (SPECT found cheaper but less effective)
	Sensitivity Analysis Results	<30% pretest likelihood: CCTA dominates 30%-60% pretest likelihood: CCTA costs £2820	NR	Using concordance of results with early revascularization as measure of effectiveness: CCTA, ECHO, PET and SPECT were all found to be more expensive and less effective than no imaging.

		>60% pretest likelihood: CCTA costs £24106 Probabilistic variations in model found results to be stable		Correct diagnosis of CAD CCTA: -€65.66/diagnosis (cost savings) ECHO: €3501.20/diagnosis (ECHO found cheaper but less effective) 11. SPECT: €5156.76/diagnosis (SPECT found cheaper but less effective)
	Author's Conclusion	CCTA was shown to be less costly and more effective than ETT for the first 12 months. This cost-effectiveness was shown to vary with the pretest likelihood of CAD.	ECHO is both cost saving and facilitated better health outcomes over ETT.	"In a contemporary European population of patients with suspected stable CAD and low prevalence of disease, diagnostic strategies combining CTCA and stress-imaging are cost-effective as gatekeepers to ICA and for selecting candidates for revascularization".

Table K3. Stable outpatients with suspected CAD (studies from other regions)

		Bertoldi 2016/2017[8]	Lee 2015[38]	Jafari 2020[33]
Study Design	**Synopsis**	CCTA appeared be a cost-effective approach for CAD in this well conducted study. ECHO testing was similarly cost-effective. SPECT tests were dominated by other test options. Additionally, sensitivity analysis showed that procedural costs and test sensitivity were significant factors in determining cost-effectiveness.	A moderately well-designed study that explored the diagnostic accuracy of CCTA and SPECT followed by a brief cost utility analysis. CCTA was shown to be the more accurate, effective and less expensive alternative in the majority of cases. Subgroup analysis by pretest likelihood showed SPECT to perform slightly better with lower pretest probability but CCTA remained cost-effective with most accepted willingness to pay thresholds.	A relatively poorly conducted study that compared several testing options including CCTA, ECHO and SPECT against ETT and ICA among others. It reported its results against a strategy using a combination of tests (that it had found to be optimal). Results reported here are compared with stand-alone ETT and ICA testing. In general, it found ETT and ICA to perform better than CCTA and ECHO. With SPECT being slightly more costly but more effective than ETT yielding small ICER of $46.74/diagnosis.
	Population	Patients without known CAD Stable CP Pretest likelihood: Baseline=50% also reported 20% and 70%	Stable CP Intermediate risk (excluded patients with "very low risk" pretest likelihood) averaged 34% probability	Stable CP Other patient demographics unclear

		Bertoldi 2016/2017[8]	Lee 2015[38]	Jafari 2020[33]
	Intervention(s)	CCTA, Stress ECHO, SPECT	CCTA	CCTA, ECHO, SPECT
	Comparator(s)	ICA	SPECT	ETT, ICA
	Country	Brazil	Korea	Iran
	Funding	CNPq from National Institute for Science and Technology	National Evidence-based Healthcare Collaborating Agency in Korea	None
	Perspective	Brazilian Public Health System	Payer perspective	Healthcare system
	Time horizon	Lifetime	1 year	1 year
	Analytic model	Markov model	Analysis of means and Decision Tree	Decision Tree analysis
	Costing year	2013	2011	2017
	Currency	USD	USD	USD
	Discounting	5%	None	None
	Key Assumptions	Sensitivity: ICA = 100 ETT = 65 (42-92) CCTA = 88 (84 -88) ECHO = 85 (83-87) SPECT = 87 (84-88) Specificity: ICA = 100 ETT = 67 (43-83) CCTA = 87 (80 -92) ECHO = 77 (74-80) SPECT = 64 (60-76) Indeterminant: ICA = 10% ETT = 18% CCTA = 2% ECHO = 15% SPECT = 6.9%	Pretest Likelihood 10-29%: CCTA = 48.30 SPECT = 40.89 30-60%: CCTA = 24.05 SPECT = 23.83 61-90%: CCTA = 27.65 SPECT = 35.29 Sensitivity: CCTA = 87.3 SPECT = 74.5 Specificity: CCTA = 82.6 SPECT = 78.6	Sensitivity: ICA = 100 ETT = 65 CCTA = 88 ECHO = 50 SPECT = 87
	Limitations	Assumes ICA to have 100% sensitivity and specificity. (though discussed in sensitivity analysis)	Baseline characteristics of groups were different. SPECT group had significantly older and had higher pretest likelihood probability	Cost data seems incomparable to US setting Assumed ICA 100% sensitive

		Bertoldi 2016/2017[8]	Lee 2015[38]	Jafari 2020[33]
			CCTA data derived from 2006 when techniques may not have been as developed in Korea	Poor description of patient characteristics: no demographic info or CAD or pretest likelihood
	QHES	90/100	77/100	62/100
Results and Conclusions	**Cost / QALY of intervention**	CCTA: $286/diagnosis ECHO: $305/diagnosis	$872/0.835diagnosis $176/0.908QALY	CCTA: $1475.13/93.9% diagnosis ECHO: $1475.13/93.9% diagnosis SPECT: $1475.13/93.9% diagnosis
	Cost / QALY of comparator(s)	ETT: $205/diagnosis	$933/0.779diagnosis $2274/0.906QALY	ETT: ICA: $1475.13/93.9% diagnosis
	ICER or C-E Measure	CCTAvsETT: CCTA costs $750/diagnosis and $3100/QALY 12. 13. ECHOvsETT: ECHO costs $623/diagnosis	14. CCTA dominates SPECT 15. Accurate diagnosis per 1000pts: 16. CCTA 835 patients 17. SPECT 779 patients	ETT: CCTA and ECHO both dominated by ETT SPECT: $46.74/diagnosis (SPECT more costly and more effective) ICA: (more costly and effective than all other options) CCTA: $13.00/diagnosis to use ICA ECHO: $12.07/diagnosis to use ICA 18. SPECT: $11.51/diagnosis to use ICA
	Sensitivity Analysis Results	20% pretest likelihood: CCTAvsETT: CCTA costs $1420/diagnosis ECHOvsETT: ECHO is dominated 70% pretest likelihood: CCTAvsETT: CCTA costs $790/diagnosis ECHOvsETT: ECHO costs $890/diagnosis	10%-29% pretest likelihood: CCTA dominates SPECT in CUA 19. Accurate diagnosis per 1000pts: 20. CCTA 833 patients SPECT 571 patients 30%-60% pretest likelihood: SPECT costs $88740/QALY in CUA 21. Accurate diagnosis per 1000pts: 22. CCTA 842 patients	Conducted one-way sensitivity analysis which suggested sensitivity of tests to be a key driving factor in cost-effectiveness. Limited reporting of sensitivity results.

		Bertoldi 2016/2017[8]	Lee 2015[38]	Jafari 2020[33]
			SPECT 536 patients 61%-90% pretest likelihood: CCTA dominates SPECT in CUA 23. Accurate diagnosis per 1000pts: 24. CCTA 814 patients SPECT 746 patients	
	Author's Conclusion	Of the numerous testing pathways evaluated CCTA consistently showed itself to be a cost-effective approach for CAD. ECHO testing was similarly cost-effective. SPECT tests were not found to be cost-effective.	CCTA demonstrated greater accuracy in diagnosing CAD than SPECT and also showed to be less expensive in the one-year time horizon.	"This study indicated that all strategies except CTA- based strategy are cost-effective, but the ECG-CA strategy is the most cost-effective strategy for acute patients. "

Table K4. Patients with suspected ACS (acute chest pain) presenting to ED or observation units

		Powell 2012[68]	Priest 2011[69]	Goehler 2020[20]
Study Design	**Synopsis**	A moderately well conducted study comparing CCTA, standard of care and "do nothing" strategies in an observation unit setting. Authors found CCTA to have similar effectiveness as the standard of care while being approximately 20% less expensive. The "do nothing" approach was the cheapest, however, also the least effective. This led CCTA to have a generally considered cost-effective ICER of $8135.	A fairly well-designed cost-effectiveness study that investigated several testing options in and emergency department. It found a combination of test strategies to be the most cost-effective. Using the results reported it was possible to compare CCTA, ECHO and SPECT against ETT. ETT was consistently dominated by all three alternative tests at varying levels of CAD prevalence. As the prevalence increase however the dominance be narrower.	A well-constructed model of short, intermediate and long-term cost-effectiveness carried out in the United States. CCTA performance was analyzed against four strategies: standard of care, expert consensus of AHA/ACD guidelines and expedited ED discharge with OP testing. Short-term results found CCTA to be both more costly and required more revascularization procedures than all other comparators. However, in the long-term model CCTA became cost-effective. Lower mortality led CCTA to dominate standard of care and ACC/AHA guidelines and have an ICER of $49,428/

				QALY when compared with expedited ED protocol.
	Population	Patients in OU for the evaluation of low-risk chest pain patients with indeterminate or positive-stress test results. Mean age: 50-year-old 46% female	Emergency department patients 2-30% CAD prevalence	Emergency department patients with suspected ACS Low-Intermediate risk of ACS 7.5% prevalence of ACS Mean age 54.2, 53% male
	Intervention(s)	CCTA	CCTA, ECHO, SPECT	CCTA
	Comparator(s)	Standard of Care "Do Nothing" strategy	ETT	Standard of Care AHA/ACD Guidelines Expedited ED discharge with OP testing
	Country	USA	USA	USA
	Funding	NR	National Health and Medical Research Council	Grants from National Heart, Lung, and Blood Institute, NIH, American Heart Association
	Perspective	Payer	Payer	Not stated (appears to be payer perspective)
	Time horizon	NR	12 months	Lifetime (also reports short and intermediate-term finding
	Analytic model	Decision Model	Decision Model	Markov model
	Costing year	2009	2010	2012 (when trial data ended– not explicitly specified as costing year)
	Currency	USD	USD	USD

	Discounting	CPI	CPI	3%
	Key Assumptions	Sensitivity: CCTA = 98.9% Specificity: CCTA = 84%	Sensitivity: CCTA = 100% ECHO = 72-83% SPECT = 84-91% ETT = 67% Specificity: CCTA = 80% ECHO = 84-95% SPECT = 69-81% ETT = 72%	Varied Sensitivity 85%–100% Specificity 50%–100% Used ROMICAT II trial to populate model
	Limitations	Doesn't consider startup costs of a CCTA Unrealistic "Do-nothing strategy" in which all patients were discharged home after positive- or indeterminate-stress tests without further testing.	Short time horizon Simplistic modeling Revisits to the emergency department and other complications were not considered Insufficient data sourcing for model parameters	Some model input parameters were sourced from older studies which may not reflect current healthcare settings
	QHES	69/100	75/100	90/100
Results and Conclusions	**Cost / QALY of intervention**	CCTA = $8306/23.54QALY	At 5% prevalence: CCTA = $4862/0.8568QALY ECHO = $7539/0.8579QALY SPECT = $10799/0.8548QALY	At index: CCTA = $2692 Total costs: $4490 (23.09 QALY)
	Cost / QALY of comparator(s)	Standard of care =10273/23.55QALY "Do nothing" = $1815/22.75QALY	At 5% prevalence: ETT = $11555/0.8468QALY	Cost at index: Standard of Care = $2535 AHA/ACD Guidelines = $2501 Expedited ED discharge with OP testing = $1891 Standard of Care = $2535 AHA/ACD Guidelines = $2501 Total costs:

				Expedited ED discharge with OP testing = $2513 (23.02 QALY) Standard of Care = $4144 (23.09 QALY) AHA/ACD Guidelines = $4064 (23.06 QALY)
	ICER or C-E Measure	25. CCTA vs Standard of care: $352652/QALY 26. (CCTA cheaper but marginally less effective) 27. 28. CCTA vs "Do nothing": 29. $8135/QALY 30. (CCTA is more expensive and effective)	The total 12-month costs with a 5% prevalence of CAD for ETT, SPEC, ECHO, CCTA and CCTA the SPECT were $10,430, $10,799, $7,539, $4,862 and $3,464 respectively. Under the same circumstances the QALYs generated for ETT, SPEC, ECHO, CCTA and CCTA the SPECT were 0.8523, 0.8548, 0.8579, 0.8568 and 0.8602. At 5% prevalence each intervention dominates ETT: CCTA = -$669300/QALY ECHO = -$138006/QALY SPECT = -$94500/QALY 31.	CCTA dominated Standard of Care and AHA/ACD Guidelines CCTA was CE against Expedited ED discharge with OP testing with an ICER of $ 49,428/QALY
	Sensitivity Analysis Results	The standard of care strategy becomes preferable only at extremely high willingness to pay thresholds because it has the slight effectiveness advantage. The do-nothing strategy was preferable at only a very low WTP ($8306).	ETT remained dominated at each of the 2%, 10%, 20% and 30% prevalence levels.	Letting the relative risk decrease by 0.18 to the lower bound of the confidence interval caused the ICER to increase to $60,000 Decreasing medical compliance increased the ICER of CCTA to $78,500/QALY Varying tests' sensitivity and specificity caused the ICER to range from $46,000 to $70,000

	Author's Conclusion	"Adding CTCA after indeterminate or positive stress testing results is a cost-effective intervention for further risk-stratifying low-risk chest pain patients in the OU setting"	"CTA with confirmatory SPECT was cost saving (lower costs, higher QALYs) compared with a CTA-only strategy, stress ECG, Echo, and SPECT. However, CTA may be associated with a higher event rate in negative patients than SPECT"	While in the short-term higher cost cause CCTA to be less attractive, longer-term health outcomes cause CCTA to be a cost-effective alternative.

Included Primary economic studies

Studies found in search and included in vanWaardhuizen 2016 systematic review

(Citation**:** van Waardhuizen, C. N., et al. (2016). "Comparative cost-effectiveness of non-invasive imaging tests in patients presenting with chronic stable chest pain with suspected coronary artery disease: a systematic review." Eur Heart J Qual Care Clin Outcomes **2**(4): 245-260.)

1. Ferreira AM, Marques H, Gonçalves PA, et al. Cost-effectiveness of different diagnostic strategies in suspected stable coronary artery disease in Portugal. Arquivos brasileiros de cardiologia. 2014 Apr;102(4):391-402. PMID: 24844876.
2. Genders TS, Petersen SE, Pugliese F, et al. The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis. Ann Intern Med. 2015 Apr 7;162(7):474-84. PMID: 25844996.
3. Halpern EJ, Savage MP, Fischman DL, et al. Cost-effectiveness of coronary CT angiography in evaluation of patients without symptoms who have positive stress test results. AJR. American journal of roentgenology. 2010 May;194(5):1257-62. PMID: 20410412.
4. Kreisz FP, Merlin T, Moss J, et al. The pre-test risk stratified cost-effectiveness of 64-slice computed tomography coronary angiography in the detection of significant obstructive coronary artery disease in patients otherwise referred to invasive coronary angiography. Heart, lung & circulation. 2009 Jun;18(3):200-7. PMID: 19250870.
5. Ladapo JA, Jaffer FA, Hoffmann U, et al. Clinical outcomes and cost-effectiveness of coronary computed tomography angiography in the evaluation of patients with chest pain. Journal of the American College of Cardiology. 2009 Dec 15;54(25):2409-22. PMID: 20082932.
6. Lee SP, Jang EJ, Kim YJ, et al. Cost-effectiveness of coronary CT angiography in patients with chest pain: Comparison with myocardial single photon emission tomography. Journal of cardiovascular computed tomography. 2015 Sep-Oct;9(5):428-37. PMID: 25977116.
7. Min JK, Gilmore A, Budoff MJ, et al. Cost-effectiveness of coronary CT angiography versus myocardial perfusion SPECT for evaluation of patients with chest pain and no known coronary artery disease. Radiology. 2010;254(3):801-8.
8. Min JK, Shaw LJ, Berman DS, et al. Costs and clinical outcomes in individuals without known coronary artery disease undergoing coronary computed tomographic angiography from an analysis of Medicare category III transaction codes. Am J Cardiol. 2008 Sep 15;102(6):672-8. PMID: 18773986.
9. Nielsen LH, Olsen J, Markenvard J, et al. Effects on costs of frontline diagnostic evaluation in patients suspected of angina: coronary computed tomography angiography vs. conventional ischaemia testing. Eur Heart J Cardiovasc Imaging. 2013 May;14(5):449-55. PMID: 22922828.
10. Shaw LJ, Marwick TH, Berman DS, et al. Incremental cost-effectiveness of exercise echocardiography vs. SPECT imaging for the evaluation of stable chest pain. European heart journal. 2006 Oct;27(20):2448-58. PMID: 17003046.
11. Shaw LJ, Wilson PW, Hachamovitch R, et al. Improved near-term coronary artery disease risk classification with gated stress myocardial perfusion SPECT. JACC Cardiovasc Imaging. 2010 Nov;3(11):1139-48. PMID: 21071002.
12. Thom H, West NE, Hughes V, et al. Cost-effectiveness of initial stress cardiovascular MR, stress SPECT or stress echocardiography as a gate-keeper test, compared with upfront invasive coronary angiography in the investigation and management of patients with stable chest pain: mid-term outcomes from the CECaT randomised controlled trial. BMJ open. 2014 Feb 7;4(2):e003419. PMID: 24508847.
13. Wennike N, Shah BN, Boger E, et al. Stress echocardiography in the district hospital setting: A cost-saving analysis. European Journal of Echocardiography. 2010;11(5):401-5.

APPENDIX L. Data Abstraction of Diagnostic Accuracy Studies

Appendix Table L1. Diagnostic accuracy: Non-invasive diagnostic tests (CCTA, CT perfusion, SNI, stress echo) compared with invasive coronary angiography as reference standard for diagnosis of CAD (NICE Guidelines, 2016)

Study (Year) Search Dates Amstar-2 rating	# of studies	Study Quality	Grade Quality*	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
NICE (2016) Up to 5/10/2016 High	25	Assessed with QUADAS-2 • No serious risk.	Very low	CCTA (50% stenosis) vs. ICA (threshold NR)†	• N=2058 • % female: NR • Mean age: NR • Condition: Stable chest pain • Pretest risk: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: 13 studies • Previous MI: 0% • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 96% (95% CI, 94% to 97%) • Specificity: 79% (95% CI, 72% to 84%) • TP: 1072 • TN: 752 • FP: 208 • FN: 26
	3	Assessed with QUADAS-2 • Risk of bias was rated as serious in 66% of contributing trials.	Very low	CCTA (70% stenosis) vs. ICA (threshold NR)†	• N=371 • % female: NR • Mean age: NR • Condition: Stable chest pain • Pretest risk: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: 1 study • Previous MI: 0% • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 96% (95% CI, 88% to 99%) • Specificity: 72% (95% CI, 55% to 85%) • TP: 112 • TN: 202 • FP: 54 • FN: 3
	1	Assessed with QUADAS-2 • No serious risk.	Low	CT Perfusion (50% stenosis) vs. ICA (threshold NR)†	• N=156 • % female: NR • Mean age: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: NR • Previous MI: 0%	• Sensitivity: 54% (95% CI, 39% to 69%)

Study (Year) Search Dates Amstar-2 rating	# of studies	Study Quality	Grade Quality*	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
					• Condition: Stable chest pain • Pretest risk: NR	• Previous revascularization (e.g., PCI, CABG): NR	• Specificity: 100% (95% CI, 92% to 100%) • TP: 26 • TN: 42 • FP: 0 • FN: 22
	1	Assessed with QUADAS-2 • No serious risk.	Low	CT Perfusion (70% stenosis) vs. ICA (threshold NR)†	• N=156 • % female: NR • Mean age: NR • Condition: Stable chest pain • Pretest risk: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: NR • Previous MI: 0% • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 66% (95% CI, 49% to 80%) • Specificity: 98% (95% CI, 90% to 100%) • TP: 25 • TN: 51 • FP: 1 • FN: 13
	11	Assessed with QUADAS-2 • Risk of bias was rated as serious or very serious in 55% of contributing trials.	Very low	MPS-SPECT (50% stenosis) vs. ICA (threshold NR)†	• N=923 • % female: NR • Mean age: NR • Condition: Stable chest pain • Pretest risk: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: 3 studies • Previous MI: 0% • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 81% (95% CI, 74% to 86%) • Specificity: 78% (95% CI, 70% to 85%) • TP: 503 • TN: 229 • FP: 68 • FN: 123
	3	Assessed with QUADAS-2 • Risk of bias was rated as serious in 66% of	Very low	MPS-SPECT (70% stenosis) vs. ICA (threshold NR)†	• N=145 • % female: NR • Mean age: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: NR • Previous MI: 0%	• Sensitivity: 76% (95% CI, 44% to 93%)

Study (Year) Search Dates Amstar-2 rating	# of studies	Study Quality	Grade Quality*	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
		contributing trials.			• Condition: Stable chest pain • Pretest risk: NR	• Previous revascularization (e.g., PCI, CABG): NR	• Specificity: 76% (95% CI, 58% to 88%) • TP: 68 • TN: 37 • FP: 11 • FN: 29
	1	Assessed with QUADAS-2 • No serious risk.	Low	MPS-PET (70% stenosis) vs. ICA (threshold NR)†	• N=44 • % female: NR • Mean age: NR • Condition: Stable chest pain • Pretest risk: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: NR • Previous MI: 0% • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 91% (95% CI, 71% to 99%) • Specificity: 86% (95% CI, 65% to 97%) • TP: 20 • TN: 19 • FP: 3 • FN: 2
	3	Assessed with QUADAS-2 • No serious risk.	Moderate	Stress Echo, perfusion (50% stenosis) vs. ICA (threshold NR)†	• N=182 • % female: NR • Mean age: NR • Condition: Stable chest pain • Pretest risk: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: 100% • Previous MI: 0% in 2 studies • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 84% (95% CI, 76% to 90%) • Specificity: 79% (95% CI, 69% to 86%) • TP: 99 • TN: 50 • FP: 13 • FN: 20
	1	Assessed with QUADAS-2 • No serious risk.	Low	Stress Echo, perfusion (70% stenosis) vs. ICA (threshold NR)†	• N=62 • % female: NR • Mean age: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: 100% • Previous MI: 0%	• Sensitivity: 90% (95% CI, 73% to 98%)

Study (Year) Search Dates Amstar-2 rating	# of studies	Study Quality	Grade Quality*	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
					• Condition: Stable chest pain • Pretest risk: NR	• Previous revascularization (e.g., PCI, CABG): NR	• Specificity: 73% (95% CI, 54% to 87%) • TP: 26 • TN: 24 • FP: 9 • FN: 3
	5	Assessed with QUADAS-2 • No serious risk.	Very low	Stress Echo, wall motion (50% stenosis) vasodilators vs. ICA (threshold NR)†	• N=422 • % female: NR • Mean age: NR • Condition: Stable chest pain • Pretest risk: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: 1 study • Previous MI: 0% • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 77% (95% CI, 69% to 83%) • Specificity: 76% (95% CI, 72% to 79%) • TP: 226 • TN: 113 • FP: 16 • FN: 67
	8	Assessed with QUADAS-2 • No serious risk.	Moderate	Stress Echo, wall motion (50% stenosis) heart rate modifiers vs. ICA (threshold NR)†	• N=899 • % female: NR • Mean age: NR • Condition: Stable chest pain • Pretest risk: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: 2 studies • Previous MI: 0% • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 76% (95% CI, 72% to 79%) • Specificity: 80% (95% CI, 71% to 88%) • TP: 458 • TN: 235 • FP: 61 • FN: 145
	7	Assessed with QUADAS-2 • Risk of bias was rated as serious in 71% of	Very low	Stress Echo, wall motion (70% stenosis) vasodilators vs. ICA (threshold NR)†	• N=767 • % female: NR • Mean age: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: 3 studies • Previous MI: 0%	• Sensitivity: 64% (95% CI, 49% to 76%)

Study (Year) Search Dates Amstar-2 rating	# of studies	Study Quality	Grade Quality*	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
		contributing trials.			• Condition: Stable chest pain • Pretest risk: NR	• Previous revascularization (e.g., PCI, CABG): NR	• Specificity: 90% (95% CI, 86% to 93%) • TP: 306 • TN: 285 • FP: 32 • FN: 144
	4	Assessed with QUADAS-2 • Risk of bias was rated as serious or very serious in 75% of contributing trials.	Very low	Stress Echo, wall motion (70% stenosis) heart rate modifiers vs. ICA (threshold NR)†	• N=257 • % female: NR • Mean age: NR • Condition: Stable chest pain • Pretest risk: NR	Stable chest pain • Known CAD: 0% • Suspected CAD: 2 studies • Previous MI: 0% • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 75% (95% CI, 62% to 85%) • Specificity: 88% (95% CI, 79% to 93%) • TP: 114 • TN: 194 • FP: 12 • FN: 37

CAD = coronary artery disease; CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; ICA = invasive coronary angiography; FN = false negative; FP = false positive; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; MPS = myocardial perfusion scan; PCI = percutaneous coronary intervention; PET = positron emission tomography; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; SNI = stress nuclear imaging; SPECT = single-photon emission computerized tomography; TN = true negative; TP = true positive.

* Grade quality rating started at High for prospective and retrospective cross sectional studies, and each major limitation (risk of bias, indirectness, inconsistency and imprecision) brought the rating down by 1 increment to a minimum grade of Very Low, as explained for intervention reviews.

† ICA threshold varies across studies.

Appendix Table L2. Diagnostic accuracy: Computed tomography (CCTA) compared with invasive coronary angiography as reference standard for diagnosis of CAD

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
Prior Washington State HTAs						
ICER (2008) 01/2005 to 10/2008 Low	41*	Assessed with QUADAS. • RoB items were rated as unclear in approximately 2.5% to 40% in all categories except true prevalence reported, and rated as no in approximately 2.5% to 75% in all categories except referent likely to classify CAD. Overall Quadas RoB rating: 9 studies rated as "good", remainder rated as "fair".	CCTA (≥50% stenosis) vs. ICA (threshold NR)	• N=3683 • % female (range across studies): 0% to 100% • Mean age (range across studies): 48 to 69 • Condition: Stable chest pain • Pretest risk: NR	Stable chest pain • Known CAD: 31 studies • Suspected CAD: NR • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 98% (95% CI, 97% to 98%) • Specificity: 82% (95% CI, 80% to 84%) • Mean prevalence of CAD: 59%
Other (New) systematic reviews or HTAs						
Haase (2019) Search Dates NR Low	65 (studies reporting on Individual patient data)	Assessed with QUADAS-2† • RoB items were rated as unclear in 17.7% of studies, and high in 23.3% of studies. Overall Quadas-2 RoB rating: Low	CCTA (>50% stenosis) vs. ICA (>50% stenosis)	• N=5332‡ • % male: NR for patients receiving >64 row CT • Mean age: NR for patients receiving >64 row CT • Condition: Stable chest pain • Pretest risk: 7% to 67%	Stable chest pain (individual patient data) • Known CAD: NR • Suspected CAD: NR • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): NR	>64 detector rows (n=558) • Sensitivity: 93.4% • Specificity: 84.4% • PPV: 83.6% • NPV: 93.7% • LR+: 5.98 • LR-: 0.08

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
						• Mean Prevalence of CAD: 46.1% • NDX: 16 • NDX rate: 2.9% • TP: 240 • TN: 254 • FP: 47 • FN: 17
Knuuti (2018) 01/1987 to 08/2017 Low	9	Assessed with QUADAS. • RoB items were rated as unclear in roughly 10% reference standard of CCTA, and high risk of bias was seen in 10% for patient selection. Overall Quadas RoB rating: Low	CCTA (>50% Stenosis) vs. ICA (>50% stenosis)	• N=2748 • % female (range across studies): 0% to 100% • Mean age (range across studies): 57 to 63 • Condition: Stable CAD • Pretest risk: +: 80%, -: 20%	Stable CAD (not acute coronary syndromes) • Known CAD: NR • Suspected CAD: NR • Previous MI: 9 studies • Previous • Revascularization (e.g., PCI, CABG): NR	• Sensitivity: 97% (95% CI, 93% to 99%) • Specificity: 78% (95% CI, 67% to 86%) • LR+: 4.44 (95% CI, 2.64 to 7.45) • LR-: 0.04 (95% CI, 0.01 to 0.09) • Mean prevalence of CAD: 24.2% to 75.5%

CAD = coronary artery disease; CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; ICA = invasive coronary angiography; ICER = Institute for Clinical and Economic Review; FN = false negative; FP = false positive; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; MI = myocardial infarction; MPS = myocardial perfusion scan; NDX = nondiagnostic results; NPV = negative predictive value; PCI = percutaneous coronary intervention; PET = positron emission tomography; PPV = positive predictive value; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RoB = risk of bias; SPECT = single-photon emission computerized tomography; TN = true negative; TP = true positive.

* 34 studies were in an outpatient setting, remaining 7 were in emergency department. Pooled analysis did not stratify by setting.

† Of the 65 referenced studies, only 62 were assessed for RoB. 2 referenced studies (Diederichsen and Ugolini) used unpublished data and were not assessed for RoB, and another (Halvorsen 2008) was not assessed for RoB.
‡ Only 558/5332 patients had the >64 row CT.

Appendix Table L3. Diagnostic accuracy: Computed tomography (CCTA) compared with computed tomography derived fractional flow reserve as reference standard for diagnosis of CAD

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
New systematic reviews or HTAs						
Zhuang (2020) 01/2008 to 05/2019 Low	7	Assessed with QUADAS. • All studies rated RoB items as no in 7% to 10% of items. Overall Quadas RoB rating: Low	CCTA (50% stenosis) vs. FFRct (≤0.80)	• N=868 • % female (range across studies): 19% to 68% • Mean age (range across studies): 58 to 65 • Condition: suspected or known CAD • Pretest risk: NR	Suspected or known CAD • Known CAD: NR • Suspected CAD: NR • Previous MI: 7 studies • Previous revascularization (e.g., PCI, CABG): 5 studies	• Sensitivity: 88% (95% CI, 85% to 97%) • Specificity: 32% (95% CI, 26% to 39% • PPV: 55% (95% CI, 53% to 57%) • NPV: 73% (95% CI, 73% (95% CI, 69% to 77%) • LR+: 1.37 (95% CI, 1.26 to 1.48) • LR-: 0.23 (95% CI, 0.12 to 0.43) • TP: 347 • TN: 161 • FP: 319 • FN: 41 • Diagnostic OR: 4.77 (95% CI, 3.28 to 6.92)

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
Pontone (2019) 01/1966 to 03/2017 Low	17	Assessed with QUADAS-2. • All studies rated RoB items as unclear in approximately 4% to 6%, and no in approximately 2% to 13% across three domains across three domains. Overall Quadas-2 RoB rating: NR*	CCTA (Stenosis NR) vs. FFRct (threshold NR)†	• N=1478 • % female (range across studies): 16% to 68% • Mean age (range across studies): 56 to 68 • Condition: Suspected or known CAD • Pretest risk: 20% to 80%	Suspected or known CAD • Known CAD: 7 studies • Suspected CAD: 17 studies • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 93% (95% CI, 91% to 95%) • Specificity: 42% (95% CI, 39% to 46%) • PPV: 62% (95% CI: 57% to 66%) • NPV: 93% (95% CI: 85% to 100%) • LR+: 1.72 (95% CI, 1.35 to 2.18) • LR-: 0.17 (95% CI, 0.10 to 0.30) • TP: 587 • TN: 358 • FP: 488 • FN: 45 • Diagnostic OR: 10.84 (95% CI: 5.85 to 20.07)
Gonzalez (2015) Up to 04/2015 Low	9	Assessed with QUADAS. • RoB items were rated as unclear in 1 to 3 items in 78% of studies, and rated as no in 1 to 4 items in 55%	CCTA (>50% Stenosis) vs. FFRct (0.75 to 0.80)	• N=1039 • % female: (range across studies) 21% to 58%	Suspected or known CAD • Known CAD: 5 studies • Suspected CAD: 8 studies • Previous MI: 8 studies	• Sensitivity: 92% (95% CI, 88% to 98%) • Specificity: 43% (95% CI: 38% to 47%)

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
		of studies. Overall Quadas RoB rating: Low		• Mean age: (range across studies) 57.4 to 70.4 • Condition: Suspected or known CAD • Pretest risk: NR	• Previous revascularization (e.g., PCI, CABG): 1 study	• PPV: 57% (95% CI: 51% to 64%) • NPV: 87% (95% CI: 78% to 94% • LR+:1.64 (95% CI: 1.38 to 1.93) • LR-: 0.19 (95% CI: 0.10 to 0.35) • Mean prevalence of CAD: 45% • Diagnostic OR: 9.17 (95% CI: 4.54 to 18.52)

CAD = coronary artery disease; CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; ICA = invasive coronary angiography; FFR = fractional flow reserve; FFRct = fractional flow reserve via coronary tomography; FN = false negative; FP = false positive; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; MI = myocardial infarction; NPV = negative predictive value; OR = odds ratio; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RoB = risk of bias; TN = true negative; TP = true positive.

* RoB not stratified by test. QUADAS reported across all 77 studies.

† Authors report as a limitation using different diagnostic thresholds to define stenosis.

Appendix Table L4. Diagnostic accuracy: Computed tomography (CCTA, FFRct) compared with fractional flow reserve via invasive coronary angiography as reference standard for diagnosis of CAD.

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
New systematic reviews or HTAs						
Knuuti (2018) 01/1987 to 08/2017 Low	7	Assessed with QUADAS. • RoB items were rated as unclear in roughly 10% for flow and timing and reference standard of CCTA, and high risk of bias was seen in 10% for flow and timing. Overall Quadas RoB rating: Low	CCTA (>50% Stenosis) vs. FFR via ICA (<0.80)*	• N=1140 • % female (range across studies): 23% to 45% • Mean age (range across studies): 58 to 64 • Condition: stable CAD • Pretest risk: +: 70%, -: 55%	Stable CAD (not acute coronary syndromes) • Known CAD: NR • Suspected CAD: NR • Previous MI: 7 studies • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 93% (95% CI, 89 to 96%) • Specificity: 53% (95% CI, 37 to 68) • LR+: 1.97 (95% CI, 1.28 to 3.03) • LR-: 0.13 (95% CI, 0.06 to 0.25) • Mean prevalence of CAD: 43.6% to 78.3%
Agasthi (2018) Up to 04/2017 Low	8	Assessed with QUADAS. • RoB items were rated as unclear in 5%, and high in 30% for patient selection. Overall Quadas RoB rating: Low	FFRct (<0.80) vs. FFR via ICA (<0.80)*	• N=1294 • % female: (range across studies) 11% to 68% • Mean age: (range across studies) 52 to 73 • Condition: Suspected CAD • Pretest risk: 25%	Suspected CAD • Known CAD: NR • Suspected CAD: NR • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 83% (95% CI, 79% to 87%) • Specificity: 72% (95% CI, 68% to 76%) • LR+: 3.00 (95% CI, 2.60 to 3.50) • LR-: 0.23 (95% CI: 0.18 to 0.29)

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
						• Mean prevalence of CAD: 32% to 100% • Diagnostic OR: 13 (95% CI: 9 to 18)
Gonzales (2015) Up to 04/2015 Low	4	Assessed with QUADAS. • RoB items were rated as unclear in 2 areas of 50% of studies, and as no in 1 to 2 areas of 50% of studies. Overall Quadas RoB rating: Low	FFRct (0.75 to 0.80) vs. FFR via ICA (0.75 to 0.80)*	• N=714 • % female: (range across studies) 28% to 36% • Mean age: (range across studies) 57.3 to 65.1 • Condition: Suspected or known CAD • Pretest risk: NR	Suspected or known CAD • Known CAD: 3 studies • Suspected CAD: 4 studies • Previous MI: 3 studies • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 90% (95% CI, 85% to 93%) • Specificity: 72% (95% CI, 67% to 76%) • PPV: 70% (95% CI, 58% to 82%) • NPV: 90% (95% CI, 84% to 95%) • LR+: 3.70 (95% CI, 2.11 to 6.49) • LR-: 0.16 (95% CI, 0.11 to 0.23) • Mean prevalence of CAD: 42% • Diagnostic OR: 24.34

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
						(95% CI, 1.84 to 54.65)
Helfand (2019) 01/2017 to 08/2019 High	2 systematic reviews of 7 studies focused on HeartFlow technology	NR	FFRct (<0.80) vs. FFR via ICA(<0.80)[†‡]	• N=8354 • % male: NR • Mean age: NR • Condition: Stable chest pain with suspected CAD • Pretest risk: (estimated mean) 50%[§]	Stable chest pain with suspected CAD • Known CAD: 0% • Suspected CAD: NR • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): 0%	• Sensitivity: 84% (95% CI, 80% to 88%) to 85% (95% CI, 81% to 90%) • Specificity: 73% (95% CI, 61% to 88%) to 87% (95% CI, 84% to 91%)
	2 systematic reviews of 15 studies focused on non-HeartFlow technologies	NR	FFRct (<0.80) vs. FFR via ICA (<0.80)[‡]	• N=8354 • % male: NR • Mean age: NR • Condition: Stable chest pain with suspected or known CAD • Pretest risk: (estimated mean) 50%[§]	Stable chest pain with suspected or known CAD • Known CAD: 0% • Suspected CAD: NR • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): 0%	• Sensitivity: 84% (80 to 88) to 86% (81 to 89) • Specificity: 75% (71 to 79) to 80% (73 to 86)
	1 primary study[**]	Assessed with QUADAS. • RoB items were rated as unclear in 2 items, and low in the remaining 3 items.	FFRct (<0.80) vs. FFR via ICA (<0.80)[†]	• N=143 • % male: NR • Mean age: NR • Condition: Suspected CAD	Suspected CAD with at least 1 coronary stenosis of 40% to 90% on CCTA undergoing clinically indicated ICA with FFR • Known CAD: 0%	• Sensitivity: 91% (95% CI, 81% to 97%) • Specificity: 55% (95% CI, 44% to 66%)

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
		Overall Quadas RoB rating: NR		• Pretest risk: (estimated mean) 50%§	• Suspected CAD: NR • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): 0%	• Mean prevalence of CAD: 41%

CAD = coronary artery disease; CABG = coronary artery bypass graft; ICA = invasive coronary angiography; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; MI = myocardial infarction; NPV = negative predictive value; OR = odds ratio; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RoB = risk of bias.

* Does not specify FFR technology used.

† Uses HeartFlow technology.

‡ Reports on per patient evaluation. Study also reports per vessel evaluation (not reported here).

§ Pretest risk not stratified by test; only summary data available.

**Authors report 3 new primary studies since previous SRs published, however 2 of the studies report per vessel.

Appendix Table L5. Diagnostic accuracy: CT myocardial perfusion imaging compared with invasive coronary angiography as reference standard for diagnosis of CAD.

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
New systematic reviews or HTAs						
Sorgaard (2016) 01/2005 to 08/2014 Low	4	Assessed with QUADAS-2. • Details on item ratings NR. Overall Quadas-2 RoB rating: Low	CT perfusion (stenosis ≥50%) + CCTA (stenosis ≥50%) vs. ICA (stenosis ≥50%)	• N=546 • % female: (range across studies) 8% to 34% • Mean age: (range across studies) 60.8 to 65.6 • Condition: Suspected or known CAD • Pretest risk: NR	Suspected or known CAD • Known CAD: NR • Suspected CAD: NR • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 91% (82% to 95%) • Specificity: 77% (66% to 86%) • PPV: 87% (82% to 90%) • NPV: 83% (77% to 88%) • Mean prevalence of CAD: 63% • Diagnostic OR: 33 (11 to 90)

CAD = coronary artery disease; CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; ICA = invasive coronary angiography; MI = myocardial infarction; NPV = negative predictive value; OR = odds ratio; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RoB = risk of bias.

Appendix Table L6. Diagnostic accuracy: CT myocardial perfusion imaging compared with computed tomography derived fractional flow reserve as reference standard for diagnosis of CAD.

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
New systematic reviews or HTAs						
Gonzalez (2015) Up to 04/2015 Low	7	Assessed with QUADAS. • Rob items were rated as unclear in 1 to 2 items in 86% of studies, and rated as no in 1 to 3 item in 29% of studies. Overall Quadas RoB rating: Low	CT perfusion (>50% Stenosis) vs. FFRct (0.75 to 0.80)	• N=444 • % female: (range across studies) 21% to 58% • Mean age: (range across studies) 60 to 70.4 • Condition: Suspected or known CAD • Pretest risk: NR	Suspected or known CAD • Known CAD: 3 studies • Suspected CAD: 6 • Previous MI: 7 studies • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 94% (95% CI, 88% to 98%) • Specificity: 77% (95% CI: 66% to 85%) • PPV: 83% (95% CI: 75% to 92%) • NPV: 92% (95% CI: 88% to 95% • LR+:3.85 (95% CI: 2.16 to 6.84) • LR-: 0.09 (95% CI: 0.04 to 0.19) • Mean prevalence of CAD: 54% • Diagnostic OR: 63.42 (95% CI: 22.41 to 179.5)
Pontone (2019) 01/1966 to 03/2017 Low	11	Assessed with QUADAS-2. • RoB items were rated in all studies as unclear in approximately 4% to 6%, and no in approximately 2% to 13% across three	CT perfusion (Stenosis NR) vs. FFRct (threshold NR)[†]	• N=410 • % female (range across studies): 16% to 36% • Mean age (range across	Suspected or known CAD • Known CAD: 4 studies • Suspected CAD: 11 studies	• Sensitivity: 79% (95% CI, 73% to 84%) • Specificity: 88% (95% CI, 82% to 92%)

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
		domains across three domains. Overall Quadas-2 RoB rating: NR*		studies): 60 to 71 • Condition: Suspected or known CAD • Pretest risk: 20% to 80%	• Previous MI: NR studies or NR • Previous revascularization (e.g., PCI, CABG): NR	• PPV: 84% (95% CI: 77% to 91%) • NPV: 81% (95% CI: 74% to 88%) • LR+: 5.15 (95% CI, 2.22 to 11.92) • LR-: 0.26 (95% CI, 0.16 to 0.42) • TP: 177 • TN: 163 • FP: 23 • FN: 47 • Diagnostic OR: 28.56 (95% CI: 15.50 to 52.62)

CAD = coronary artery disease; CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; ICA = invasive coronary angiography; MI = myocardial infarction; NPV = negative predictive value; OR = odds ratio; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RoB = risk of bias.

* RoB not stratified by test. QUADAS reported across all 77 studies.

† Authors report as a limitation using different diagnostic thresholds to define stenosis.

Appendix Table L7. Diagnostic accuracy: Stress nuclear imaging (SPECT, PET) compared with invasive coronary angiography as reference as reference standard for diagnosis of CAD

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
New systematic reviews or HTAs						
Knuuti (2018) 01/1987 to 08/2017 Low	41	Assessed with QUADAS. • RoB items were rated as unclear in roughly 5% to 20% for the domains across studies of exercise, 20% to 30% in vasodilator, and high risk of bias was seen in 20% across some domains for exercise and vasodilator. Overall Quadas RoB rating: Unclear/high*	SPECT (>50% stenosis) vs. ICA (>50% stenosis)	• N=10897 • % female (range across studies): 0.33% to 100% NR • Mean age (range across studies): 54 to 72.1 • Condition: Stable CAD • Pretest risk: +: 75%, -: 48%	Stable CAD (not acute coronary syndromes) • Known CAD: NR • Suspected CAD: NR • Previous MI: 39 studies • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 87% (95% CI, 83% to 90%) • Specificity: 70% (95% CI, 63% to 76%) • LR+: 2.88 (95% CI, 2.33 to 3.56) • LR-: 0.19 (95% CI, 0.15 to 0.24) • Mean prevalence of CAD: 14.1% to 86%
	3	Assessed with QUADAS. • RoB items were rated as low risk in all domains. Overall Quadas RoB rating: Low	PET (>50% stenosis) vs. ICA (>50% stenosis)	• N=418 • % female (range across studies): 45% to 54% • Mean age (range across studies): 63 to 67 • Condition: Stable CAD • Pretest risk: +: 52%, -: 60%	Stable CAD (not acute coronary syndromes) • Known CAD: NR • Suspected CAD: NR • Previous MI: 3 studies • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 90% (95% CI, 78% to 96%) • Specificity: 85% (95% CI, 78% to 90%) • LR+: 5.87 (95% CI, 3.40 to 10.15) • LR-: 0.12 (95% CI, 0.05 to 0.29)

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
						• Mean prevalence of CAD: 36.5% to 62.5%

CAD = coronary artery disease; CABG = coronary artery bypass graft; ICA = invasive coronary angiography; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention; PET = positron emission tomography; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RoB = risk of bias; SPECT = single-photon emission computerized tomography.
* Authors report balanced proportion of unclear and high RoB in all domains.

Appendix Table L8. Diagnostic accuracy: Stress nuclear imaging (SPECT, PET) compared with other referents (FFRct, FFR via ICA) as reference standard for diagnosis of CAD

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
Prior Washington State HTAs						
ICER (2013) 01/1996 to 02/2013 Critically low	4	Assessed with QUADAS. • RoB items were rated as unclear in 12.5% of domains, and high risk in 25% of domains. Overall Quadas RoB rating: NR	SPECT (>50% stenosis) vs. FFR via ICA (0.75 to 0.80)	• N=584 • % female: NR • Mean age: NR • Condition: Suspected or known CAD • Pretest risk: Varies (low, medium, and high) between studies.	Suspected or known CAD • Known CAD: 100% in 2 studies • Suspected CAD: NR • Previous MI: 70% to 100% 2 studies • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: (range across studies) 66% to 90% • Specificity: (range across studies) 50% to 87% • PPV: (range across studies) 73% to 81% • NPV: (range across studies) 58% to 91%
	2	Assessed with QUADAS. • RoB items were rated as unclear in 30% of domains, and high risk in 30% of domains. Overall Quadas RoB rating: NR	PET (>50% stenosis) vs. FFR via ICA (0.75 to 0.80)	• N=227 • % female: NR • Mean age: NR • Condition: Suspected or known CAD • Pretest risk: Varies (low, medium, and high) between studies.	Suspected or known CAD • Known CAD: NR • Suspected CAD: NR • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: (range across studies) 76% to 95% • Specificity: (range across studies) 83% to 91% • PPV: (range across studies) 76% to 86%

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
						• NPV: (range across studies) 83% to 97%
Other (New) systematic reviews or HTAs						
Knuuti (2018) 01/1987 to 08/2017 Low	5	Assessed with QUADAS. • RoB items were rated as unclear in roughly 5% to 20% for the domains across studies of exercise, 20% to 30% in vasodilator, and high risk of bias was seen in 20% across some domains for exercise and vasodilator. Overall Quadas RoB rating: Authors report balanced proportion of unclear and high RoB in all domains.	SPECT (>50% stenosis) vs. FFR via ICA (<0.80)	• N=740 • % female (range across studies): 29% to 36% • Mean age (range across studies): 58 to 65 • Condition: Stable CAD • Pretest risk: +: 62%, -: 35%	Stable CAD (not acute coronary syndromes) • Known CAD: NR • Suspected CAD: NR • Previous MI: 4 studies Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 73% (95% CI, 62% to 82%) • Specificity: 83% (95% CI, 71% to 90%) • LR+: 4.21 (95% CI, 2.62 to 6.76) • LR-: 0.33 (95% CI, 0.24 to 0.46) • Mean prevalence of CAD: 20% to 49.6%
	4	Assessed with QUADAS. • RoB items were rated as low risk in all domains. Overall Quadas RoB rating: Low	PET (>50% stenosis) vs. FFR via ICA (<0.80)	• N=709 • % female (range across studies): 32% to 62% • Mean age (range across studies): 58 to 64 • Condition: Stable CAD	Stable CAD (not acute coronary syndromes) • Known CAD: NR • Suspected CAD: NR • Previous MI: 0% • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 89% (95% CI, 82% to 93%) • Specificity: 85% (95% CI, 81% to 88%) • LR+: 6.04 (95% CI, 4.29 to 8.51)

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
				• Pretest risk: +: 50%, 55%		• LR-: 0.13 (95% CI, 0.08 to 0.22) • Mean prevalence of CAD: 39.9% to 44.1%
Pontone (2019) 01/1966 to 03/2017 Low	19	Assessed with QUADAS-2. • RoB items were rated in all studies as unclear in approximately 4% to 6%, and no in approximately 2% to 13% across three domains. Overall Quadas-2 RoB rating: NR[*]	SPECT (Stenosis NR) vs. FFRct (threshold NR)[†]	• N=682 • % female (range across studies): 16% to 44% • Mean age (range across studies): 53 to 73 • Condition: Suspected or known CAD • Pretest risk: 20% to 80%	Suspected or known CAD • Known CAD: 13 studies • Suspected CAD: 7 studies • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 71% (95% CI, 66% to 76%) • Specificity: 79% (95% CI, 74% to 83%) • PPV: 75% (95% CI: 69% to 80%) • NPV: 70% (95% CI: 65% to 75%) • LR+: 2.94 (95% CI, 1.96 to 4.40) • LR-: 0.42 (95% CI, 0.28 to 0.62) • TP: 224 • TN: 289 • FP: 78 • FN: 91 • Diagnostic OR: 7.99 (95% CI: 3.69 to 17.30)

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
	5	Assessed with QUADAS-2. • RoB items were rated in all studies as unclear in approximately 4% to 6%, and no in approximately 2% to 13% across three domains. Overall Quadas-2 RoB rating: NR*	PET (Stenosis NR) vs. FFRct (threshold NR)†	• N=609 • % female (range across studies): 33% to 42% • Mean age (range across studies): 57 to 64 • Condition: Suspected or known CAD • Pretest risk: 20% to 80%	Suspected or known CAD • Known CAD: NR • Suspected CAD: 5 studies • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 88% (95% CI, 83% to 92%) • Specificity: 86% (95% CI, 82% to 89%) • PPV: 85% (95% CI: 82% to 89%) • NPV: 88% (95% CI: 84% to 92%) • LR+: 6.35 (95% CI, 4.45 to 9.07) • LR-: 0.13 (95% CI, 0.06 to 0.28) • TP: 207 • TN: 321 • FP: 52 • FN: 29 • Diagnostic OR: 51.79 (95% CI: 18.46 to 145.33)

CAD = coronary artery disease; CABG = coronary artery bypass graft; ICA = invasive coronary angiography; ICER = Institute for Clinical and Economic Review; FFR = fractional flow reserve; FFRct = fractional flow reserve via coronary tomography; FN = false negative; FP = false positive; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; MI = myocardial infarction; NPV = negative predictive value; OR = odds ratio; PCI = percutaneous coronary intervention; PET = positron emission tomography; PPV = positive predictive value; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RoB = risk of bias; SPECT = single-photon emission computerized tomography; TN = true negative; TP = true positive.

* RoB not stratified by test. QUADAS reported across all 77 studies.

† Authors report as a limitation using different diagnostic thresholds to define stenosis.

Appendix Table L9. Diagnostic accuracy: Stress echocardiography compared with invasive coronary angiography as reference standard for diagnosis of CAD

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
AHRQ 2016 Report						
de Jong (2012)* 01/2000 to 05/2011 Low	10	Assessed with QUADAS. • Rob items were rated as unclear in 1 to 3 items across 50% of studies, and rated as no in 1 to 5 items across all studies. Overall Quadas RoB rating: NR	Stress Echo (Stenosis NR) vs. ICA (≥50 to ≥75% stenosis)	• N=798 • % female (range across studies): 18% to 39% • Mean age (range across studies): 56 to 67 • Condition: Suspected CAD, without known CAD • Pretest risk: NR	Suspected or known CAD • No known history of CAD, MI, PCI or CABG	• Sensitivity: 87% (95% CI, 81% to 91%) • Specificity: 72% (95% CI, 56% to 83%) • PPV: 85% • NPV: 73% • LR+: 3.08 (95% CI, 1.65 to 4.50) • LR-: 0.18 (95% CI, 0.13 to 0.24) • Mean prevalence of CAD: 66% • Diagnostic OR: 16.94 (95% CI, 9.84 to 29.15)
	1	Assessed with QUADAS. • Rob items were rated as unclear in 1 item, and rated as no in 4 items. Overall Quadas RoB rating: NR	Stress Echo (Stenosis NR) vs. ICA (≥50 stenosis)	• N=50 • % female: 32% • Mean age: 67 • Condition: Suspected CAD, without known CAD • Pretest risk: NR	Suspected CAD • No known history of CAD, MI, PCI or CABG	• Sensitivity: 88% (95% CI, 60% to 97%) • Specificity: 89% (95% CI, 58% to 98%) • PPV: 93% • NPV: 80%

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
						• LR+: 8.35 (95% CI, 6.67 to 21.76) • LR-: 0.13 (95% CI, 0.05 to 0.32) • Mean prevalence of CAD: 64% • Diagnostic OR: 62.76 (95% CI, 7.37 to 534.54)
Ladapo (2013) 01/1990 to 11/2012 Critically low	4	NR	Stress Echo (Stenosis NR) vs. ICA (≥50 to ≥75% stenosis)	• N=5216 • % male (range across studies): 0% to 54% • Mean age (range across studies): 53 to 62 • Condition: Suspected or known CAD • Pretest risk: high	Suspected or known CAD (Excluded studies with ≥ 15% history of MI or revascularization) • Known CAD: NR • Suspected CAD: 4 studies • Previous MI: 0% (in 2 studies) • Previous revascularization (e.g., PCI, CABG): 0% (in 2 studies)	• Sensitivity: 84% (95% CI, 80% to 89%) • Specificity: 77% (95% CI, 69% to 86%) • PPV: 89% • NPV: 69% • LR+: 3.65 (95% CI, 3.33 to 4.00 • LR-: 0.21 (95% CI, 0.19 to 0.23) • Mean prevalence of CAD (estimated): 68%

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
Other (New) systematic reviews or HTAs						
Knuuti (2018) 01/1987 to 08/2017 Low	56	Assessed with QUADAS. • RoB items were rated as unclear in roughly 20% to 40% for the domains across studies of stress echo (exercise or pharmacologic), and high risk of bias was seen in some domains for exercise. Overall Quadas RoB rating: Low	Stress Echo (>50 stenosis) vs. ICA (>50% stenosis)	• N=9512 • % female (range across studies): 11% to 100% • Mean age (range across studies): 46 to 75 • Condition: Stable CAD • Pretest risk: +: 60%, -: 49%	Stable CAD (not acute coronary syndromes) • Known CAD: NR • Suspected CAD: NR • Previous MI: 41 studies • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 85% (95% CI, 80% to 89%) • Specificity: 82% (95% CI, 72% to 89) • LR+: 4.67 (95% CI, 2.95 to 7.41) • LR-: 0.18 (95% CI, 0.13 0.25) • Mean prevalence of CAD: 35.1% to 90.8%

CAD = coronary artery disease; CABG = coronary artery bypass graft; ICA = invasive coronary angiography; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; MI = myocardial infarction; NPV = negative predictive value; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RoB = risk of bias.

* Suspected and known CAD outcomes include all stress Echo studies, additional row for suspected CAD includes only the single study not looking at known CAD.

Appendix Table L10. Diagnostic accuracy: Stress echocardiography compared with computed tomography derived fractional flow reserve as reference standard for diagnosis of CAD.

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
New systematic reviews or HTAs						
Pontone (2019) 01/1966 to 03/2017 Low	10	Assessed with QUADAS-2. • RoB items were rated in all studies as unclear in approximately 4% to 6%, and no in approximately 2% to 13% across three domains across three domains. Overall Quadas-2 RoB rating: NR*	Stress Echo (Stenosis NR) vs. FFRct (threshold NR)†	• N=361 • % female (range across studies): 14% to 48% • Mean age (range across studies): 54 to 69 • Condition: Suspected or known CAD • Pretest risk: 20% to 80%	Suspected or known CAD • Known CAD: 5 studies • Suspected CAD: 5 studies • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 64% (95% CI, 56% to 71%) • Specificity: 84% (95% CI, 78% to 89%) • PPV: 81% (95% CI: 74% to 88%) • NPV: 70% (95% CI: 64% to 76%) • LR+: 3.51 (95% CI, 2.53 to 4.87) • LR-: 0.45 (95% CI, 0.35 to 0.57) • TP: 106 • TN: 164 • FP: 31 • FN: 60 • Diagnostic OR: 11.09 (95% CI: 6.31 to 19.48)

CAD = coronary artery disease; CABG = coronary artery bypass graft; ICA = invasive coronary angiography; FFR = fractional flow reserve; FFRct = fractional flow reserve via coronary tomography; FN = false negative; FP = false positive; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; MI = myocardial infarction; NPV = negative predictive value; OR = odds ratio; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RoB = risk of bias; TN = true negative; TP = true positive.

* RoB not stratified by test. QUADAS reported across all 77 studies.

† Authors report as a limitation using different diagnostic thresholds to define stenosis.

Appendix Table L11. Diagnostic accuracy: Non-invasive diagnostic tests (CCTA, SNI, stress echo) compared with invasive coronary angiography as reference standard for diagnosis of CAD in emergency departments

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
Prior Washington State HTAs						
ICER 2008	3 prospective studies[*]	NR	CCTA (>50% stenosis) vs. ICA (threshold NR)	• N=216 • % female (range across studies): 36% to 40% • Mean age (range across studies): 54 to 56 • Condition: Patients presenting to the ED with and without ACS, or with possible ischemic chest pain • Pretest risk: NR	Patients presenting to the ED with and without ACS, or with possible ischemic chest pain • Known CAD: 9.7% to 38% • Suspected CAD: NR • Previous MI: 9.7% to 24% • Previous revascularization (e.g., PCI, CABG): 10% to 29%	• Sensitivity (range across studies): 94% to 100% • Specificity (range across studies: 77% to 92% • PPV (range across studies): 47% to 87% • NPV (range across studies): 91% to 100%
Other (New) systematic reviews or HTAs						
Iannaccone (2019)[†] Search dates NR Low	10	Assessed with QUADAS-2. • RoB items were rated as unclear in 5% to 25%, and high in 5% to 20% of studies across some domains. Overall Quadas-2 RoB rating: NR	CCTA (Stenosis NR) vs. ICA (threshold NR)	• N=2833 • % female (range across studies): 30% to 66% • Mean age (range across studies): 47 to 60.3 • Condition: Suspected or known CAD	Suspected or known CAD • Known CAD: 29.4%[‡] • Suspected CAD: NR • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 93% (95% CI, 81% to 98%) • Specificity: 90% (95% CI, 93% to 94%) • LR+: 9.40 (95% CI, 5.20 to 16.50)

Study (Year) Search Dates Amstar-2 rating	# of Studies	Study Quality	Reference Standard (threshold)	Population Pre-test risk	History of CAD, MI, or Revascularization	Diagnostic Accuracy Outcomes
				• Pretest risk: NR		• LR-: 0.10 (95% CI, 0.02 to 0.20)
	14	Assessed with QUADAS-2. • RoB items were rated as unclear in 5% to 30%, and high in 5% to 30% of studies across some domains. Overall Quadas-2 RoB rating: NR	SPECT (Stenosis NR) vs. ICA (threshold NR)	• N=7044 • % female (range across studies): 25% to 60.4% • Mean age (range across studies): 53.8 to 63.7 • Condition: Suspected or known CAD • Pretest risk: NR	Suspected or known CAD • Known CAD: 29.4%‡ • Suspected CAD: NR • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 85% (95% CI, 77% to 91%) • Specificity: 92% (95% CI, 83% to 96%) • LR+: 10.48 (95% CI, 5.32 to 20.60) • LR-: 0.19 (95% CI, 0.01 to 0.35)
	8	Assessed with QUADAS-2. • RoB items were rated as unclear in 5% to 35%, and high in 5% to 20% of studies across some domains. Overall Quadas-2 RoB rating: NR	Stress Echo (Stenosis NR) vs. ICA (threshold NR)	• N=3073 • % female (range across studies): 25% to 55.3% • Mean age (range across studies): 47 to 63 • Condition: Suspected or known CAD • Pretest risk: NR	Suspected or known CAD • Known CAD: 29.4%‡ • Suspected CAD: NR • Previous MI: NR • Previous revascularization (e.g., PCI, CABG): NR	• Sensitivity: 75% (95% CI, 59% to 89%) • Specificity: 96% (95% CI, 91% to 98%) • LR+: 18.67 (95% CI, 8.30 to 42.10) • LR-: 0.25 (95% CI, 0.14 to 0.46

CAD = coronary artery disease; CABG = coronary artery bypass graft; CCTA = computed coronary tomography angiography; ICA = invasive coronary angiography; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; MI = myocardial infarction; MPS = myocardial perfusion scintigraphy; PCI = percutaneous coronary intervention; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RoB = risk of bias; SNI = stress nuclear imaging.

* Subset of studies included in the ICER 2008 report. Data was abstracted directly from the individual studies.
† Patient population were patients with non-ST segment elevation myocardial infarction (NSTEMI) and without troponin. Authors do not report prevalence of CAD, pretest likelihood, or true and false positives or negative.
‡ Only summary data available.

APPENDIX M. Definitions of Pretest Risk Assessments

Appendix Table M1. Definition of pre-test risk assessments commonly used by included studies
(taken from the 2016 AHRQ report on Noninvasive Testing for Coronary Artery Disease)

Risk Criteria	Description
Cardiac Society of Australia and New Zealand guidelines[1]	Low risk (<2%): Any pain Intermediate risk (2%-10%): Any pain and/or pain at rest, repetitive or prolonged pain High risk (>10%): Any pain, pain at rest, repetitive or prolonged pain, and changes on electrocardiogram or elevated troponin level Risk categories are based on the presence of clinical factors known to increase rates of myocardial infarction and death within 6 months.
CCS Angina Grading Scale[9]	Commonly used for the classification of severity of angina: Class I – Angina only during strenuous or prolonged physical activity Class II – Slight limitation, with angina only during vigorous physical activity Class III – Symptoms with everyday living activities, i.e., moderate limitation Class IV – Inability to perform any activity without angina or angina at rest, i.e., severe limitation
Diamond-Forrester risk algorithm[90]	"This model takes into account age, sex, and type of chest pain, which was classified as typical, atypical or non-anginal.9 The commonly used classification cut-offs of 30% and 70% were used.10 Consequently, a score below 30% was considered low, 30%-70% intermediate and >70% high risk of having significant CAD."
Established criteria[55]	"patients with very low likelihood atypical chest pain presentations (e.g., costochondral point tenderness) to high-risk patients (e.g., those manifesting a classic ST-elevation MI or arrhythmias or those with unstable hemodynamics) were screened for enrollment"
Framingham risk score[90]	"A multivariable risk function that predicts 10-year risk of developing cardiovascular disease events (coronary heart disease, stroke, peripheral artery disease or heart failure). The sex-specific scores incorporate age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetic status. A score below 10% is considered low, 10%-20% intermediate, and >20% high 10-year risk of cardiovascular events."
Goldman Reilly Criteria [21,24,71]	Low-risk: By these criteria, low-risk patients had no ECG evidence of acute infarction or ischemia (including new left bundle branch block), no pain that was worse than usual angina or like a previous myocardial infarction, no recent revascularization, no rates above both bases, and a systolic blood pressure that was greater than 110 mm Hg.
TIMI risk score[5]	% risk at 14 days of: all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization. • Score of 0-1=4.7% risk • Score of 2=8.3% risk • Score of 3=13.2% risk • Score of 4=19.9% risk • Score of 5=26.2% risk • Score of 6-7=at least 40.9% risk

Risk Criteria	Description
Pryor et al.[70]	The probability of significant coronary artery disease was calculated as: $1/(1 + e^{-x})$ Where *e*=base of natural logarithm *Where* $x=a_1y_1 + a_2y_2 + \ldots + a_ky_k + B$ Where $y_1, y_2, \ldots, y_k$ are the characteristics, $a_1, a_2, \ldots, a_k$ are the corresponding logistic regression coefficients, and *B* is the intercept term (in this case, -7.376).
Predicted annualized risk of death or MI[82]	Determining 10-year (short term) risk for developing CHD is carried out using Framingham risk scoring. The risk factors included in the Framingham calculation are age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking. Because of a larger database, Framingham estimates are more robust for total cholesterol than for LDL cholesterol. Note, however, that LDL cholesterol remains the primary target of therapy. Risk score is calculated using a downloadable excel file or risk assessment tool available here: http://cvdrisk.nhlbi.nih.gov/calculator.asp .

CAD=coronary artery disease, CASS=Coronary Artery Surgery Study risk score, CCS=Canadian Cardiovascular Society, ECG=electrocardiogram, MI=myocardial infarction, TIMI=Thrombolysis in Myocardial Infarction

APPENDIX N. Citations from CCTA payer policies

Aetna (2019)

1. Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: Pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association Writing Group. Circulation. 1996;94:1175-1192.
2. Marwick TH. Screening for coronary artery disease. Med Clin North Am. 1999; 83(6):1375-1402.
3. Laudon DA. Use of electron-beam computed tomography in the evaluation of chest pain patients in the emergency department. Ann Emerg Med. 1999;33(1):15-21.
4. O'Malley PG. Rationale and design of the Prospective Army Coronary Calcium (PACC) Study: Utility of electron beam computed tomography as a screening test for coronary artery disease and as an intervention for risk factor modification among young, asymptomatic, active-duty United States Army Personnel. Am Heart J. 1999;137(5):932-941.
5. Secci A, Wong N, Tang W, et al. Electron beam computed tomography coronary calcium as a predictor of coronary events. Circulation. 1997;96:1122-1129.
6. Rumberger JA, Sheedy PF, Breen JF, et al. Electron beam computed tomography and coronary artery disease: Scanning for coronary artery calcification. Mayo Clin Proc. 1996;71:369-377.
7. Budoff MJ, Georgiou D, Brody A, et al. Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: A multicenter study. Circulation. 1996;93:898-904.
8. Fallavollita JA, Brody AS, Bunnell IL, et al. Fast computed tomography detection of coronary calcification in the diagnosis of coronary artery disease: Comparison with angiography in patients < 50 years old. Circulation. 1994;89(1):285-290.
9. Kaufmann RB, Peyser PA, Sheedy PF, et al. Quantification of coronary artery calcium by electron beam computed tomography for determination of severity of angiographic disease in younger patients. J Am Coll Cardiol. 1995;25:626-632.
10. Guerci AD, Spadaro LA, Popma JJ, et al. Relation of coronary calcium score by electron beam computed tomography to arteriography findings in asymptomatic and symptomatic adults. Am J Cardiol. 1997;79:128-133.
11. Mann JM, Davies MJ. Vulnerable plaque: Relation of characteristics to degree of stenosis in human coronary arteries. Circulation. 1996;94:928-931.
12. Detrano R, Hsiai T, Wang S, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. J Am Coll Cardiol. 1996;27:285-290.
13. Arad Y, Spadaro LA, Goodman K, et al. Predictive value of electron beam computed tomography of the coronary arteries: 19-month follow-up of 1173 asymptomatic subjects. Circulation. 1996;93:1951-1953.
14. Breen JF, Sheedy PF, Shwartz RS, et al. Coronary artery calcification detected with ultrafast CT as an indication of coronary artery disease. Radiology. 1992;185:435-439.
15. Committee on Advanced Cardiac Imaging and Technology, Council on Clinical Cardiology, and Committee on Newer Imaging Modalities, Council on Cardiovascular Radiology, American Heart Association. Potential value of ultrafast computed tomography to screen for coronary artery disease. Circulation. 1993;87(6):2071.
16. Wong ND, Detrano RC, Diamond G, et al. Does coronary artery screening by electron

beam computed tomography motivate potentially beneficial lifestyle behaviors? Am J Cardiol. 1996;78:1220-1223.
17. Wang S, Detrano RC, Secci A, et al. Detection of coronary calcification with electron beam computed tomography: Evaluation of interexamination reproducibility and comparison of 3 image acquisition protocols. Am Heart J. 1996;132:550-558.
18. Rumberger JA, Sheedy PF, Breen JF, et al. Electron beam computed tomographic coronary calcium score cut points and severity of associated angiographic lumen stenosis. J Am Coll Cardiol. 1997;29:1542-1548.
19. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15:827-832.
20. Berry E, Kelly S, Hutton J, et al. A systematic literature review of spiral and electron beam computed tomography: With particular reference to clinical applications in hepatic lesions, pulmonary embolus, and coronary artery disease. Health Technol Assess. 1999;3(18):i-iv, 1-118.
21. Bielak LF, Rumberger JA, Sheedy PF 2nd, et al. Probabilistic model for predication of angiographically defined obstructive coronary artery disease using electron beam computed tomography Calcium Score Strata. Circulation. 2000;102(4):380-385.
22. Carr JJ, Crouse JR 3rd, Goff DC Jr, et al. Evaluation of subsecond gated spiral CT for quantification of coronary artery calcium and comparison with electron beam CT. AJR Am J Roentgenol. 2000;174(4):915-921.
23. Detrano R, Wong ND, Doherty TM, et al. Coronary calcium does not accurately predict near-term future coronary events in high-risk adults. Circulation. 1999;99(20):2633-2638.
24. O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association expert consensus document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. J Am Coll Cardiol. 2000;36(1):326-340.
25. Ratko T. Electron beam computed tomography. Technology Report. UHC Clinical Practice Advancement Center. Oak Brook, IL: University Hospital Consortium (UHC); October 1999.
26. Rumberger JA. Tomographic (plaque) imaging: State of the art. Am J Cardiol. 2001;88(2-A):66E-69E.
27. Naghavi M, Madjid M, Khan MR, et al. New developments in the detection of vulnerable plaque. Curr Atheroscler Rep. 2001;3(2):125-135.
28. National Horizon Scanning Centre (NHSC). Imaging in coronary heart disease - horizon scanning review. Birmingham, UK: National Horizon Scanning Centre (NHSC); 2001.
29. Redberg RF, Shaw LJ. A review of electron beam computed tomography: Implications for coronary artery disease screening. Prev Cardiol. 2002;5(2):71-78.
30. Nieman K, van Geuns RJ, Wielopolski P, et al. Noninvasive coronary imaging in the new millennium: A comparison of computed tomography and magnetic resonance techniques. Rev Cardiovasc Med. 2002;3(2):77-84.
31. Thomson LE, Hachamovitch R. Coronary artery calcium scoring using electron-beam computed tomography: Where does this test fit into a clinical practice? Rev Cardiovasc Med. 2002;3(3):121-128.
32. O'Malley PG, Feuerstein IM, Taylor AJ. Impact of electron beam tomography, with or without case management, on motivation, behavioral change, and cardiovascular risk profile: A randomized controlled trial. JAMA. 2003;289(17):2215-2223.
33. Greenland P. Improving risk of coronary heart disease. JAMA. 2003;289:2270-2272.
34. New Zealand Health Technology Assessment (NZHTA). What is the prognostic value of calcium scoring in screening asymptomatic populations for cardiovascular disease?

Evidence Tables. Christchurch, NZ: NZHTA; 2003. Available at: http://nzhta.chmeds.ac.nz. Accessed April 16, 2004.
35. Pwee KH. Multislice/spiral computed tomography for screening for coronary artery disease. Issues in Emerging Health Technologies. Issue 43. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); February 2003. Available at: http://www.ccohta.ca/. Accessed March 23, 2004.
36. Budoff MJ, Mao S, Zalace CP, et al. Comparison of spiral and electron beam tomography in the evaluation of coronary calcification in asymptomatic persons. Int J Cardiol. 2001;77(2-3):181-188.
37. U.S. Preventive Services Task Force. Screening for coronary heart disease. Report of the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); February 2004. Available at: http://www.ahrq.gov/clinic/uspstf/uspsacad.htm. Accessed March 23, 2004.
38. No author listed. AHA will not endorse EBT to assess heart attack risk [news]. Pharmaceutical Executive. October 10, 2004. Available at http://www.pharmexec.com. Accessed November 3, 2004.
39. Jacoby DS, Mohler III ER, Rader DJ. Noninvasive atherosclerosis imaging for predicting cardiovascular events and assessing therapeutic interventions. Curr Atheroscler Rep. 2004;6(1):20-26.
40. Mazzone T. The role of electron beam computed tomography for measuring coronary artery atherosclerosis. Curr Diab Rep. 2004;4(1):20-25.
41. Traversi E, Bertoli G, Barazzoni G, et al. Non-invasive coronary angiography with multislice computed tomography. Technology, methods, preliminary experience and prospects. Ital Heart J. 2004;5(2):89-98.
42. Schoepf UJ, Becker CR, Ohnesorge BM, Yucel EK. CT of coronary artery disease. Radiology. 2004;232(1):18-37.
43. Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: A systematic review and meta-analysis. Arch Intern Med. 2004;164(12):1285-1292.
44. Ewy GA. The search for the 'holy grail' of clinically significant coronary atherosclerosis. Arch Intern Med. 2004;16412):1266-1268.
45. Finnish Medical Society Duodecim. Coronary heart disease (CHD): Symptoms, diagnosis and treatment. In: EBM Guidelines. Evidence-Based Medicine [CD-ROM]. Helsinki, Finland: Duodecim Medical Publications Ltd.; September 14, 2004.
46. Finnish Medical Society Duodecim. Coronary angiography and indications for CABG or angioplasty. In: EBM Guidelines. Evidence-Based Medicine [CD-ROM]. Helsinki, Finland: Duodecim Medical Publications Ltd.; September 14, 2004.
47. Finnish Medical Society Duodecim. Unstable angina pectoris. In: EBM Guidelines. Evidence-Based Medicine [CD-ROM]. Helsinki, Finland: Duodecim Medical Publications Ltd.; September 14, 2004.
48. Finnish Medical Society Duodecim. Myocardial infarction. In: EBM Guidelines. Evidence-Based Medicine [CD-ROM]. Helsinki, Finland: Duodecim Medical Publications Ltd.; September 13, 2004.
49. American College of Cardiology Foundation, American Heart Association. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to update the 1999 guidelines). Bethesda, MD: American College of Cardiology Foundation; 2002.

50. Snow V, Barry P, Fihn SD, et al. Primary care management of chronic stable angina and asymptomatic suspected or known coronary artery disease: A clinical practice guideline from the American College of Physicians. Ann Intern Med. 2004;141(7):562-567.
51. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 guidelines). Bethesda, MD: American College of Cardiology, American Heart Association; 2004.
52. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol. 1997l 30(1):260-311.
53. American College of Cardiology Foundation, American Heart Association. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Bethesda, MD: American College of Cardiology Foundation (ACCF); March 2002.
54. Medical Services Advisory Committee (MSAC). Diagnostic and therapeutic modalities for coronary artery disease. Horizon Scanning 003. Canberra, ACT: MSAC; 2003.
55. Institute for Clinical Systems Improvement (ICSI). Electron-beam and helical computed tomography for coronary artery disease. Technology Assessment No. 34. Bloomington, MN: ICSI; 2004.
56. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Contrast-enhanced cardiac computed tomographic angiography for coronary artery evaluation. TEC Assessment Program. Chicago, IL: BCBSA; May 2005;20(4).
57. Lauer M, Froelicher ES, Williams M, Kligfield P. Exercise testing in asymptomatic adults: A statement for professionals from the American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. Circulation. 2005;112(5):771-776.
58. American College of Cardiology Foundation, American Heart Association. ACC/AHA guideline update for exercise testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Bethesda, MD: American College of Cardiology Foundation; 2002.
59. Schuijf JD, Bax JJ, Shaw LJ, et al. Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and multislice computed tomography for noninvasive coronary angiography. Am Heart J. 2006;151(2):404-411.
60. Ontario Ministry of Health and Long-Term Care, Medical Advisory Secretariat (MAS). Multidetector computed tomography angiography for coronary artery disease. Health Technology Literature Review. Toronto, ON: MAS; April 2005.
61. National Health Service Quality Improvement Scotland (NHS QIS). The use of multislice computed tomography angiography (CTA) for the diagnosis of coronary artery disease. Evidence Note 9. Glasgow, Scotland: NHS QIS; June 2005.
62. Foerster V, Murtagh J, Lentle BC, et al. CT and MRI for selected clinical disorders: A systematic review of clinical systematic reviews. Technology Report No. 59. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment (CADTH); 2005.
63. Bardach A, Garcia Marti S, Lopez A, Glujovsky D. Usefulness of multislice computed tomography (MSCT) for coronary disease. Report IRR No. 49. Buenos Aires, Argentina: Institute for Clinical Effectiveness and Health Policy (IECS); 2005.

64. National Horizon Scanning Centre (NHSC). Computed tomography angiography for the diagnosis and management of coronary artery disease. Horizon Scanning Technology Briefing. Birmingham, UK: NHSC; December 2006.
65. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography. A Scientific Statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation. 2006;114:1761-1791.
66. German Agency of Health Technology Assessment (DAHTA) at German Institute for Medical Documentation and Information (DIMDI). Computed tomography for the measurement of coronary calcification in asymptomatic risk patients [summary]. Technology Assessment. Cologne, Germany; DIMDI; 2006.
67. Adelaide Health Technology Assessment (AHTA). Computed tomography coronary angiography. Horizon Scanning Prioritising Summary - Volume 12. Adelaide, SA: AHTA on behalf of National Horizon Scanning Unit (HealthPACT and MSAC); 2006.
68. Waugh N, Black C, Walker S, et al. The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: Systematic review. Health Technol Assess. 2006;10(39):1-60.
69. Murtagh J, Foerster V, Warburton RN, et al. Clinical and cost effectiveness of CT and MRI for selected clinical disorders: Results of two systematic reviews. Technology Overview No. 22. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); 2006.
70. Murtagh J, Warburton RN, Foerster V, et al. CT and MRI for selected clinical disorders: A systematic review of economic evaluations. Technology Report No. 68. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); 2006.
71. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery-executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Am Coll Cardiol. 2002;39:542-53.
72. Goldstein JA, Gallagher MJ, O'Neill WW, et al. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. J Am Coll Cardiol. 2007;49(8):863-871.
73. Ivan M, Kreisz F, Merlin T, et al. Multi-slice computed tomography coronary angiography in the visualization of coronary arteries. Assessment Report. MSAC Application 1105. Canberra, ACT: MSAC; November 2007.
74. Mowatt G, Cummins E, Waugh N, et al. Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. Health Technol Assess. 2008;12(17):1-164.
75. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA. 2007;298(3):317-323.
76. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008;358(13):1336-1345.
77. Mowatt G, Cook JA, Hillis GS, et al. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: Systematic review and metaanalysis. Heart. 2008;94(11):1386-1393.
78. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by

64-row CT. N Engl J Med. 2008;359(22):2324-2336.
79. Baig SZ, Coats WC, Aggarwal KB, Alpert MA. Assessing cardiovascular disease in the dialysis patient. Adv Perit Dial. 2009;25:147-154.
80. U.S. Preventive Services Task Force (USPSTF). Using nontraditional risk factors in coronary heart disease risk assessment. Recommendations of the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); October 2009.
81. Machaalany J, Yam Y, Ruddy TD, et al. Potential clinical and economic consequences of noncardiac incidental findings on cardiac computed tomography. J Am Coll Cardiol. 2009;54(16):1533-1541.
82. American College of Cardiology Foundation Task Force on Expert Consensus Documents, Mark DB, Berman DS, Budoff MJ, et al. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. Circulation. 2010;121(22):2509-2543.
83. Ma ES, Yang ZG, Li Y, et al. Correlation of calcium measurement with low dose 64-slice CT and angiographic stenosis in patients with suspected coronary artery disease. Int J Cardiol. 2010;140(2):249-252.
84. Cademartiri F, Maffei E, Palumbo A, et al. Coronary calcium score and computed tomography coronary angiography in high-risk asymptomatic subjects: Assessment of diagnostic accuracy and prevalence of non-obstructive coronary artery disease. Eur Radiol. 2010;20(4):846-854.
85. Hadamitzky M, Distler R, Meyer T, et al. Prognostic value of coronary computed tomographic angiography in comparison with calcium scoring and clinical risk scores. Circ Cardiovasc Imaging. 2011;4(1):16-23.
86. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Coronary computed tomographic angiography in the evaluation of patients with acute chest pain. TEC Assessment Program. Chicago, IL: BCBSA; November 2011;26(9).
87. Alsheikh-Ali AA, Kitsios GD, Balk EM, et al. The vulnerable atherosclerotic plaque: Scope of the literature. Ann Intern Med. 2010;153(6):387-395.
88. von Ballmoos MW, Haring B, Juillerat P, Alkadhi H. Meta-analysis: Diagnostic performance of low-radiation-dose coronary computed tomography angiography. Ann Intern Med. 2011;154(6):413-420.
89. Arbab-Zadeh A, Miller JM, Rochitte CE, et al. Diagnostic accuracy of computed tomography coronary angiography according to pre-test probability of coronary artery disease and severity of coronary arterial calcification the CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) international multicenter study. J Am Coll Cardiol. 2012;59(4):379-387.
90. Nissen SE. Coronary computed tomography angiography: The challenge of coronary calcium. J Am Coll Cardiol. 2012;59(4):388-389.
91. Kavousi M, Elias-Smale S, Rutten JH, et al. Evaluation of newer risk markers for coronary heart disease risk classification: A cohort study. Ann Intern Med. 2012;156(6):438-444.
92. Cho I, Chang HJ, Sung JM, et al; CONFIRM Investigators. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the CONFIRM Registry (coronary CT angiography evaluation for clinical outcomes: An international multicenter registry). Circulation. 2012;126(3):304-313.
93. Woodard PK, White RD, Abbara S, et al; Expert Panel on Cardiac Imaging. ACR

Appropriateness Criteria chronic chest pain - low to intermediate probability of coronary artery disease [online publication]. Reston, VA: American College of Radiology (ACR); 2012.
94. Gorenoi V, Schönermark MP, Hagen A. CT coronary angiography vs. invasive coronary angiography in CHD. GMS Health Technol Assess. 2012;8:Doc02.
95. Liew GY, Feneley MP, Worthley SG. Appropriate indications for computed tomography coronary angiography. Med J Aust. 2012;196(4):246-249.
96. Greenland P, Alpert JS, Beller GA, et al.; American College of Cardiology Foundation, American Heart Association. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010;56(25):e50-e103.
97. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the assessment of cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;63(25 Pt B):2935-2959.
98. Peters SA, den Ruijter HM, Bots ML, Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: A systematic review. Heart. 2012;98:177-184.
99. Kherada N, Mehran R. Pursuit of perfection: Three-dimensional CT angiographic “objective quantification” of aortic valve structures for transcatheter aortic valve implantation. Cathet Cardiovasc Intervent. 2013;81:160–161.
100. Westwood M, Al M, Burgers L, et al. A systematic review and economic evaluation of newgeneration
computed tomography scanners for imaging in coronary artery disease and congenital heart disease: Somatom Definition Flash, Aquilion ONE, Brilliance iCT and Discovery CT750 HD. Health Technol Assess. 2013;17(9):1-243.
101. Kim KJ, Choi SI, Lee MS, et al. The prevalence and characteristics of coronary atherosclerosis in asymptomatic subjects classified as low risk based on traditional risk stratification algorithm: Assessment with coronary CT angiography. Heart. 2013;99(15):1113-1117.
102. Dorr R, Kadalie CT, Franke WG, Gutberlet M. Hybrid imaging in diagnostics and therapy of chronic myocardial ischemia. Clinical value. Herz. 2013;38(4):367-375.
103. Kang EJ, Kim SM, Choe YH, et al. Takayasu arteritis: Assessment of coronary arterial abnormalities with 128-section dual-source CT angiography of the coronary arteries and aorta. Radiology. 2014;270(1):74-81.
104. Criqui MH, Denenberg JO, Ix JH, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA. 2014;311(3):271-278.
105. Jiang B, Wang J, Lv X, Cai W. Dual-source CT versus single-source 64-section CT angiography for coronary artery disease: A meta-analysis. Clin Radiol. 2014;69(8):861-869.
106. Dedic A, Lubbers MM, Schaap J, et al. Coronary CT angiography for suspected ACS in the era of high-sensitivity troponins: Randomized multicenter study. J Am Coll Cardiol. 2016;67(1):16-26.
107. Knapper JT, Khosa F, Blaha MJ, et al. Coronary calcium scoring for long-term mortality prediction in patients with and without a family history of coronary disease. Heart. 2016;102(3):204-208.
108. National Institute for Health and Care Excellence (NICE). HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography. Medical Technology Consultation

Document. London, UK: NICE; July 2016.
109. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Fractional flow reserve and coronary artery revascularization. TEC Assessment Program. Chicago, IL: BCBSA; July 2011;26(2).
110. van den Hoogen IJ, de Graaf MA, Roos CJ, et al. Prognostic value of coronary computed tomography angiography in diabetic patients without chest pain syndrome. J Nucl Cardiol. 2016;23(1):24-36.
111. Cantoni V, Green R, Acampa W, et al. Long-term prognostic value of stress myocardial perfusion imaging and coronary computed tomography angiography: A meta-analysis. J Nucl Cardiol. 2016;23(2):185-197.
112. Wu W, Pan DR, Foin N, et al. Noninvasive fractional flow reserve derived from coronary computed tomography angiography for identification of ischemic lesions: A systematic review and meta-analysis. Sci Rep. 2016;6:29409
113. Baumann S, Renker M, Hetjens S, et al. Comparison of coronary computed tomography angiography-derived vs invasive fractional flow reserve assessment: Meta-analysis with subgroup evaluation of intermediate stenosis. Acad Radiol. 2016;23(11):1402-1411.
114. Opolski MP, Staruch AD, Jakubczyk M, et al. CT angiography for the detection of coronary artery stenoses in patients referred for cardiac valve surgery: Systematic review and metaanalysis. JACC Cardiovasc Imaging. 2016;9(9):1059-1070.
115. Curzen NP, Nolan J, Zaman AG, et al. Does the routine availability of CT-derived FFR influence management of patients with stable chest pain compared to CT angiography alone?: The FFR(CT) RIPCORD Study. JACC Cardiovasc Imaging. 2016;9(10):1188-1194.
116. Douglas PS, De Bruyne B, Pontone G, et al.; PLATFORM Investigators. 1-year outcomes of FFRCT-guided care in patients with suspected coronary disease: The PLATFORM Study. J Am Coll Cardiol. 2016;68(5):435-445.
117. Nørgaard BL, Hjort J, Gaur S, et al. Clinical use of coronary CTA-derived FFR for decisionmaking in stable CAD. JACC Cardiovasc Imaging. 2017;10(5):541-550.
118. Douglas PS, Pontone G, Hlatky MA, et al.; PLATFORM Investigators.. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: The prospective longitudinal trial of FFR(CT): Outcome and resource impacts study. Eur Heart J. 2015;36(47):3359-3367.
119. Hlatky MA, De Bruyne B, Pontone G, et al.; PLATFORM Investigators.. Quality-of-life and economic outcomes of assessing fractional flow reserve with computed tomography angiography: PLATFORM. J Am Coll Cardiol. 2015;66(21):2315-2323.
120. Leipsic J, Yang TH, Thompson A, et al. CT angiography (CTA) and diagnostic performance of noninvasive fractional flow reserve: Results from the Determination of Fractional Flow Reserve by Anatomic CTA (DeFACTO) study. AJR Am J Roentgenol. 2014;202(5):989-994.
121. Nørgaard BL, Leipsic J, Gaur S, et al; NXT Trial Study Group. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: The NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol. 2014;63(12):1145-1155.
122. Min JK, Koo BK, Erglis A, et al. Effect of image quality on diagnostic accuracy of noninvasive fractional flow reserve: Results from the prospective multicenter international DISCOVER-FLOW study. J Cardiovasc Comput Tomogr. 2012;6(3):191-199.

123. National Institute for Health and Care Excellence (NICE). HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography. Medical Technology Guidance 32. London, UK: NICE; February 2017.
124. U.S. Food and Drug Administration (FDA). HeartFlow FFRCT Coronary Physiologic Simulation Software Device. 510(k) Summary. 510(k) No. K161772. Silver Spring, MD: FDA; August 24, 2016.
125. Messenger JC, Moussa ID, Masoudi FA. Upcoming changes and rationale in the NCDR CathPCI data requirements. Expert Analysis. Washington, DC: American College of Cardiology; January 23, 2017.
126. Chen MY, Shanbhag SM, Arai AE. Submillisievert median radiation dose for coronary angiography with a second-generation 320–detector row CT scanner in 107 consecutive patients. Radiology. 2013;267(1):76-85.
127. Foy AJ, Dhruva SS, Peterson B, et al. Coronary computed tomography angiography vs functional stress testing for patients with suspected coronary artery disease: A systematic review and meta-analysis. JAMA Intern Med. 2017;177(11):1623-1631.
128. Tan XW, Zheng Q, Shi L, et al. Combined diagnostic performance of coronary computed tomography angiography and computed tomography derived fractional flow reserve for the evaluation of myocardial ischemia: A meta-analysis. Int J Cardiol. 2017;236:100-106.
129. Kishi S, Giannopoulos AA, Tang A, et al. Fractional flow reserve estimated at coronary CT angiography in intermediate lesions: Comparison of diagnostic accuracy of different methods to determine coronary flow distribution. Radiology. 2018;287(1):76-84.
130. Abbara S, Blanke P, Maroules CD, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: A report of the society of Cardiovascular Computed Tomography Guidelines Committee: Endorsed by the North American Society for Cardiovascular Imaging (NASCI). J Cardiovasc Comput Tomogr. 2016;10(6):435-449.
131. Fihn SD, Gardin JM, Abrams J, et al.; American College of Cardiology Foundation.; American Heart Association Task Force on Practice Guidelines.; American College of Physicians.; American Association for Thoracic Surgery.; Preventive Cardiovascular Nurses Association.; Society for Cardiovascular Angiography and Interventions.; Society of Thoracic Surgeons.. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012;60(24):e44-e164.
132. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014;64(18):1929-49.
133. Hoffmann U, Ferencik M, Udelson JE, et al; PROMISE Investigators.. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: Insights from the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain).

Circulation. 2017;135(24):2320-2332.
134. Jørgensen ME, Andersson C, Nørgaard BL, et al. Functional testing or coronary computed tomography angiography in patients with stable coronary artery disease. J Am Coll Cardiol. 2017;69(14):1761-1770.
135. Marwick TH, Cho I, Ó Hartaigh B, et al. Finding the gatekeeper to the cardiac catheterization laboratory: coronary CT angiography or stress testing? J Am Coll Cardiol. 2015;65(25):2747-56.
136. Williams MC, Hunter A, Shah ASV, et al.; SCOT-HEART Investigators.. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. J Am Coll Cardiol. 2016;67(15):1759-1768.
137. Williams MC, Moss A, Nicol E, et al. Cardiac CT improves outcomes in stable coronary heart disease: Results of recent clinical trials. Current Cardiovascular Imaging Reports. 2017;10(5):14.
138. Lin EC. Coronary CT angiography. Medscape. 2017. Available at: https://emedicine.medscape.com/article/1603072-overview#showall. Accessed May 15, 2018.
139. Maurya VK, Ravikumar R, Sharma P, et al. Coronary CT angiography: A retrospective study of 220 cases. Medical Journal, Armed Forces India. 2016;72(4):377-383.
140. Ramjattan NA, Makaryus AN. Coronary CT angiography. 2017. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-. Available From http://www.ncbi.nlm.nih.gov/books/NBK470279/. Accessed May 16, 2018.
141. HeartFlow, Inc. HeartFlow announces its novel, non-invasive FFRct technology for coronary artery disease receives positive review from Blue Cross Blue Shield. Business Wire. Redwood, CA. June 2017. Available at: https://www.businesswire.com/news/home/20170612005544/en/HeartFlow-Announces-Non-Invasive-FFRct-Technology-Coronary-Artery. Accessed May 15, 2018.
142. Bluemke DA, Achenbach S, Budoff M, et al. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography: A scientific statement from the american heart association committee on cardiovascular imaging and intervention of the council on cardiovascular radiology and intervention, and the councils on clinical cardiology and cardiovascular disease in the young. Circulation. 2008;118(5):586-606.
143. Ollendorf DA, Kuba M, Pearson SD. The diagnostic performance of multi-slice coronary computed tomographic angiography: A systematic review. Journal of General Internal Medicine. 2011;26(3):307-316.
144. Lin FY, Shaw LJ, Dunning AM, et al. Mortality risk in symptomatic patients with nonobstructive coronary artery disease: a prospective 2-center study of 2,583 patients undergoing 64-detector row coronary computed tomographic angiography. J Am Coll Cardiol. 2011;58(5):510-9.
145. SCOT-HEART investigators.. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): An open-label, parallel-group, multicentre trial. Lancet. 2015;385(9985):2383-91.
146. Hulten E, Bittencourt MS, Singh A, et al. Coronary artery disease detected by coronary computed tomographic angiography is associated with intensification of preventive medical therapy and lower low-density lipoprotein cholesterol. Circ Cardiovasc Imaging. 2014;7(4):629-38.
147. Hulten EA. Does FFRct have proven utility as a gatekeeper prior to invasive angiography? J. Nucl. Cardiol. 2017;24(5):1619-25.

148. Blaha MJ, Cainzos-Achirica M, Greenland P, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: The Multi-Ethnic Study Of Atherosclerosis (MESA). Circulation. 2016;133(9):849-858.
149. Bell DJ, Wichmann JL, et al. Cardiac CT. Radiopaedia. Available at: https://radiopaedia.org/articles/cardiac-ct-1. Accessed May 18, 2018.
150. Soman P, Truong QA, Udelson JE. Noninvasive testing and imaging for diagnosis in patients at low to intermediate risk for acute coronary syndrome. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed July 2017.
151. Yang L, Xu L, Schoepf UJ, et al. Prospectively ECG-triggered sequential dual-source coronary CT angiography in patients with atrial fibrillation: Influence of heart rate on image quality and evaluation of diagnostic accuracy. Zhang H, ed. PLoS ONE. 2015;10(7):e0134194.
152. Prazeres CEED, Magalhães TA, de Castro Carneiro AC, et al. Image quality and radiation exposure comparison of a double high-pitch acquisition for coronary computed tomography angiography versus standard retrospective spiral acquisition in patients with atrial fibrillation. J Comput Assist Tomogr. 2018;42(1):45-53.
153. Mangold S, Wichmann JL, Schoepf UJ, et al. Coronary CT angiography in obese patients using 3(rd) generation dual-source CT: effect of body mass index on image quality. Eur Radiol. 2016;26(9):2937-46.
154. Chinnaiyan KM, McCullough PA, Flohr TG, et al. Improved noninvasive coronary angiography in morbidly obese patients with dual-source computed tomography. J Cardiovasc Comput Tomogr. 2009;3(1):35-42.
155. Taylor AJ, Cerqueira M, Hodgson JM, et al.; American College of Cardiology Foundation Appropriate Use Criteria Task Force.; Society of Cardiovascular Computed Tomography.; American College of Radiology.; American Heart Association.; American Society of Echocardiography; American Society of Nuclear Cardiology.; North American Society for Cardiovascular Imaging.; Society for Cardiovascular Angiography and Interventions.; Society for Cardiovascular Magnetic Resonance.. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Cardiovasc Comput Tomogr. 2010;4(6):407.e1-e33.
156. Muhlestein JB, Moreno FL. Coronary computed tomography angiography for screening in patients with diabetes: Can enhanced detection of subclinical coronary atherosclerosis improve outcome? Curr Atheroscler Rep. 2016;18(11):64.
157. Guaricci AI, De Santis D, Carbone M, et al. Coronary atherosclerosis assessment by coronary CT angiography in asymptomatic diabetic population: A critical systematic review of the literature and future perspectives. Biomed Res Int. 2018;2018:8927281.
158. Lee CH, Lee SW, Park SW. Diabetes and subclinical coronary atherosclerosis. Diabetes Metab J. 2018;42(5):355-363.
159. Bax JJ, Wackers FJT, Delgado V. Screening for coronary heart disease in patients with diabetes mellitus. UpToDate Inc., Waltham, MA. Last reviewed November 2018.
160. National Institute for Health and Clinical Excellence (NICE) . Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected

cardiac origin (update). Clinical Guideline 95. London, UK: NICE; 2016.
161. Douglas PS, Hoffman U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015;372:1291-1300.

BCBS of NC Corporate Medical Policy (2018)

1. Jensen JM1, Bøtker HE1, Mathiassen ON1, Grove EL1, et al. Computed tomography derived fractional flow reserve testing in stable patients with typical angina pectoris: influence on downstream rate of invasive coronary angiography. Eur Heart J Cardiovasc Imaging. 2017 Apr 20. doi: 10.1093/ehjci/jex068
2. SCOT-HEART Investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet (London, England). 2015;385(9985):2383-91.
3. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol. 2008;52(21):1724-32.
4. Chinnaiyan KM, Peyser P, Goraya T, et al. Impact of a continuous quality improvement initiative on appropriate use of coronary computed tomography angiography. Results from a multicenter, statewide registry, the Advanced Cardiovascular Imaging Consortium. J Am Coll Cardiol. 2012;60(13):1185-91.
5. Chinnaiyan KM, Raff GL, Goraya T, et al. Coronary computed tomography angiography after stress testing: results from a multicenter, statewide registry, ACIC (Advanced Cardiovascular Imaging Consortium). J Am Coll Cardiol. 2012;59(7):688-95.
6. Dewey M, Rief M, Martus P, et al. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. BMJ (Clinical research ed). 2016;355:i5441.
7. Douglas PS, De Bruyne B, Pontone G, et al. 1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: The PLATFORM Study. J Am Coll Cardiol. 2016;68(5):435-45.
8. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015;372(14):1291-300.
9. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. European heart journal. 2015;36(47):3359-67.
10. Halpern EJ, Fischman D, Savage MP, et al. Decision analytic model for evaluation of suspected coronary disease with stress testing and coronary CT angiography. Academic radiology. 2010;17(5):577-86.
11. Hamilton-Craig C, Fifoot A, Hansen M, et al. Diagnostic performance and cost of CT angiography versus stress ECG--a randomized prospective study of suspected acute coronary syndrome chest pain in the emergency department (CT-COMPARE). International journal of cardiology. 2014;177(3):867-73.
12. Hlatky MA, De Bruyne B, Pontone G, et al. Quality-of-Life and Economic Outcomes of Assessing Fractional Flow Reserve With Computed Tomography Angiography: PLATFORM. J Am Coll Cardiol. 2015;66(21):2315-23.
13. Hoffmann U, Ferencik M, Udelson JE, et al. Prognostic Value of Noninvasive Cardiovascular Testing in Patients With Stable Chest Pain: Insights From the PROMISE Trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation. 2017;135(24):2320-32.
14. Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med. 2012;367(4):299-308.

15. Jorgensen ME, Andersson C, Norgaard BL, et al. Functional Testing or Coronary Computed Tomography Angiography in Patients With Stable Coronary Artery Disease. J Am Coll Cardiol. 2017;69(14):1761-70.
16. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol. 2011;58(19):1989-97.
17. Levin DC, Parker L, Halpern EJ, et al. The lack of growth in use of coronary CT angiography: is it being appropriately used? AJR American journal of roentgenology. 2011;196(4):862-7.
18. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med. 2012;366(15):1393-403.
19. Lubbers M, Dedic A, Coenen A, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. European heart journal. 2016;37(15):1232-43.
20. McEvoy JW, Blaha MJ, Nasir K, et al. Impact of coronary computed tomographic angiography results on patient and physician behavior in a low-risk population. Archives of internal medicine. 2011;171(14):1260-8.
21. McKavanagh P, Lusk L, Ball PA, et al. A comparison of cardiac computerized tomography and exercise stress electrocardiogram test for the investigation of stable chest pain: the clinical results of the CAPP randomized prospective trial. European heart journal cardiovascular Imaging. 2015;16(4):441-8.
22. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol. 2008;52(25):2135-44.
23. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med. 2008;359(22):2324-36.
24. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. Jama. 2012;308(12):1237-45.
25. Nakazato R, Park HB, Berman DS, et al. Noninvasive fractional flow reserve derived from computed tomography angiography for coronary lesions of intermediate stenosis severity: results from the DeFACTO study. Circulation Cardiovascular imaging. 2013;6(6):881-9.
26. Nielsen LH, Ortner N, Norgaard BL, et al. The diagnostic accuracy and outcomes after coronary computed tomography angiography vs. conventional functional testing in patients with stable angina pectoris: a systematic review and meta-analysis. European heart journal cardiovascular Imaging. 2014;15(9):961-71.
27. Norgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol. 2014;63(12):1145-55.
28. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med. 2010;362(10):886-95.
29. Rajani R, Webb J, Marciniak A, et al. Comparative efficacy testing - fractional flow reserve by coronary computed tomography for the evaluation of patients with stable chest pain. International journal of cardiology. 2015;183:173-7.
30. Rogers IS, Banerji D, Siegel EL, et al. Usefulness of comprehensive cardiothoracic computed tomography in the evaluation of acute undifferentiated chest discomfort in the emergency department (CAPTURE). The American journal of cardiology. 2011;107(5):643-50.

31. Roifman I, Wijeysundera HC, Austin PC, et al. Comparison of Anatomic and Clinical Outcomes in Patients Undergoing Alternative Initial Noninvasive Testing Strategies for the Diagnosis of Stable Coronary Artery Disease. Journal of the American Heart Association. 2017;6(7).
32. Ropers D, Moshage W, Daniel WG, et al. Visualization of coronary artery anomalies and their anatomic course by contrast-enhanced electron beam tomography and three-dimensional reconstruction. The American journal of cardiology. 2001;87(2):193-7.
33. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. Jama. 2011;306(19):2128-36.
34. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-24.
35. Williams MC, Hunter A, Shah ASV, et al. Use of Coronary Computed Tomographic Angiography to Guide Management of Patients With Coronary Disease. J Am Coll Cardiol. 2016;67(15):1759-68.
36. ECRI Institute. FFRct Software (HeartFlow, Inc.) for Evaluating Coronary Artery Disease. In: Service. HTAI, editor.: ECRI Institute.; 2017. p.
37. National Institute for Health and Care Excellence (NICE). HeartFlow FFRct for estimating fractional flow reserve from coronary CT angiography MTG32. Medical technology consultation document. London: Royal College of Physicians (UK); National Clinical Guideline Centre.; 2017. p. 28.
38. Graham TP, Jr., Driscoll DJ, Gersony WM, et al. Task Force 2: congenital heart disease. J Am Coll Cardiol. 2005;45(8):1326-33.
39. Grani C, Buechel RR, Kaufmann PA, et al. Multimodality Imaging in Individuals With Anomalous Coronary Arteries. JACC Cardiovascular imaging. 2017;10(4):471-81.
40. Mark DB, Berman DS, Budoff MJ, et al. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. Catheterization & Cardiovascular Interventions. 2010;76(2):E1-42.
41. Nagaraja V, Mamas M, Mahmoudi M, et al. Change in angiogram-derived management strategy of patients with chest pain when some FFR data are available: How consistent is the effect? Cardiovascular revascularization medicine : including molecular interventions. 2017;18(5):320-7.
42. Nakanishi R, Budoff MJ. Noninvasive FFR derived from coronary CT angiography in the management of coronary artery disease: technology and clinical update. Vascular health and risk management. 2016;12:269-78.
43. Marwick TH, Cho I, B OH, et al. Finding the Gatekeeper to the Cardiac Catheterization Laboratory: Coronary CT Angiography or Stress Testing? J Am Coll Cardiol. 2015;65(25):2747-56.
44. Taylor A, ACCF/SCCT/ACR/AHA/ASE/ASNC/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. J Am Coll Cardiol, 2010; 56:1864-1894.
45. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. Dec 18 2012;60(24):e44-e164. PMID 23182125
46. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. Oct 1 2014;35(37):2541-2619. PMID 25173339
47. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for coronary revascularization in patients with stable ischemic heart disease: a report of the

American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. J Am Coll Cardiol. May 02 2017;69(17):2212-2241. PMID 28291663

Cigna (2020)

1. Hendel RC, Kramer CM, Patel MR, Poon M. ACCF/ACR/SCCT/SCMR/ASNC/ NASCI/SCAI/SIR 2006 Appropriateness Criteria for computed tomography and cardiac magnetic resonance imaging. *J Am CollCardiol. 2006*;48(7):1475-1497.
2. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/ NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Am CollCardiol.* 2010;56:1864-1894.
3. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol*. 2007;49:378.
4. Andreini D, Pontone G, Pepi M, et al. Diagnostic accuracy of multidetector computed tomography coronary angiography in patients with dilated cardiomyopathy. *J Am CollCardiol*. 2007 May;49:2044-2050.
5. Berbarie RF, Dockery WD, Johnson KB, et al. Use of multislice computed tomographic coronary angiography for the diagnosis of anomalous coronary arteries. *Am J Cardiol*. 2006;98:402-406.
6. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: Scientific Statement From the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology .*Circulation.* 2006;114:1761-1791.
7. Einstein A, Henzlova M, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. *JAMA.* 2007;298:317-323.
8. Schlosser T, Konorza T, Hunold P, et al. Noninvasive visualization of coronary artery bypass grafts using 16-detector row computed tomography. *J Am CollCardiol*. 2004;44:1224-1229.
9. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/ NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *Journal of the American College of Cardiology.* 2010;56:1864-1894.
10. Douglas PS, DeBruyne B, Pontone G, Patel MR, et al. 1-year outcomes of FFRct-guided care in patients with suspected coronary disease: The PLATFORM Study. *Journal of the American College of Cardiology.* 2016;68:435-45.
11. Norgaard B, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve

derived from coronary computed tomography angiography in suspected coronary artery disease. *Journal of the American College of Cardiology*. 2014;63:1145-55.
12. Ko BS, Cameron JD, Munnur RK, Wong DTL, et al. Cardiac CT: atherosclerosis to acute coronary syndrome. *Journal of the American College of Cardiology*. December 2016;4(6).
13. Holmes D Jr, Mack M, Kaul S, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. *Journal of the American College of Cardiology*. 2012;59:1200.
14. NICE Guidelines. Heart Flow FFRCT for estimating factional flow reserve from coronary CT angiography Medical Technologies Evaluation Programme: Process guide. National Institute for Health and Clinical Excellence, 2011. February 2017. https://www.nice.org.uk/guidance/mtg32.
15. American College of Cardiology Foundation Task Force on Expert Consensus Documents, Mark DB, Berman DS, et al. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Journal of the American College of Cardiology.* 2010;55:2663.
16. Doherty JU, Kort S, Mehran R, Schoenhagen P, Soman P. ACC/AATS/AHA/ASE/ASNC/HRS/SCAI/SCCT/SCMR/STS 2017 Appropriate Use Criteria for Multimodality Imaging in Valvular Heart Disease. Journal of Nuclear Cardiology. 2017;24(6):2043-2063. doi:10.1007/s12350-017-1070-1.
17. American College of Cardiology (ACC)/American Association for Thoracic Surgery (AATS)American Heart Association (AHA)/American Society of Echocardiography (ASE)/ American Society of Nuclear Cardiology (ASNC)/Heart Rhythm Society (HRS)/Society for Cardiovascular Angiography and Interventions (SCAI)/Society of Cardiovascular Computed Tomography (SCCT)/Society for Cardiovascular Magnetic Resonance (SCMR)/Society of Thoracic Surgeons (STS): Appropriate use criteria for multimodality imaging in valvular heart disease (2017).
18. The Medicare Learning Network®. MEDICARE PREVENTIVE SERVICES. Preventive Services Chart | Medicare Learning Network® | ICN MLN006559. https://www.cms.gov/Medicare/Prevention/PrevntionGenInfo/medicare-preventive-services/MPSQuickReferenceChart-1.html#CARDIO_DIS. Published June 2019. ICN MLN006559 June 2019.
19. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25). doi:10.1161/cir.0000000000000625.
20. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *Circulation*. 2019;140(11):e596-e646. doi:10.1161/cir.0000000000000678.

National Government Services, Inc. (2016)

1. Achenbach S, Giesler T, Ropers D, et al. Detection of coronary artery stenoses by contrast-enhanced, retrospectively electrocardiographically-gated, multislice spiral computed tomograhy. Circulation Journal [serial on line]. May 2001.
2. ACR practice guideline for the performance of computed tomography (CT) for the detection of pulmonary embolism in adults. ACR Practice Guideline CT Pulmonary Embolism.2000; 8:189-192. Revised 2005;27. Effective 10/01/2005.
3. ACR practice guideline for the performance and interpretation of CT Angiography (CTA). ACR Practice Guideline CT Angiography. 2005; 30:271-274. Amended 2006;17,35. Effective 10/01/05.

4. Budoff MJ, Achenbach S, Duerinckx A, et al. Clinical utility of computed tomography and magnetic resonance techniques for noninvasive coronary angiography. The American Journal of Cardiology [serial online]. November 2003;42.
5. Budoff MJ, Achenbach S, Blumenthal, J, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on cardiovascular imaging and intervention, council on cardiovascular radiology and intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation. October 2006;114;1761-1791.
6. Budoff MJ, Cohen MC, Garcia MJ, et al. ACCF/AHA clinical competence statement on cardiac imaging with computed tomography and magnetic resonance: a report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on clinica competence and training (ACC/AHA Committee on CV Tomography). J Am Coll Cardiol. 2005;46:388–402.
7. Chiles C, Carr JJ. Vascular diseases of the thorax: evaluation with multidetector CT. Radiologic Clinics of North America [serial on line]. May 2005;43;3.
8. de Feyter PJ, van Pelt N. Spiral computed tomography coronary angiography: a new diagnostic tool developing its role in clinical cardiology, editorial. Journal of the American College of Cardiology. 2007;49;872-874.
9. Ehara M, Kawai M, Surmely JF, et al. Diagnostic accuracy of coronary in-stent restenosis using 64-slice computed tomography. Journal of the American College of Cardiology. 2007;49:951-959. 10. Gaspar T, Halon DA, Lewis BS, et al. Diagnosis of coronary in-stent restenosis with multidetector row spiral computed tomography. Journal of the American College of Cardiology. 2005;46:1573-1579.
11. Goldstein JA, Gallagher MJ, O'Neill WW, et al. A randomized controlled trial of multislice coronary computed tomography for evaluation of acute chest pain. Journal of the American College of Cardiology. 2007;49:863-871.
12. Hausleiter J, Meyer T, Hadmitzky M, et al. Prevalence of noncalcified plaques by 64-slice computed tomography in patients with an immediate risk for significant coronary artery disease. Journal of the American College of Cardiology. 2006;48:312-318.
13. Hendel RC, Patel MR, Kramer CM, et al. ACCF/ACR/SCMR/ASNC/NASCI/SCAI/SIR Appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging. Journal of the American College of Cardiology. 2006;48:1475-1497.
14. Hoffman U, Moselewski F, Cury RC, et al. Predictive value of 16-slice multidetector spiral computed tomography to detect significant obstructive coronary disease in patients at high risk for coronary artery disease. Patient- Versus Segment-Based Analysis. Circulation. 2004;110:2638-2643.
15. Jongbloed MRM, Lamb HJ, Bax JJ, et al. Noninvasive visualization of the cardiac venous system using multislice computed tomography. Journal of the American College of Cardiology. 2005;45:749-753.
16. Kopp AF, Schroeder S, Kuettner A, et al. Non-invasive coronary angiography with high resolution multidetector-row computed tomography. The European Society of Cardiology. Elsevier Science Ltd. European Heart Journal. 2002;23:1714-1725.
17. Kuettner A, Beck T, Drosch T, et al. Diagnostic accuracy of noninvasive coronary imaging using 16-detector slice spiral computed tomography with 188ms temporal resolution. Journal of the American College of Cardiology. 2005;45:123-127.
18. Lardo AC, Cordeiro MA, Silva C, et al. Contrast-enhanced multidetector computed tomography viability imaging after myocardial infarction. Characterization of myocyte death, microvascular obstruction, and chronic scar. Circulation. 2006;113:394-404.
19. Lawler LP, Fishman EK. Multi-detector row CT of thoracic disease with emphasis on 3D volume rendering and CT angiography. RadioGraphics. 2001;21:1257-1273.

20. Leber AW, Kenz A, von Ziegler F, et al. Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography. Journal of the American College of Cardiology. 2005;46:147-154.
21. Lewis B, Halon D. Integrating multidetector computed tomography into clinical practice. Editorial. Journal of the American College of Cardiology. 2007;49:960-962.
22. Matchar DB, Mark DB, Patel MR, et al. Technology assessment: non-invasive imaging for coronary artery disease. *AHRQ Technology Assessment Program*. October 3, 2006.
23. Meyer TS, Martinoff S, Hadamitzky M, et al. Improved noninvasive assessment of coronary artery bypass grafts with 64-slice computed tomographic angiography in an unselected patient population. *Journal of the American College of Cardiology*. 2007;49:946-950.
24. Mollet NR, Cademartiri F, van Mieghem CA, et al. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic convential coronary angiography. *Circulation*. 2005;112:2318-2323.
25. Mollet NR, Cademartiri F, Krestin GP, et al. Improved diagnostic accuracy with 16-row multi-slice computed tomography coronary angiography. *Journal of the American College of Cardiology*. 2005;45:128-132.
26. Narevic E, Schoenbert NE. Lay explanations for Kentucky's "Coronary Valley". *J Community Health*. 2002 Feb;27(1):53-62.
27. Moussa I, Jones M, Kereiakes DJ, et al. Stone Cardiovascular Research Foundation, Lenox Hill Heart & Vascular Institute of New York. Does culprit lesion calcification affect the performance of the Paclitaxel-Eluting Stent? A TAXUS-IV Substudy. *Am J Cardiol*. 2004;94(suppl 6A):66E.
28. Pijls NH, van Schaardenburgh P. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *Am J Cardiol*. 2007;49(21):2105-11.
29. Raff GL, Gallagher MJ, O'Neill WW, et al. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. *Journal of the American College of Cardiology*. 2005;46:552-557.
30. Raman SV, Shah M, McCarthy B, et al. Multi-detector row cardiac computed tomography accurately quantifies right and left ventricular size and function compared with cardiac magnetic resonance. *American Heart Journal*. 2006;151;3:736-744.
31. Redberg RF. Evidence, appropriateness, and technology assessment in cardiology: A case study of computed tomography. *Health Affairs*. 2007;27;86-95. 10.1377/hlthaff.26.1.86.
32. Romeo G, Houyel L, Angel CY, et al. Coronary stenosis detection by 16-slice computed tomography in heart transplant patients. *Journal of the American College of Cardiology* 2005;45:1826-1831.
33. Ropers D, Baum U, Pohle K, et al. Detection of coronary artery stenoses with thin-slice multi-detector row spiral computed tomography and multiplanar reconstruction. *Circulation Journal* [serial on line]. February 2003.
34. Ropers D, Rixe J. Usefulness of multidetector row spiral computed tomography with 64- x 0.6-mm collimation and 330-ms rotation for the noninvasive detection of significant coronary artery stenoses. *Am J Cardiol*. 2006 Feb 1;97(3):343-8.
35. Rubinshtein R, Halon D, Gaspar T, et al. Usefulness of 64-slice cardiac computed tomographic angiography for diagnosing acute coronary syndromes and predicting clinical outcome in emergency department patients with chest pain of uncertain origin. *Circulation*. 2007;115;1762-1768.
36. Sato U, Matsumoto N, Kato M, et al. Noninvasive assessment of coronary artery disease by multislice spiral computed tomography using a new retrospectively ECG-gated image reconstruction technique – comparison with angiopgraphic results. *Circulation Journal,* [serial on line]. May 2003;67.
37. Schindler TH, Magosaki N, Jeserich M, et al. 3D assessment of myocardial perfusion parameter combined with 3D reconstructed coronary artery tree from digital coronary angiograms. *International Journal of Cardiac Imaging*. 2000;16:1-12.

38. Schoepf UJ, Costello P. CT angiography for diagnosis of pulmonary embolism: state of the art. *Radiology*. [serial on line]. 1148/radiol.2302021489. 2004:329-337.
39. Schroeder S, Kopp AF, Baumbach A, et al. Non-invasive characterization of coronary lesion morphology by multislice computed tomography: a promising new technology for risk stratification of patient with coronary artery disease. @ http://heart.bmjjournals.com/cgi/contebt/full/85/5/576a
40. Schuijf JD, Pundziute G, Jukema JW, et al. Diagnostic accuracy of 64-slice multislice computed tomography in the noninvasive evaluation of significant coronary artery disease. *American Journal of Cardiology*. 2006;98:145-148.
41. Schuijf JD, Bax JJ, Salm LP, et al. Noninvasive coronary imaging and assessment of left ventricular function using 16-slice computed tomography. *American Journal of Cardiology*. 2005;95:571-574.
42. Shapiro M, Butler J. Analytic approaches to establish the diagnostic accuracy of coronary computed tomography angiography as a tool for clinical decision making. *Am J Cardiol*. 2007;Apr 15;99(8):1122-7.
43. Tobis J. A non-biased assessment of the usefulness of computed tomographic angiography. *Am J Cardiol*. 2007;Apr 15;99(8):1165.
44. Vliegenthart R, Oudkerk M, Hofman A, et al. Coronary calcification improves cardiovascular risk prediction in the elderly. *Circulation*. 2005;112:572-577.
45. White RD, Setser RM. Integrated approaches to evaluating coronary artery disease and ischemic heart disease. *The American Journal of Cardiology* [serial on line]. November 2002;90.

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1. Bruyne B. “Fractional Flow Reserve guided Percutaneous Coronary Interventions vs. medical therapy in stable Coronary Disease” NEJM 2012 367(11): 991-1001.
2. Min JK, Leipsic J et al. Diagnostic Accuracy of Fractional Flow Reserve from anatomic CT angiography. JAMA 2012; DOI: 10.100/12012.jama.11274.
3. Nakanishi, R, Matsumoto S. Diagnostic performance of Transluminal Attenuation Gradient by FFRct compared to invasive FFR: a subgroup analysis from the DISCOVER-FLOW and DeFACTO studies Int J Cardiovasc Imaging 2015 Aug; 31(6): 1251-9.
4. Norgaard BI, Leipsic J, Gaur S et al. Diagnostic performance of non-invasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial. J Am Coll Cardiology. 2014; 63(12): 1145-1155.
5. Lu MT, Ferencik M, Roberts, RS, et al Noninvasive FFR Derived From Coronary CT Angiography, Management and Outcomes in the Promise Trial. JACC Cardiovasc Imaging. 2017; 10(11): 1350-1358.
6. Douglas PS, Hoffman U, Patel MR, et al. Outcome of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015; 372(14):1291-1300.
7. Curzen BM, Nolan J et al. Does the Routine Availability of CT-Derived FFR Influence Management of Patients with Stable Chest Pain Compared to CT Angiography Alone: The FFRct Ripcord Study. JACC Cardiovasc Imaging. 2016 9(10) 1188-1195.
8. Douglas PS, De Bruyne B, Pontone G, et al. 1-Yr Outcomes of FFRct-Guided Care in Patients with Suspectd Coronary Disease: The PLATFORM study. J Am Coll Cardiol. 2016;681(5) 435-445.
9. Douglas P, Pontone G, Hlatsky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFRct, outcome and resource impacts study. Eur Heart J 2015;36(47): 3359-3367.
10. Fairbairn TA, Nieman K, Akasaka T, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry. Eur Heart J. 2018;39(41):3701-3711.

11. Norgaard BL, Terkelsen CJ, Mathiassen ON, et al. Coronary CT Angiographic and Flow Reserve Guided Management of Patients with Stable Ischemic Heart Disease. J Am Coll Cardiology. 2018;72(18): 2123-2134.

APPENDIX O. Supplemental summary tables

Appendix Table O1. Cumulative frequency of secondary outcomes in trials comparing stress echocardiography versus exercise ECG in stable patients with suspected CAD treated on an outpatient basis

Outcome	Author (year) Trial name	F/U	Echocardiography % (n/N)	Exercise ECG % (n/N)	Risk Ratio (95% CI)*
MACE†	Zacharias 2017, Gurunathan 2018	36 months	10.5% (20/191)	13.4% (26/194)	RR 0.78 (0.45 to 1.35)
	Sanfilippo 2005	Mean 28 months	7.8% (8/104)	7.4% (4/54)	RR 1.04 (0.33 to 3.29)
UA‡	Sanfilippo 2005	Mean 28 months	Overall: 1.3% (2/158)§		NA
MI or UA‡	Sanfilippo 2005	Mean 28 months	Overall: 2.5% (4/158)§		NA
Acceleration of chest pain syndrome**	Sanfilippo 2005	Mean 28 months	Overall: 9.5% (15/158)§		NA
Cardiology visit	Zacharias 2017, Gurunathan 2018	36 months	31 visits (n=191)	59 visits (n=194)	NA, p<0.01

CAD = coronary artery disease; CI = confidence interval; ECG = electrocardiogram; ETT = exercise treadmill testing; F/U = follow-up period; NA = not applicable; NC = not calculable; N = number; UA = unstable angina.
*Calculated unless otherwise indicated.
†Zacharias 2017/Gurunathan 2018: defined as death, nonfatal myocardial infarction, late revascularization (>6 months), and hospitalization for chest pain; Sanfilippo 2005: not defined, called “clinical events”.
‡Unstable angina defined as prolonged or accelerating chest pain with EKG changes but no enzyme rise diagnostic of infarction.
§Not reported by treatment arm.
**Did not fulfill criteria for myocardial infarction or unstable angina but resulted in frequent presentation to clinic and ED

Appendix Table O2. Cumulative frequency of secondary outcomes in trials comparing stress echocardiography versus exercise ECG in patients with suspected ACS presenting to the ED and in mixed populations with suspected or known CAD who are hospitalized

Outcome	Author (year) Trial name	F/U	Echocardiography % (n/N)	Exercise ECG % (n/N)	Risk Ratio (95% CI)*
MACE†	**Jeetley, 2006** (Suspected or known CAD [27% with IHD])	Mean 8.5 months	12.7% (18/142)	16.6% (25/151)	RR 0.77 (95% CI 0.44 to 1.34)
	Desideri, 2005 COSTAMI-II (Uncomplicated MI)	12 months	19.7% (26/132)	13.8% (18/130)	RR 1.42 (95% CI 0.82 to 2.47)
Death or MI	**Jeetley, 2006** (Suspected or known CAD [27% with IHD])	Mean 8.5 months	1.4% (2/142)	2.0% (3/151)	RR 0.71, 95% CI 0.12 to 4.18
ACS	**Nucifora 2009** ASSENCE trial (Suspected ACS)	2 months	3% (2/77)	7% (5/75)	RR 0.36 (95% CI0.07 to 1.94)
UA (requiring admission)	**Desideri, 2005** COSTAMI-II (Uncomplicated MI)	12 months	15.2% (20/132)	12.3% (16/130)	RR 1.23 (95% CI 0.67 to 2.27)
Medication changes	**Nucifora 2009** ASSENCE trial (Suspected ACS)	Prescribed at discharge			
Beta-blocker			21% (16/77)	23% (17/75)	RR 0.92 (95% CI 0.50 to 1.68)
Calcium channel blockers			21% (16/77)	19% (14/75)	RR 1.11 (95% CI 0.59 to 2.12)
Antiplatelet drugs			30% (23/77)	33% (25/75)	RR 0.90 (95% CI 0.56 to 1.43)
Nitrates			13% (10/77)	16% (12/75)	RR 0.81 (95% CI 0.37 to 1.76)
			Echocardiography Mean (SD)	**Exercise ECG Mean (SD)**	**Mean Difference (95% CI)***
Hospital length of stay	**Nucifora 2009** ASSENCE trial (suspected ACS)	Index visit	mean 40 (42) hours	mean 39 (35) hours	MD 1.0 (–11.4 to 13.4)
	Desideri, 2005 COSTAMI-II (uncomplicated MI)	12 months (index and subsequent admissions)	mean 9 (13.4) days	mean 10 (13.3) days	MD –1.0 (–5.3 to 3.3)

Nottingham Health Profile (0-100)‡	**Nucifora 2009** ASSENCE trial (suspected ACS)	2 months			
Physical mobility			15 (16)	14 (16)	MD 1.0 (–4.1 to 6.1)
Pain			7 (10)	6 (14)	MD 1.0 (–2.9 to 4.9)
Social isolation			4 (9)	6 (17)	MD –2.0 (–6.3 to 2.3)
Emotional reactions			21 (25)	14 (23)	MD 7.0 (–0.7 to 14.7)
Energy levels			14 (14)	11 (16)	MD 3.0 (–1.8 to 7.8)
Sleep			22 (17)	23 (22)	MD –1.0 (–7.3 to 5.3)

ACS = acute coronary syndrome**;** CAD = coronary artery disease; CI = confidence interval; ECG = electrocardiogram; ETT = exercise treadmill testing; F/U = follow-up period; IHD = ischemic heart disease; NA = not applicable; NC = not calculable; N = number; UA = unstable angina.

*Calculated unless otherwise indicated.

†Jeetley 2006: defined as death, MI or revascularization; Desideri 2005: defined as death, nonfatal MI, or UA.

‡Each dimension is scored from 0 (no handicap) to 100 (major handicap); a score of 100 points represented an extensive personal restriction.

Appendix Table O3. Seattle Angina Questionnaire and SF-36 Quality of Life Questionnaire results from the CECaT trial comparing stress echocardiography with ICA in patient with stable symptoms and suspected or known CAD.

Author (year) Trial name Population	Outcome	F/U	Echocardiography (N=226) Mean (SD)	ICA (N=222) Mean (SD)	MD (95% CI)*
Sharples 2007 **Thom 2014** CECaT Suspected or known CAD Low (21%) and high (69%) risk.	**SAQ (0-100)§**				
	Exertional capacity	6 months	81 (20.5)	80.2 (19.3)	0.80 (95% CI -2.90 to 4.50)
		18 months	81.5 (20)	81.7 (19.2)	-0.20 (95% CI -3.84 to 3.44)
	Angina stability	6 months	65.2 (26.6)	66.6 (24.7)	-1.40 (95% CI -5.61 to 2.81)
		18 months	64.4 (20)	64.6 (25.1)	-0.20 (95% CI -4.41 to 4.01)
	Anginal frequency	6 months	84 (23.1)	83.8 (21.1)	0.20 (95% -3.91 to 4.31)
		18 months	86.8 (21.8)	84.2 (21.4)	2.60 (95% CI 1.41 to 6.61)
	Treatment satisfaction	6 months	91.6 (14.8)	90.4 (15.1)	1.20 (95% CI -1.58 to 3.98)
		18 months	91.9 (16.1)	91.8 (15.0)	0.10 (95% CI -2.79 to 2.99)
	Disease perception	6 months	75.6 (22.2)	73.1 (22.5)	2.50 (95% CI -1.65 to 6.65)
		18 months	78.4 (22)	77.4 (21.2)	1.0 (95% CI -3.01 to 5.01)
	SF-36 PCS (0-100),†	6 months	NR	NR	Adj. MD 0.0 (–2.0 to 1.9)‡
		18 months	NR	NR	Adj. MD –0.5 (–2.8 to 1.7)‡
	SF-36 MCS (0-100),†	6 months	NR	NR	Adj. MD 0.1 (–1.9 to 2.0)‡
		18 months	NR	NR	Adj. MD –1.1 (–3.2 to 1.1)‡

Adj. adjusted, CAD = coronary artery disease, CI = confidence interval, F/U = follow-up, ICA = invasive coronary angiography, MCS = mental component summary, MD = mean difference, PCS = physical component summary, SAQ = Seattle Angina Questionnaire, SD = standard deviation, SPECT = single photon emission tomography.
*Calculated unless otherwise indicated
†Negative value favors SPECT over angiography.
‡ Adjusted mean difference provided by authors; adjusted for baseline scores.

Appendix Table O4. Cumulative Frequency of secondary outcomes in trials evaluating SPECT versus Stress Echocardiography in stable women with suspected CAD treated on an outpatient basis.

Author (year) Trial name	Outcome	F/U Months	SPECT % (n/N)	Exercise ECG % (n/N)	Risk Ratio (95% CI)*
Shaw 2011 WOMEN trial	**MACE† –** *Overall*	24 months	2.3% (9/384)	1.7% (8/388)	1.14 (0.44 to 2.92)
	MACE† – *Patients with normal results*		1.2% (4/347)	0.4% (1/249)	2.87 (0.32 to 25.53)
	MACE† – *Patients with abnormal results*		13.1% (5/37)	5.1% (7/139)	2.68 (0.90 to 7.97)
	ACS (requiring hospitalization)	24 months	Overall: 1.6% (12/772)‡		NA
	Heart failure (requiring hospitalization)	24 months	Overall: 0.1% (1/772)‡		NA
	Angina-free status	6 months	51.0% (196/384)	50.6% (196/388)	1.01 (0.88 to 1.16)
		12 months	49.5% (190/384)	48.9% (190/388)	1.01 (0.88 to 1.17)
		24 months	64.9% (249/384)	60.4% (234/388)	1.08 (0.96 to 1.20)

ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; ECG = electrocardiogram; ECHO = echocardiogram; ECT = Exercise electrocardiogram test; ETT = exercise treadmill testing; F/U = follow-up period; NA= not applicable; N = number; NC = not calculable; NR = Not reported; RR = risk ratio; SPECT = single photon emission computed tomography; UA = unstable angina; vs = versus

*Calculated unless otherwise indicated. For dichotomous values, calculated the Risk Ratio/Relative Risk (RR) and associated 95% CI using the Rothman Episheet.

† Composite of cardiac death, nonfatal MI, or hospital admission for an ACS or heart failure

‡Only reports overall % of cases (not by testing arm).

Appendix Table O5. Cumulative frequency of secondary outcomes in trials comparing SPECT with stress echocardiography in patients with stable or acute symptoms.

Author (year) Trial name Population	Outcome	F/U	SPECT % (n/N)	Echocardiography % (n/N)	Risk Ratio (95% CI)*
Sharples 2007, Thom 2014 CECaT trial (Stable, suspected or known CAD; outpatient setting)	**Total nonfatal events†**	18 months	10.7% (24/224)	13.7% (31/226)	RR 0.78 (0.47 to 1.29)
	Total nonfatal plus fatal events‡	18 months	12.9% (29/224)	16.4% (37/226)	RR 0.79 (0.50 to 1.24)
	Significant improvement in CCS angina class (≥2 decrease)	6 months	33% (66/224)	31% (67/226)	RR 0.99 (0.75 to 1.32)
		18 months	42% (87/224)	34% (70/226)	RR 1.25 (0.97 to 1.62)
	Outcome	**F/U**	**SPECT Mean (SD)**	**Echocardiography Mean (SD)**	**MD (95% CI)***
	SAQ (0-100)§				
	Exertional capacity	6 months	77.5 (21.3)	81 (20.5)	-3.30 (95% CI -7.17 to 0.57)
		18 months	78.5 (23)	81.5 (20)	-2.7 (95% CI -6.69 to 1.29)
	Angina stability	6 months	61.9 (24.1)	65.2 (26.6)	-3.3 (95% CI -8.00 to 1.40)
		18 months	62.6 (25.1)	64.4 (20)	-1.8 (95% CI -6.00 to 2.40)
	Anginal frequency	6 months	83.5 (21.7)	84 (23.1)	-0.5 (95% CI -4.65 to 3.65)
		18 months	86.9 (19.4)	86.8 (21.8)	0.10 (95% CI -3.72 to 3.92)
	Treatment satisfaction	6 months	92 (12.7)	91.6 (14.8)	0.40 (95% CI -2.16 to 2.96)
		18 months	91.2 (14.6)	91.9 (16.1)	-0.70 (95% CI -3.55 to 2.15)
	Disease perception	6 months	74.8 (20.1)	75.6 (22.2)	-0.80 (95% CI -4.73 to 3.13)
		18 months	77 (21.9)	78.4 (22)	-1.40 (95% CI -5.47 to 2.67)
Salame 2018 (Acute, ED presentation, subsequently hospitalized)	**Hospital length of stay (hours)**	Index	Median 25.5 (IQR 19.4 to 42.5)	Median 26 (IQR 20.3 to 40.6)	NC
	Duration of imaging (hours)	Index	Median 4.1 (IQR 3.2 to 5.2)	Median 1.8 (IQR 1.3 to 2.6)	NC

ACS = acute coronary syndrome; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CI = confidence interval; F/U = follow-up period; IQR = interquartile range; MD = mean difference; NA = not applicable; NC = not calculable; NR = Not reported; RR = risk ratio; SPECT = single photon emission computed tomography.
*Calculated unless otherwise indicated. For dichotomous values, calculated the Risk Ratio/Relative Risk (RR) and associated 95% CI using the Rothman Episheet.
†Admission for chest pain or acute MI, unplanned PCI or CABG, other (other for the SPECT group = 1 post-CABG wound infection, 1 admission for breathlessness, 1 admission for ICD implant, 1 admission for suspected MI found to be muscular pain, 1 seen in A&E with chest pain in SPECT; and for the echocardiography group = 1 transient ischemic attack).
‡Nonfatal events as above. There were 5 fatal events in the SPECT arm (all 5 cardiac deaths) and 6 in the echocardiography arm (1 cardiac, 2 other cardiovascular and 3 other [pneumonia, respiratory failure, and road traffic accident]).

§SAQ: Scores range from 0 to 100: Physical Limitation (9 items), Angina Stability (1 item), Angina Frequency (2 items), Treatment Satisfaction (4 items), and Quality of Life (3 items). Higher score=better status.

Appendix Table O6. Seattle Angina Questionnaire and SF-36 Quality of Life Questionnaire results from the CECaT trial comparing SPECT with ICA in patient with stable symptoms and suspected or known CAD.

Author (year) Trial name Population	Outcome	F/U	SPECT (N=224) Mean (SD)	ICA (N=222) Mean (SD)	MD (95% CI)*
Sharples 2007 **Thom 2014** CECaT Suspected or known CAD Low (21%) and high (69%) risk.	**SAQ (0-100)§**				
	Exertional capacity	6 months	77.5 (21.3)	80.2 (19.3)	-2.7 (95% CI -6.48 to 1.08)
		18 months	78.5 (23)	81.7 (19.2)	-3.2 (95% CI -7.14 to 0.75)
	Angina stability	6 months	61.9 (24.1)	66.6 (24.7)	-4.70 (95% CI -9.34 to -0.06)
		18 months	62.6 (25.1)	64.6 (25.1)	-2.0 (95% CI -6.68 to 2.68)
	Anginal frequency	6 months	83.5 (21.7)	83.8 (21.1)	-0.30 (95% CI -4.28 to 3.68)
		18 months	86.9 (19.4)	84.2 (21.4)	2.70 (95% CI -1.10 to 6.50)
	Treatment satisfaction	6 months	92 (12.7)	90.4 (15.1)	1.60 (95% CI -1.0 to 4.20)
		18 months	91.2 (14.6)	91.8 (15.0)	-0.60 (95% CI -3.20 to 2.0)
	Disease perception	6 months	74.8 (20.1)	73.1 (22.5)	1.70 (95% CI -2.27 to 5.67)
		18 months	77 (21.9)	77.4 (21.2)	-0.40 (95% CI -4.41 to 3.61)
	SF-36 PCS (0-100),†	6 months	NR	NR	Adj. MD –0.5 (–2.5 to 1.5)‡
		18 months	NR	NR	Adj. MD 0.8 (–1.4 to 3.0)‡
	SF-36 MCS (0-100),†	6 months	NR	NR	Adj. MD –0.3 (–2.3 to 1.6)‡
		18 months	NR	NR	Adj. MD 0.3 (–1.9 to 2.4)‡

Adj. adjusted, CAD = coronary artery disease, CI = confidence interval, F/U = follow-up, ICA = invasive coronary angiography, MCS = mental component summary, MD = mean difference, PCS = physical component summary, SAQ = Seattle Angina Questionnaire, SD = standard deviation, SPECT = single photon emission tomography.
*Calculated unless otherwise indicated
†Negative value favors SPECT over angiography.
‡ Adjusted mean difference provided by authors; adjusted for baseline scores.
§SAQ: Scores range from 0 to 100: Physical Limitation (9 items), Angina Stability (1 item), Angina Frequency (2 items), Treatment Satisfaction (4 items), and Quality of Life (3 items). Higher score=better status.

Appendix Table O7. Subgroup analyses for NICE classification of non-anginal chest pain

Trial name	Timing	Subgroup (N)	Test % (n/N) or Mean (SD)	Comparator (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
Fatal and non-fatal MI						
SCOT-HEART, 2018	Median 3.2 year follow-up	NICE classification of non-anginal chest pain*	1.0% (7/712)	1.5% (11/735)	HR 0.65 (95% CI 0.25 to 1.69)	0.836
		NICE classification of possible anginal chest pain*	1.9% (22/1174)	3.2% (37/1149)	HR 0.58 (95% CI 0.34 to 0.99)	
Fatal MI, non-fatal MI and stroke						
SCOT-HEART, 2018	Median 3.2 year follow-up	NICE classification of non-anginal chest pain*	1.1% (8/712)	2.2% (16/735)	HR 0.51 (95% CI 0.22 to 1.2)	0.554
		NICE classification of possible anginal chest pain*	2.4% (28/1174)	3.5% (40/1149)	0.69 (0.42 to 1.11)	
Non-fatal MI						
SCOT-HEART, 2018	Median 3.2 year follow-up	NICE classification of non-anginal chest pain*	1.2% (9/712)	1.0% (7/735)	0.8 (0.3 to 2.14)	0.509
		NICE classification of possible	1.6% (19/1174)	3.0% (34/1149)	0.54 (0.31 to 0.96)	

		anginal chest pain*				
Non-fatal stroke						
SCOT-HEART, 2018	Median 3.2 year follow-up	NICE classification of non-anginal chest pain*	0.1% (2/712)	0.7% (5/735)	0.21 (0.02 to 1.8)	0.200
		NICE classification of possible anginal chest pain*	0.5% (6/1174)	0.5% (6/1149)	1.01 (0.32 to 3.12)	
All-cause mortality						
SCOT-HEART, 2018	Median 3.2 year follow-up	NICE classification of non-anginal chest pain*	1.0% (7/712)	0.5% (4/735)	1.81 (0.53 to 6.18)	0.200
		NICE classification of possible anginal chest pain*	1.5% (18/1174)	1.9% (22/1149)	0.82 (0.44 to 1.53)	
Coronary Heart Disease Death						
SCOT-HEART, 2018	Median 3.2 year follow-up	NICE classification of non-anginal chest pain*	0% (0/712)	0.3% (2/735)	0 (0 to Infinity)	0.998
		NICE classification of possible anginal chest pain*	0.3% (3/1174)	0.3% (4/1149)	0.78 (0.17 to 3.48)	
Non-coronary Heart Disease Death						

SCOT-HEART, 2018	Median 3.2 year follow-up	NICE classification of non-anginal chest pain*	1.0% (7/712)	0.3% (2/735)	3.64 (0.75 to 17.57)	0.096
		NICE classification of possible anginal chest pain*	1.3% (15/1174)	1.6% (18/1149)	0.83 (0.42 to 1.65)	
CABG						
SCOT-HEART, 2018	Median 3.2 year follow-up	NICE classification of non-anginal chest pain*	0.3% (2/712)	0.1% (1/735)	1.85 (95% CI 0.16 to 20.92)	0.704
		NICE classification of possible anginal chest pain*	4.8% (56/1174)	3.7% (43/1149)	1.3 (0.87 to 1.94)	

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation.

* Participants with non-anginal chest pain had the lowest event rates. Patients with possible angina had a higher and time-varying event rate with increased early hazards. Additionally, study reports third group of patients with known CAD that were already on established preventative therapies which were not reported in this data.

Appendix Table O8. Subgroup analyses for composite outcome (including cardiovascular death and myocardial infarction)

Trial name	Timing	Subgroup (N)	Test % (n/N) or Mean (SD)	Comparator (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
PROMISE trial	Median follow-up: 25 months	With diabetes (N=NR)	1.1% (10/936)	Any functional test: 2.6% (25/972)	Adj. HR 0.38, 95% CI 0.18 to 0.79*	0.020
		Without diabetes (N=NR)	1.4% (50/3564)	Any functional test: 1.29% (45/3494)	Adj. HR 1.03, 95% CI 0.69 to 1.54*	
SCOT-HEART, 2018	Median 4.8 year follow-up	Diabetes (N=NR)	2.2% (41/1850)	3.5% (64/1852)	HR 0.63 (95% CI 0.43 to 0.94)	0.40
		No diabetes (N=NR)	3.1% (7/223)	7.7% (17/221)	HR 0.36 (95% CI 0.15 to 0.87)	
	Median 4.8 year follow-up	< 65 years (N=NR)	2.1% (32/1538)	3.3% (51/1554)	HR 0.62 (95% CI 0.40 to 0.96)	0.68
		>65 years (N=NR)	3.0% (16/535)	5.8% (30/519)	HR 0.53 (95% CI 0.29 to 0.98)	
	Median 4.8 year follow-up	Female (N=NR)	1.2% (11/911)	22/910 (2.4)	HR 0.50 (95% CI 0.24 to 1.04)	0.57
		Male (N=NR)	3.2% (37/1162)	5.1% (59/1163)	HR 0.63 (95% CI	

					0.42 to 0.95)	
	Median 4.8 year follow-up	10 year cardiovascular risk <15% (N=NR)	1.5% (15/969)	2.0% (21/1067)	HR 0.78 (95% CI 0.40 to 1.51)	0.21
		10 year cardiovascular risk ≥15% (N=NR)	3.0% (33/1104)	6.0% (60/1006)	HR 0.50 (95% CI 0.33 to 0.77)	
	Median 4.8 year follow-up	No previous coronary heart disease (N=NR)	1.9% (35/1887)	3.3% (62/1887)	HR 0.57 (95% CI 0.37 to 0.86)	0.68
		Previous coronary heart disease (N=NR)	7.0% (13/187)	10.1% (19/189)	HR 0.65 (95% CI 0.32 to 1.32)	
	Median 3.2 year follow-up	NICE classification of non-anginal chest pain	1.1% (8/712)	2.4% (18/735)	HR 0.45 (95% CI 0.19 to 1.03)	0.58
		NICE classification anginal chest pain	2.3% (27/1174)	3.8% (44/1149)	HR 0.60 (95% CI 0.37 to 0.96)	

CI = confidence interval; HR = hazard ratio; NR = not reported; SD = standard deviation.

* Author's do not state what they adjusted for.

Appendix Table O9. Subgroup analyses for any downstream testing

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

NR = not reported; SD = standard deviation.

Appendix Table O10. Subgroup analyses for ICA

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

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

Appendix Table O11. Subgroup analyses for any revascularization

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

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

Appendix Table O12. Subgroup analyses for PCI

Trial name	Timing	Subgroup (N)	Test % (n/N) or Mean (SD)	Comparator (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
ROMICAT-II trial	Index Visit	Females (N=NR)	2% (5/239)	1% (2/229)	NR	0.69
		Males (N=NR)	7% (19/262)	4% (12/270)	NR	
	28 day follow-up	Females (N=NR)	3% (6/239)	1% (2/229)	NR	0.45
		Males (N=NR)	8% (21/262)	6% (15/270)	NR	
	Index Visit	With diabetes (N=NR)	7% (6/86)	2% (2/87)	NR	0.41
		Without diabetes (N=NR)	4% (18/415)	3% (12/412)	NR	
	28 day follow-up	With diabetes (N=NR)	7% (6/86)	2% (2/87)	NR	0.37
		Without diabetes (N=NR)	5% (21/415)	4% (15/412)	NR	
SCOT-HEART, 2018	Median 3.2 year follow-up	NICE classification of non-anginal chest pain	2.0% (14/712)	1.8% (13/735)	1.13 (0.53 to 2.40)	0.978
		NICE classification of possible anginal chest pain	14.5% (170/1174)	13.1% (170/1149)	1.11 (95% CI 0.89 to 1.38)	

NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation

Appendix Table O13. Subgroup analyses for NICE classification of non-anginal chest pain: CABG

Trial name	Timing	Subgroup (N)	Test % (n/N) or Mean (SD)	Comparator (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
CABG						
SCOT-HEART, 2018	Median 3.2 year follow-up	NICE classification of non-anginal chest pain*	0.3% (2/712)	0.1% (1/735)	1.85 (95% CI 0.16 to 20.92)	0.704

Appendix Table O14. Subgroup analyses for medication use

Trial name	Timing	Subgroup (N)	Test % (n/N) or Mean (SD)	Comparator (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
Aspirin						
PROMISE trial	60-day visit	With diabetes (N=NR)	62.1% (530/854)	Any functional test: 57.3% (504/879)	Adj. OR 1.23 (95% CI 1.01 to 1.50)*	0.907
		Without diabetes (N=NR)	52.4% (1658/3167)	Any functional test: 47.5% (1452/3059)	Adj. OR 1.25 (95% CI 1.13 to 1.38)*	
Statin						
PROMISE trial	60-day visit	With diabetes (N=NR)	71.4% (610/854)	Any functional test: 64.3% (565/879)	Adj. OR 1.40 (95% CI 1.14 to 1.72)*	0.783
		Without diabetes (N=NR)	52.9% (1675/3167)	Any functional test: 45.8% (1401/3059)	Adj. OR 1.36 (95% CI 1.23 to 1.50)*	
Beta blocker						
PROMISE trial	60-day visit	With diabetes (N=NR)	35.3% (301/854)	Any functional test: 33.3% (293/879)	Adj. OR 1.10 (95% CI 0.89 to 1.34)*	0.941
		Without diabetes (N=NR)	28.7% (909/3167)	Any functional test: 27.3% (835/3059)	Adj. OR 1.10 (95% CI 0.99 to 1.24)*	
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker						
PROMISE trial	60-day visit	With diabetes (N=NR)	70.6% (603/854)	Any functional test: 68.7% (604/879)	Adj. OR 1.10 (95% CI 0.89 to 1.35)*	0.339
		Without diabetes (N=NR)	37.3% (1180/3167)	Any functional test: 37.8% (1157/3059)	Adj. OR 0.98 (95% CI 0.88 to 1.09)*	

CI = confidence interval; NR = not reported; OR = odds ratio; SD = standard deviation.

* Adjusted model controls for noninvasive testing results (positive vs. negative), sex, and age

Appendix Table O15. Subgroup analyses for test positive rate (≥70% stenosis in at least one epicardial artery or ≥50% stenosis in the left main

Trial name	Timing	Subgroup (N)	Test % (n/N) or Mean (SD)	Comparator (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
PROMISE trial	Index test	Male (N=NR)	16.1% (350/2168)	Any functional test: 14.0% (290/2078)	adj. OR 1.23 (95% CI 1.04 to 1.47)*	CCTA vs. any functional test: <0.001†
				Nuclear Stress: 16.9% (230/1362)	adj. OR 1.03 (95% CI 0.85 to 1.25)*	
				Stress Echo: 7.7% (36/465)	adj. OR 2.10 (95% CI 1.45 to 3.04)*	
				Ex ECG: 9.6% (24/251)	adj. OR 1.79 (95% CI 1.15 to 2.80)*	
		Female (N=NR)	7.9% (184/2332)	Any functional test: 11.5% (274/2388)	adj. OR 0.67 (95% CI 0.55 to 0.82)*	
				Nuclear Stress: 12.0% (205/1704)	adj. OR 0.66 (95% CI 0.53 to 0.82)*	
				Stress Echo: 7.7% (39/505)	adj. OR 0.90 (95% CI 0.63 to 1.30)*	
				Ex ECG: 16.8% (30/179)	adj. OR 0.39 (95% CI 0.25 to 0.61)*	
PROMISE trial	Index test	BMI <35 (N=NR)	12.2% (439/3589)	Nuclear Stress: 13.1% (310/2361)	NR	0.003
				Stress Echo: 7.8% (62/795)	NR	
				Ex ECG: 12.8% (47/368)	NR	
		BMI ≥35 (N=NR)	10.3% (90/872)	Nuclear Stress: 18.1% (123/679)	NR	
				Stress Echo: 7.9% (13/165)	NR	
				Ex ECG: 11.7% (7/60)	NR	
PROMISE trial	Index test	Age <65 years (N=NR)	10.1% (328/3249)	Any functional test: 11.2% (350/3129)	Adj. OR 1.13 (95% CI 0.96 to 1.33)	0.20

		Age 65-74 (N=NR)	15.2% (1553/1008)	Any functional test: 15.6% (164/1054)	Adj. OR 1.04 (95% CI 0.82 to 1.33)	
		Age ≥75 (N=NR)	21.8% (53/243)	Any functional test: 17.7% (50/283)	Adj. OR 0.74 (95% CI 0.48 to 1.15)	
PROMISE trial	Index test	With diabetes (N=NR)	14.9% (139/936)	Nuclear Stress: 17.7% (126/711)	NR	0.930
				Stress Echo: 9.2% (17/185)	NR	
				Ex ECG: 9.2% (7/76)	NR	
		Without diabetes (N=NR)	11.1% (395/3564)	Nuclear Stress: 13.1% (309/2355)	NR	
				Stress Echo: 7.4% (58/785)	NR	
				Ex ECG: 13.3% (47/354)	NR	

CCTA = coronary computed tomography angiography; CI = confidence interval; Ex ECG = exercise electrocardiography; NR = not reported; OR = odds ratio; SD = standard deviation.

* Adjusted for age, race, body mass index, coronary artery disease (CAD) equivalent, Framingham risk score, ASCVD score, 2011 Diamond and Forrester score, hypertension, dyslipidemia, diabetes, family history of premature CAD, sedentary lifestyle, smoking, typicality of chest pain, and physician's estimation of likelihood of significant CAD.

† All other tests: p=NR.

Appendix Table O16. Subgroup analyses for single administrative outcomes

Trial name	Timing	Subgroup (N)	Test % (n/N) or Mean (SD)	Comparator (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
Direct ED Discharge						
ROMICAT-II trial	Index Visit	Females (N=NR)	55% (132/239)	14% (33/229)	NR	0.22
		Males (N=NR)	41% (107/262)	12% (33/270)	NR	
	Index Visit	With diabetes (N=NR)	40% (34/86)	14% (12/87)	NR	0.27
		Without diabetes (N=NR)	49% (205/415)	13% (54/412)	NR	
	Index Visit	White (N=NR)	46% (153/330)	11% (35/329)	NR	0.27
		Black (N=NR)	43% (61/141)	14% (19/140)	NR	
Hospital length of stay (hours)						
ROMICAT-II trial	Index Visit	Females (N=NR)	17.0 (24.5)	30.7 (24.1)	NR	0.006
		Males (N=NR)	28.8 (44.7)	31.0 (30.9)	NR	
	Index Visit	With diabetes (N=NR)	32.2 (43.2)	32.0 (20.1)	NR	0.08
		Without diabetes (N=NR)	21.3 (35.3)	30.6 (29.4)	NR	
Hospital admission						
ROMICAT-II trial	Index Visit	Females (N=NR)	33% (14/239)	25% (57/229)	NR	0.005
		Males (N=NR)	29% (75/262)	26% (69/270)	NR	
	Index Visit	With diabetes (N=NR)	35% (30/86)	29% (25/87)	NR	0.09
		Without diabetes (N=NR)	19% (78/415)	25% (101/412)	NR	
	Index Visit	White (N=NR)	23% (75/330)	25% (82/329)	NR	0.31
		Black (N=NR)	18% (25/141)	26% (36/140)	NR	

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

Appendix Table O17. Subgroup analyses for repeat ED visit or hospitalization for chest pain

Trial name	Timing	Subgroup (N)	Test % (n/N) or Mean (SD)	Comparator (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
ROMICAT-II trial	28 day follow-up	Females (N=NR)	3% (6/239)	1% (2/229)	NR	0.11
		Males (N=NR)	3% (9/262)	6% (17/270)	NR	
	28 day follow-up	With diabetes (N=NR)	0% (0/86)	5% (4/87)	NR	0.97
		Without diabetes (N=NR)	3% (14/415)	4% (15/412)	NR	
	28 day follow-up	White (N=NR)	2% (8/330)	5% (16/329)	NR	0.049
		Black (N=NR)	4% (6/141)	1% (2/140)	NR	

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

Appendix Table O18. Subgroup analyses for primary composite end point* + catheterization without obstructive CAD

Trial name	Timing	Subgroup (N)	Test % (n/N) or Mean (SD)	Comparator (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
PROMISE trial	Median follow-up: 25 months	Age <65 (N=7111)	NR	NR	HR: 0.94 (95% CI 0.78 to 1.13)	0.695
		Age ≥65 (N=2892)	NR	NR	HR: 0.87 (95% CI 0.68 to 1.12)	
	Median follow-up: 25 months	Male (N=4733)	NR	NR	HR: 0.94 (95% CI 0.76 to 1.15)	0.633
		Female (N=5270)	NR	NR	HR: 0.87 (95% CI 0.70 to 1.09)	
	Median follow-up: 25 months	White (N=8371)	NR	NR	HR: 0.88 (95% CI 0.74 to 1.03)	0.260
		Non-white (N=1545)	NR	NR	HR: 1.12 (95% CI 0.75 to 1.69)	
	Median follow-up: 25 months	Low pre-test risk (≤30%) (N=3755)	NR	NR	HR: 0.95 (95% CI 0.73 to 1.24)	0.839
		Intermediate pre-test risk (31%-70%) (N=5750)	NR	NR	HR: 0.90 (95% CI 0.74 to 1.10)	
		High pre-test risk (>70%) (N=481)	NR	NR	HR: 0.81 (95% CI 0.50 to 1.30)	
	Median follow-up: 25 months	Low pre-test probability (N=250)	NR	NR	HR: 0.85 (95% CI 0.33 to 2.20)	0.980
		Intermediate pre- test probability (N=9258)	NR	NR	HR: 0.90 (95% CI 0.77 to 1.06)	
		High pre-test probability (N=495)	NR	NR	HR: 0.96 (95% CI 0.57 to 1.61)	

CI = confidence interval; HR = hazard ratio; NR = not reported; SD = standard deviation.

* Primary endpoint includes death from any cause, nonfatal MI, hospitalization for unstable angina, or major procedural complication.

Appendix Table O19 Subgroup analyses for composite outcome (including cardiovascular death, myocardial infarction, and unstable angina hospitalization)

Trial name	Timing	Subgroup (N)	Test % (n/N) or Mean (SD)	Comparator (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value

PROMISE trial	Median follow-up: 25 months	With diabetes (N=NR)	3.4% (32/936)	Any functional test: 4.4% (43/972)	Adj. HR 0.74, 95% CI 0.47 to 1.18*	0.096
		Without diabetes (N=NR)	3.0% (105/3564)	Any functional test: 2.4% (85/3494)	Adj. HR 1.18, 95% CI 0.88 to 1.57*	

CI = confidence interval; HR = hazard ratio; NR = not reported; SD = standard deviation.
* Author's do not state what they adjusted for.

Appendix Table O20. Subgroup analyses for MACE*

Trial name	Timing	Subgroup (N)	Test % (n/N) or Mean (SD)	Comparator (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
ROMICAT-II trial	28 day follow-up	Females (N=NR)	0.4% (1/239)	0.4% (1/229)	NR	0.48
		Males (N=NR)	0.4% (1/262)	1.9% (5/270)	NR	
ROMICAT-II trial	28 day follow-up	With diabetes (N=NR)	0% (0/86)	1% (1/87)	NR	0.97
		Without diabetes (N=NR)	0.5% (2/415)	1.2% (5/412)	NR	

MACE = major adverse coronary event; NR = not reported; SD = standard deviation
* MACE included death, myocardial infarction, unstable angina, or urgent coronary revascularization

Appendix Table O21. Subgroup analyses for Primary composite end points (including death from any cause, nonfatal myocardial infarction, hospitalization for unstable angina, or major procedural complication)

Trial name	Timing	Subgroup (N)	Test % (n/N) or Mean (SD)	Comparator (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
PROMISE trial	Median follow-up: 25 months	Age <65 (N=7111)	NR	NR	HR: 1.10 (95% CI 0.82 to 1.47)	0.591
		Age ≥65 (N=2982)	NR	NR	HR: 0.97 (95% CI 0.69 to 1.36)	
	Median follow-up: 25 months	Male (N=4733)	NR	NR	HR: 0.99 (95% CI 0.74 to 1.32)	0.698
		Female (N=5270)	NR	NR	HR: 1.08 (95% CI 0.76 to 1.51)	
	Median follow-up: 25 months	White (N=8371)	NR	NR	HR: 0.95 (95% CI 0.74 to 1.20)	0.100
		Non-white (N=1545)	NR	NR	HR: 1.62 (95% CI 0.89 to 2.92)	
	Median follow-up: 25 months	Low pre-test risk (≤30%) (N=3755)	NR	NR	HR: 1.33 (95% CI 0.88 to 2.00)	0.341
		Intermediate pre-test risk (31%-70%) (N=5750)	NR	NR	HR: 0.92 (95% CI 0.69 to 1.23)	
		High pre-test risk (>70%) (N=481)	NR	NR	HR: 0.94 (95% CI 0.51 to 1.74)	
	Median follow-up: 25 months	Low pre-test probability (N=250)*	NR	NR	HR: 2.30 (95% CI 0.45 to 11.88)	0.603
		Intermediate pre-test probability (N=9258)*	NR	NR	HR: 1.00 (95% CI 0.79 to 1.26)	
		High pre-test probability (N=495)*	NR	NR	HR: 1.08 (95% CI 0.53 to 2.23)	

CI = confidence interval; HR = hazard ratio; NR = not reported; SD = standard deviation.

* Pre-test probability estimated using the Diamond-Forrester model where patients were categorized as being at low risk (<30%), moderate risk (30–70%), or high risk (> 70%) of having obstructive CAD. Additionally, the pretest probability of CAD varied with age and affects interpretation of both positive and negative test results.

Appendix Table O22. Subgroup analyses for safety outcomes

Trial name	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Functional Test % (n/N) or Mean (SD)	Interaction p-value
PROMISE trial	≤90 days	Cumulative radiation effective dose among those patients intended for nuclear stress testing	<65 years	12.2 (8.1) (N=2178)	15.3 (6.9) (N=2159)	0.072
			≥65 years	12.6 (8.9) (N=968)	15.0 (6.7) (N=1044)	
			Male	13.7 (9.0) (N=1452)	160 (7.4) (N=1694)	0.82
			Female	11.2 (7.5) (N=1694)	14.6 (6.3) (N=1786)	
			Not Obese (<30 kg/m2)	11.1 (8.0) (N=1556)	14.9 (6.9) (N=1537)	0.10
			Obese (≥30 kg/m2)	13.6 (8.5) (N=1570)	15.5 (6.7) (N=1638)	
			Heart rate <75 bpm*	11.9 (8.4)	15.3 (6.9)	0.042
			Heart rate ≥75 bpm*	13.0 (8.3)	15.0 (6.6)	
ROMICATT-II	Index test only	Radiation Dose During the Index Visit	Female	10.8 (8.7)	4.7 (8.1)	0.003
			Male	14.2 (11.2)	4.7 (8.7)	
	28 days	Mean (SD) cumulative radiation dose (mSv)	Female	11.0 (8.9)	6.0 (8.2)	0.002
			Male	14.7 (12.0)	5.6 (10.7)	
			With diabetes	18.4 (14.7)	6.6 (10.4)	0.04
			Without diabetes	13.4 (9.8)	5.1 (9.5)	
			White	Median (IQR) 12.0 (7.9 to 17.2)	Median (IQR) 0.0 (0.0 to 12.4)	0.60
			Black	Median (IQR) 11.7 (8.6 to 16)	Median (IQR) 0.0 (0.0 to 0.0)	

CCTA = coronary computed tomography angiography; IQR = interquartile range; NR = not reported; SD = standard deviation.

* Baseline resting heart rate was recorded at the enrollment physical examination.

Appendix Table O23. Summary table of adverse events related to the use of dobutamine (± atropine*) during stress echocardiography

Adverse event	Author Year	Study design	% (n/N)
Known or suspected CAD			
Hypertension	Baudhuin 1993	Prospective CS	3.7% (5/136)
	Mertes 1993	Retrospective CS	1.1% (12/1118)
	Minardi 2007	Prospective CS	0% (0/265)
	Poldermans 1994	Prospective CS	0.2% (1/650)
	Sitges 2000	Prospective CS	7.5% (9/122)
Chest pain	Dakik 1996	Prospective CS	30.5% (309/1012)
	Mertes 1993	Retrospective CS	37.6% (36/1118)
Arrhythmia, palpitation	Sitges 2000	Prospective CS	18% (22/122)
	Baudhuin 1993	Prospective CS	11.0% (15/136)
	Dakik 1996	Prospective CS	9.7% (98/1012)
	Mertes 1993	Retrospective CS	2.1% (24/1118)
	Minardi 2007	Prospective CS	24.2% (64/265)
	Poldermans 1994	Prospective CS	3.7% (24/650)
	Sitges 2000	Prospective CS	9.0% (11/122)
Nausea, vomiting	Dakik 1996	Prospective CS	8.0% (81/1012)
	Gordon 1995	Retrospective CS	12.6% (16/127)
	Karabinos 2004	Retrospective CS	21% (168/802)
	Minardi 2007	Prospective CS	3.4% (9/265)
	Sitges 2000	Prospective CS	9.0% (11/122)
Hypotension	Baudhuin 1993	Prospective CS	12.5% (17/136)
	Mertes 1993	Retrospective CS	3.2% (36/1118)
	Minardi 2007	Prospective CS	1.1% (3/265)
	Poldermans 1994	Prospective CS	5.2% (34/650)
	Picano 1999	Prospective CS	0.1% (2/2799)
	Sitges 2000	Prospective CS	1.5% (2/122)
	Karabinos 2004	Retrospective CS	0.3% (3/802)
Dyspnea	Baudhuin 1993	Prospective CS	4.4% (6/136)
	Dakik 1996	Prospective CS	13.6% (138/1012)
	Minardi 2007	Prospective CS	0% (0/265)
Headache	Dakik 1996	Prospective CS	13.6% (138/1012)
	Gordon 1995	Retrospective CS	1.6% (2/127)
	Minardi 2007	Prospective CS	1.1% (3/265)
	Sitges 2000	Prospective CS	0.8% (1/122)
Flushing	Dakik 1996	Prospective CS	10.3% (104/1012)
	Gordon 1995	Retrospective CS	1.6% (2/127)
Tremors	Dakik 1996	Prospective CS	1.1% (11/1012)
	Gordon 1995	Retrospective CS	2.4% (3/127)
	Minardi 2007	Prospective CS	0.4% (1/265)
Anxiety	Gordon 1995	Retrospective CS	3.2% (4/127)
	Karabinos 2004	Retrospective CS	31% (248/802)
	Minardi 2007	Prospective CS	0% (0/265)
Acute MI	Karabinos 2004	Retrospective CS	0.1% (1/802)
	Mertes 1993	Retrospective CS	0% (0/1118)
	Picano 1999	Prospective CS	0.1% (3/2799)
Ventricular, supraventricular tachycardia	Karabinos 2004	Retrospective CS	0.6% (5/802)
	Mertes 1993	Retrospective CS	0% (0/1118)

Adverse event	Author Year	Study design	% (n/N)
	Picano 1999	Prospective CS	0.1% (3/2799)
Atrial or ventricular fibrillation	Karabinos 2004	Retrospective CS	0.3% (3/802)
	Picano 1999	Prospective CS	0.1% (2/2799)
Bradycardia	Mertes 1993	Retrospective CS	0.2% (2/1118)
	Picano 1999	Prospective CS	0.04% (1/2799)
Numbness	Gordon 1995	Retrospective CS	3.2% (4/127)
ST-segment changes	Mertes 1993	Retrospective CS	1.1% (12/1118)
Back pain	Gordon 1995	Retrospective CS	1.6% (2/127)
Dizziness	Gordon 1995	Retrospective CS	0.8% (1/127)
Weakness	Gordon 1995	Retrospective CS	0.8% (1/127)
Hip spasm	Gordon 1995	Retrospective CS	0.8% (1/127)
Urinary retention	Karabinos 2004	Retrospective CS	0.1% (1/802)
Urinary urgency	Karabinos 2004	Retrospective CS	3% (25/802)
Abdominal pain-tenesmus	Karabinos 2004	Retrospective CS	0.3% (3/802)
Unstable angina	Karabinos 2004	Retrospective CS	0.1% (1/802)
Acute pulmonary edema	Karabinos 2004	Retrospective CS	0.1% (1/802)
Left ventricular outflow tract obstruction	Mertes 1993	Retrospective CS	0.1% (1/1118)
Syncope	Mertes 1993	Retrospective CS	0% (0/1118)
General discomfort	Minardi 2007	Prospective CS	0.4% (1/265)
Chills	Poldermans 1994	Prospective CS	1.8% (12/650)
Prolonged ischemia	Picano 1999	Prospective CS	0.04% (1/2799)
Intraventricular gradient	Sitges 2000	Prospective CS	4.9% (6/122)
Facial paresthesia	Sitges 2000	Prospective CS	73.0% (89/122)
Other†	Baudhuin 1993	Prospective CS	1.5% (2/136)
Suspected ACS			
Chest pain	Geleijnse 2000	Prospective CS	31.4% (27/86)
Nausea, vomiting	Geleijnse 2000	Prospective CS	12.8% (11/86)
Hypotension	Geleijnse 2000	Prospective CS	1.2% (1/86)
Headache	Geleijnse 2000	Prospective CS	4.7% (4/86)
Anxiety	Geleijnse 2000	Prospective CS	1.2% (1/86)
Ventricular, supraventricular tachycardia	Geleijnse 2000	Prospective CS	7.0% (6/86)
ST-segment changes	Geleijnse 2000	Prospective CS	2.3% (2/86)

ACS = acute coronary syndrome, CAD = coronary artery disease, CS = case series

* Proportion of patients receiving atropine: Baudhuin 1993 (0%), Dakik 1996 (0%), Gordon 1995 (0%), Karabinos 2004 (96%), Mertes 1993 (38%), Minardi 2007 (0%), Poldermas 1994 (37%), Picano 1994 (NR), Geleijnse 2000 (100%), Stiges 2000 (100%)

† Includes cough, discomfort, facial flush

Appendix Table O24. Summary table of adverse events related to the use of dipyridamole (± atropine*) during stress echocardiography

Adverse event	Author Year	Study design	% (n/N)
Known or suspected CAD			
Fatigue	Gaibazzi 2009	Prospective CS	0.4% (2/500)
Arrhythmias	Gaibazzi 2009	Prospective CS	10.4% (52/500)
	Minardi 2002	Retrospective CS	2.1% (7/337)
Hypotension, bradycardia	Gaibazzi 2009	Prospective CS	0.8% (4/500)
	Ferrara 1991	Prospective CS	6.4% (7/109)
	Minardi 2002	Retrospective CS	0.9% (3/337)
Troponin I elevation	Gaibazzi 2009	Prospective CS	0% (0/500)
Xerostomia	Gaibazzi 2009	Prospective CS	19% (97/500)
Vomiting, nausea	Gaibazzi 2009	Prospective CS	0.2% (1/500)
	Ferrara 1991	Prospective CS	5.5% (7/109)
	Minardi 2002	Retrospective CS	1.5% (/337)
Headache	Gaibazzi 2009	Prospective CS	43% (214/500)
	Ferrara 1991	Prospective CS	30% (33/109)
	Minardi 2002	Retrospective CS	2.1% (7/337)
Pain at injection site	Gaibazzi 2009	Prospective CS	0.2% (1/500)
Chest pain	Ferrara 1991	Prospective CS	36.7% (40/109)
Flushing	Ferrara 1991	Prospective CS	22% (24/109)
Dyspnea	Ferrara 1991	Prospective CS	11% (13/109)
Dizziness	Ferrara 1991	Prospective CS	4.5% (5/109)
ST depression	Ferrara 1991	Prospective CS	49.5% (54/109)
Right/left bundle branch block	Minardi 2002	Retrospective CS	0.6% (2/337)

CAD = coronary artery disease, CS = case series

* Proportion of patients receiving atropine: Gaibazzi 2009 (100%), Ferrara 1991 (0%), Minardi 2002 (75%)

Appendix Table O25. Summary table of adverse events related to the use of adenosine during stress echocardiography

Author Year Study design	Adverse event	% (n/N)
Known or suspected CAD		
Montisci 2017 Prospective CS	Arythmias	2.9% (42/1429)
	Hyperpnea	16.7% (239/1429)
	Headache	6.6% (95/1429)
	Flushing	9.4% (134/1429)
	Atypical chest pain	9.9% (140/1429)
	Marked asthenia and general malaise	5.5% (80/1429)
	Typical angina	1.5% (22/1429)
	Palpitations	0.9% (13/1429)
	Symptomatic hypotension	0.2% (5/1429)

Appendix Table O26. Summary table of adverse events related to the use of Regadenoson and Dipyridamole during SPECT MPI

Adverse event	Author Year	Study design	Regadenoson, % (n/N)	Dipyrdamole, % (n/N)	p-value
Known or suspected CAD					
Dyspnea	Amer 2017	Retrospective CC	52.5% (149/284)	2.1% (6/284)	<0.0001
	Meyers 2002	Prospective CS	N/A	4.5% (27/604 AEs)	N/A
	Koutsikos 2017	Prospective CS	30.2% (29/96)	N/A	N/A
Gastrointestinal upset, nausea	Amer 2017	Retrospective CC	27.8% (79/284)	8.1% (23/284)	<0.0001
	Meyers 2002	Prospective CS	N/A	11.1% (67/604 AEs)	N/A
	Koutsikos 2017	Prospective CS	3.1% (3/96)	N/A	N/A
Chest pain	Amer 2017	Retrospective CC	15.8% (45/284)	3.9% (11/284)	<0.0001
	Meyers 2002	Prospective CS	N/A	12.1% (73/604 AEs)	N/A
	Koutsikos 2017	Prospective CS	9.4% (9/96)	N/A	N/A
Headache	Amer 2017	Retrospective CC	11.6% (33/284)	12.7% (36/284)	0.69
	Meyers 2002	Prospective CS	N/A	37.1% (224/604 AEs)	N/A
	Koutsikos 2017	Prospective CS	7.3% (7/96)	N/A	N/A
Dizziness, lightheadedness	Amer 2017	Retrospective CC	7.7% (22/284)	5.6% (16/284)	0.31
	Meyers 2002	Prospective CS	N/A	5.1% (31/604 AEs)	N/A
	Koutsikos 2017	Prospective CS	12.5% (12/96)	N/A	N/A
Ischemic ST-segment depression	Amer 2017	Retrospective CC	7.1% (20/284)	3.2% (9/284)	0.35
Flushing	Amer 2017	Retrospective CC	5.6% (16/284)	3.5% (10/284)	0.23
	Meyers 2002	Prospective CS	N/A	8.4% (51/604 AEs)	N/A
	Koutsikos 2017	Prospective CS	4.2% (4/96)	N/A	N/A
Supraventricular tachycardia	Amer 2017	Retrospective CC	1.1% (3/284)	2.1% (6/284)	0.31
Heart block	Amer 2017	Retrospective CC	1.1% (3/284)	0.4% (1/284)	0.32
Hypotension	Amer 2017	Retrospective CC	1.1% (3/284)	0% (0/284)	NR
Ventricular tachycardia	Amer 2017	Retrospective CC	0.4% (1/284)	0.1% (1/284)	1.0
Throat, neck, or jaw pain or tightness	Amer 2017	Retrospective CC	0.4% (1/284)	0.1% (1/284)	1.0
	Meyers 2002	Prospective CS	N/A	6.1% (37/604 AEs)	N/A
	Koutsikos 2017	Prospective CS	3.1% (3/96)	N/A	N/A
Discomfort	Koutsikos 2017	Prospective CS	11.5% (11/96)	N/A	N/A
Epigastric pain	Koutsikos 2017	Prospective CS	6.3% (6/96)	N/A	N/A
Heart burn	Koutsikos 2017	Prospective CS	4.2% (4/96)	N/A	N/A
Weakness	Koutsikos 2017	Prospective CS	1% (1/96)	N/A	N/A
Numbness	Koutsikos 2017	Prospective CS	1% (1/96)	N/A	N/A
Other (NOS)	Meyers 2002	Prospective CS	N/A	7.0% (42/604 AEs)	N/A

AEs = adverse events, CAD = coronary artery disease, CC = comparative cohort, CS = case series, N/A = not applicable, NOS = not otherwise specified, NR = not reported.

Appendix Table O27. Medication changes in trials evaluating CCTA in patients with suspected CAD, stable patients treated as outpatients

Medication	Author (year) Trial name	F/U	Medication disposition	CCTA % (n/N)	COMPARATOR % (n/N)	Risk Ratio (95% CI)* (p-value between groups if no effect size)
Aspirin	**CCTA vs. any functional testing**					
	Douglas, 2015 (Ladapo, 2016) PROMISE trial	3 months (60-day visit)	Initiated medication	11.8% (NR†)	7.8% (NR†),	p<0.0001‡
			Discontinued medication	2.7% (NR†)	2.9% (NR†),	
	CCTA vs. SPECT					
	Min, 2012	<2 months (Mean 55 days)	Percent change in medication	40%* (40/91)	36% (32/89)	RR 1.22 (95% CI 0.85 to 1.76), p=0.27*
ACE inhibitors (Angiotensin converting enzyme inhibitor) or ARBs (Angiotensin receptor blocker)	**CCTA vs. any functional testing**					
	Douglas, 2015 (Ladapo, 2016) PROMISE trial	3 months (60-day visit)	Initiated medication	3.6% (NR†)	3.3% (NR†),	p= 0.8552
			Discontinued medication	2.5% (NR†)	2.52% (NR†),	
	CCTA vs. SPECT					
	Min, 2012	<2 months (Mean 55 days)	Percent change in ACE	22.2%* (20/91)	21.6% (19/89)	RR 1.03 (95% CI 0.60 to 1.80), p=0.92*
			Percent change in ARB	14.4%* (13/91)	19.3% (17/89)	RR 0.75 (95% CI 0.39 to 1.45) * p=0.39
Antiarrhythmic agent (Beta-blocker)	**CCTA vs. any functional testing**					
	Douglas, 2015 (Ladapo, 2016) PROMISE trial	3 months (60-day visit)	Initiated medication	8.1% (NR†)	5.3% (NR†)	p<0.0001‡
			Discontinued medication	2.3% (NR†)	1.9% (NR†),	
	CCTA vs. SPECT					
	Min 2012	<2 months (Mean 55 days)	Percent change in medication	16.7%* (15/91)	25% (22/89)	RR 0.67 (95% CI 0.37 to 1.20), p=0.17*
Antiarrhythmic agent (Calcium channel blockers)	**CCTA vs. SPECT**					
	Min 2012	<2 months (Mean 55 days)	Percent change in medication	17.8%* (16/91)	19.3% (17/89)	RR 0.92 (95% CI 0.50 to 1.70), p=0.80*
Statins	**CCTA vs. any functional testing**					

Medication	Author (year) Trial name	F/U	Medication disposition	CCTA % (n/N)	COMPARATOR % (n/N)	Risk Ratio (95% CI)* (p-value between groups if no effect size)
	Douglas, 2015 (Ladapo, 2016) PROMISE trial	3 months (60-day visit)	Initiated medication	12.7% (NR†),	6.2% (NR†),	p<0.0001‡
	Douglas, 2015 (Ladapo, 2016) PROMISE trial	3 months (60-day visit)	Discontinued medication	2.2% (NR†)	2.1% (NR†),	
	CCTA vs. SPECT					
	Min 2012	<2 months (Mean 55 days)	Percent change in medication	34.4%* (31/91)	39.8% (35/89)	RR 0.87 (95% CI 0.59 to 1.27), p=0.47*
Non statin lipid-lowering	**CCTA vs. SPECT**					
	Min 2012	<2 months (Mean 55 days)	Percent change in medication	13.3%* (12/91)	15.9% (14/89)	RR 0.84 (95% CI 0.41 to 1.71), p=0.63*
Prescription or use of medications change	**CCTA vs. ETT (ECG)**					
	McKavanagh, 2015 CAPP trial	12 months	Medical management	40.7% (99/243)	14.3% (35/245)	RR 2.85 (95% CI 2.03 to 4.02), p<0.001*
	The SCOT-HEART Investigators, 2015, 2018 SCOT-HEART trial	6 weeks	Initiated medication	14% (293/2073)	4% (84/2073)	RR 3.49 (95% CI 2.76 to 4.41), p<0.001*
		6 weeks	Discontinued medication	3.7% (77/2073)	0.4% (8/2073)	RR 9.63 (95% CI 4.66 to 19.89), p<0.001*
		Median 4.8 years	Initiated medication	19.4% (402/2073)	14.7% (305/2073)	RR 1.32 (95% CI 1.15 to 1.51), p<0.001*
		6 weeks	Initiated antianginal medication	4.0% (82/2073)	0.5% (11/2073)	RR 7.45 (95% CI 3.98 to 13.95), p<0.001*
		6 weeks	Discontinued antianginal medication	5.4% (112/2073)	0.3% (6/2073)	RR 18.67 (95% CI 8.23 to 42.34), p<0.001*
		Median 4.8 years	Initiated antianginal medication	13.2% (273/2073)	10.7% (221/2073)	RR 1.24 (95% CI 1.05 to 1.46), p<0.013* initiated medication OR 1.27 (95% CI 1.05 to 1.54), p=NR

Δ = change; ACE = Angiotensin converting enzyme inhibitor; adj. = adjusted; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiogram; ETT = exercise treadmill testing; F/U = follow-up period; ICA = invasive coronary angiography; MD = mean difference; NA = not applicable; N = number; NR = not reported; OR= odds ratio; RR = relative risk; SAQ = Seattle Angina Questionnaire; SD= standard deviation; SPECT = single photon emission computed tomography; vs. = versus

*Calculated unless otherwise indicated. (For **Min, 2021** baseline medication percentages calculated from (n/N) in Table 4.)

†Douglas, 2015 reports the proportion of patients who initiated a preventive medication, and who were not initially using the medication at baseline, only % and p-values reported, sample size not reported.

‡ Authors report chi-square test across categories of medication initiation, discontinuation and continuation and never used.

Appendix Table O28. Medication changes in trials evaluating CCTA in patients with suspected ACS presenting to the ED

Medication	Author (year) Trial name	F/U	Medication disposition	CCTA % (n/N)	COMPARATOR % (n/N)	Risk Ratio (95% CI)*
Aspirin	**CCTA vs. any functional testing**					
	Linde 2013, 2015 CATCH Trial	After index visit	Initiated medication	47% (134/285)	36% (106/291)	RR 1.29 (95% CI 1.06 to 1.57), p=0.01*
	Litt 2012, Hollander 2016 ACRIN-PA trial	Index visit	Initiated medication	26% (233/908)	24% (110/462)	RR 1.08 (95% CI 0.88 to 1.27), p=0.45* difference 1.9% (95% CI -3.8% to 7.5%), p=NR
		1 month	Continued medication	22% (196/884)	25% (113/452)	RR 0.89 (95% CI 0.72 to 1.09), p=0.25* difference -2.8% (95% CI -8.5% to 2.8%), p=NR
		12 months	Continued medication	34% (283/843)	37% (159/433)	RR 0.91 (95% CI 0.78 to 1.07), p=0.26* difference –3.2% (95% CI –8.9% to 2.7%), p=NR
	CCTA vs. SPECT					
	Levsky 2009, 2015 PROSPECT trial	41.7 months (Median)	Initiated medication	40% (79/200)	34% (63/200)	RR 1.25 (95% CI 0.96 to 1.64), p=0.10* difference 5.5% (95% CI -4.3% to 15%), p=0.30
	CCTA vs. ECHO					
	Levsky 2014, 2018	2 years (Median)	Initiated medication	13% (27/201)	8.0% (15/199)	RR 1.78 (95% CI 0.98 to 3.25), p=0.55*
	Uretsky 2017, PERFECT trial	48.5 hours (Median)	Percent change in medication	24% (50/206)	16% (33/205)	RR 1.51 (95% CI 1.02 to 2.24), p=0.04*
ACE inhibitors (Angiotensin converting enzyme inhibitor) or ARBs (Angiotensin receptor blocker)	**CCTA vs. any functional testing**					
	Linde 2013, 2015 CATCH Trial	After index visit	Initiated medication	27% (76/285)	24% (69/291)	RR 1.12 (95% CI 0.85 to 1.49), p=0.41*
Antiarrhythmic agent (Beta-blocker)	**CCTA vs. any functional testing**					
	Linde 2013, 2015 CATCH Trial	After index visit	Initiated medication	24% (67/285)	19% (54/291)	RR 1.27 (95% CI 0.92 to 1.74), p=0.15*
	CCTA vs. ECHO					

Medication	Author (year) Trial name	F/U	Medication disposition	CCTA % (n/N)	COMPARATOR % (n/N)	Risk Ratio (95% CI)*
	Levsky 2014, 2018	2 years (Median)	Initiated medication	9% (18/201)	4% (7/199)	RR 2.55 (95% CI 1.09 to 5.96), p=0.025*
	Uretsky 2017, PERFECT trial	8.5 hours (Median)	Percent change in medication	8% (18/206)	6% (13/205)	RR 1.38 (95% CI 0.69 to 2.74), p=0.36*
Antiarrhythmic agent (Calcium channel blockers)	**CCTA vs. any functional testing**					
	Linde 2013, 2015 CATCH Trial	After index visit	Initiated medication	18% (52/285)	11% (33/291)	RR 1.61 (95% CI 1.07 to 2.41), p=0.02*
	CCTA vs. ECHO					
	Uretsky 2017, PERFECT trial	8.5 hours (Median)	Percent change in medication	5% (11/206)	3% (5/205)	RR 2.19 (95% CI 0.77 to 6.19), p=0.13*
Statins	**CCTA vs. any functional testing**					
	Linde 2013, 2015 CATCH Trial	After index visit	Initiated medication	44% (125/285)	38% (110/291)	RR 1.16 (95% CI 0.95 to 1.41), p=0.14*
	Litt 2012, Hollander 2016 ACRIN-PA trial	Index visit	Initiated medication	17% (153/908)	16% (75/462)	RR 1.04 (95% CI 0.81 to 1.34), p=0.77*
		1 month	Continued medication	14% (120/885)	11% (48/452)	RR 1.28 (95% CI 0.93 to 1.75), p=0.13*
		12 months	Continued medication	24% (198/835)	18% (78/431)	RR 1.31 (95% CI 1.04 to 1.66), p=0.022
	CCTA vs. SPECT					
	Levsky 2009, 2015 PROSPECT trial	41.7 months (Median)	New statin prescription	25% (50/200)	18% (36/200)	RR 1.39 (95% CI 0.95 to 2.03), p=0.089*
	Levsky 2009, 2015 PROSPECT trial	41.7 months (Median)	Increased dose	3% (6/200)	3% (6/200)	RR 1.0 (95% CI 0.33 to 3.05), p=1.0*
	CCTA vs. ECHO					
	Uretsky 2017, PERFECT trial	8.5 hours (Median)	Percent change in medication	18% (37/206)	17% (35/205)	RR 1.05 (95% CI 0.69 to 1.60), p=0.81*
New or increased lipid prescription	**CCTA vs. ECHO**					
	Levsky 2014, 2018	2 years (Median)	New or Increased dose	14% (28/201)	6% (12/199)	RR 2.31 (95% CI 1.21 to 4.41), p=0.009*
Antiplatelet drugs *Adenosine diphosphate (ADP) receptor inhibitors*	**CCTA vs. any functional testing**					
	Linde 2013, 2015 CATCH Trial	After index visit	Initiated medication	14% (40/285)	6% (18/291)	RR 2.27 (95% CI 1.33 to 3.86), p=0.002*

Medication	Author (year) Trial name	F/U	Medication disposition	CCTA % (n/N)	COMPARATOR % (n/N)	Risk Ratio (95% CI)*
Platelet inhibitors Thienopyridines	**Litt 2012 (Hollander 2016)** † ACRIN-PA trial	Index visit	Initiated medication	3% (24/908)	2% (7/462)	RR 1.74 (95% CI 0.76 to 4.02), p=018*
		1 month	Continued medication	4% (31/884)	2% (8/452)	RR 1.98 (95% CI 0.92 to 4.27), p=0.074*
		12 months	Continued medication	4% (37/830)	3% (12/430)	RR 1.60 (95% CI 0.84 to 3.03), p=0.15*
	CCTA vs. ECHO					
	Levsky 2014, 2018 ‡	2 years (Median)	Initiated medication	4% (8/201)	44% (7/199)	RR 1.13 (95% CI 0.42 to 3.06), p=0.81*
	Uretsky 2017, PERFECT trial	48.5 hours (Median)	Percent change in medication	3% (6/206)	3% (7/205)	RR 0.85 (95% CI 0.29 to 2.49), p=0.77*
General: Anti-hypertensive drugs	**CCTA vs. ECHO**					
	Uretsky 2017, PERFECT trial	48.5 hours (Median)	Percent change in medication	10% (20/206)	18% (37/205)	RR 0.54 (95% CI 0.32 to 0.89), p=0.015*
Nitrates	**CCTA vs. any functional testing**					
	Linde 2013, 2015 CATCH Trial	After index visit	Initiated medication	17% (49/285)	11% (33/291)	RR 1.52 (95% CI 1.01 to 2.28), p=0.045*
	CCTA vs. ECHO					
	Uretsky 2017, PERFECT trial	48.5 hours (Median)	Percent change in medication	5% (9/206)	4% (9/205)	RR 1.0.995 (95% CI 0.40 to 2.46), p=1.0*
Diuretics	**CCTA vs. any functional testing**					
	Linde 2013, 2015 CATCH Trial	After index visit	Initiated medication	21% (61/285)	14% (41/291)	RR 1.52 (95% CI 1.06 to 2.18), p=0.022*
Medication to control diabetes	**CCTA vs. ECHO**					
	Uretsky 2017, PERFECT trial	48.5 hours (Median)	Percent change Insulin use	1% (3/206)	1% (2/205)	RR 1.49 (95% CI 0.25 to 8.84), p=0.66*
			Percent change Oral Hypoglycemics	0% (0/206)	0% (0/205)	NC

ACE = Angiotensin converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ED = emergency department; ETT = exercise treadmill testing; F/U = follow-up period; HR = hazard ratio; ICA = invasive coronary angiography; IRQ = interquartile range; NA = not applicable; NC = not calculable; N = number; NR = not reported; OR= odds ratio; RR = relative risk; SD= standard deviation; SPECT = single photon emission computed tomography; UA = unstable angina; vs. = versus

*Calculated unless otherwise indicated.

†**Litt 2012 (Hollander 2016):** reports Thienopyridines.

‡ **Levsky 2014, 2018:** reports Clopidogrel.

Appendix Table O29. Cumulative Frequency of Acute Coronary Syndrome (ACS), Unstable Angina (UA) in trials comparing CCTA versus functional testing in stable outpatients with suspected CAD

Outcome	Author (year) Trial name	F/U	CCTA % (n/N)	COMPARATOR % (n/N)	Risk Ratio (95% CI) *
ACS	**CCTA vs. any functional testing, CCTA vs. SPECT, CCTA vs. ETT (ECG), and CCTA vs. ICA**				
	No Studies				
UA	**CCTA vs. any functional testing**				
	Douglas, 2015† PROMISE trial	12 months	1% (49/4996)	0.7% (34/5007)	RR 1.44 (95% CI 0.93 to 2.23), p=0.096 *
		Median 25 months	1.2% (61/4996)	0.8% (41/5007)	RR 1.49 (95% CI 1.01 to 2.21), p=0.045 *
	CCTA vs. ETT (ECG)				
	McKavanagh, 2015 CAPP Trial	12 months	0.41% (1/243)	1.2% (3/245)	RR 0.34 (95% CI 0.04 to 3.21), p=0.32*

ABBREVIATIONS: ACS = acute coronary syndrome; adj. = adjusted; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; CT = computed tomography; ECG = electrocardiogram; ECT = Exercise stress electrocardiogram test; ETT = exercise treadmill testing; F/U = follow-up period; ICA = invasive coronary angiography; NC = not calculable; N = number; RR = relative risk; SPECT = single photon emission computed tomography; UA = unstable angina; vs = versus

*Calculated unless otherwise indicated. For dichotomous values, calculated the Risk Ratio/Relative Risk (RR) and associated 95% CI using the Rothman Episheet.

†Douglas, 2015: Hospitalization for unstable angina; included in meta-analysis for cardiac hospitalization, Hazard Ratio (HR) not reported.

Appendix Table O30. Cumulative Frequency of Acute Coronary Syndrome (ACS), Unstable Angina (UA) in trials comparing CCTA with functional testing in patients with suspected ACS presenting to the ED

Outcome	Author (year) Trial name	F/U	CCTA % (n/N)	COMPARATOR % (n/N)	-Risk Ratio (95% CI)*
ACS	**CCTA vs. any functional testing**				
	Chang, 2008	1 month (30 days)	29% (39/133)	29% (39/133)	RR 1.00 (95% CI 0.69 to 1.45), p=1.0*
	Dedic, 2016 † BEACON trial	At discharge	9% (22/250)	7% (17/250)	RR 1.29 (95% CI 0.70 to 2.38), p=0.40*
		1 month	0.5% (1/250)	1% (3/250)	RR 0.33 (95% CI 0.04 to 3.18), p=0.32*
	Hoffman, 2012 ROMICAT-II trial	28 days	9% (43/501)	6% (32/499)	RR 1.34 (95% CI 0.86 to 2.08), p=0.19*
	Linde 2013, 2015 CATCH Trial §	4 months (120 days)	0% (0/285)	1% (3/291), p=NR	(NC)‡
		Median 18.7 months	0.7% (2/285)	2% (7/291)	RR 0.29 (95% CI 0.06 to 1.39), p=0.1*
	Litt 2012, Hollander 2016 ACRIN-PA trial	Index visit	3% (28/908)	2% (7/462)	RR 2.04 (95% CI 0.90 to 4.62), p=0.08* difference 1.6% (95% CI -4.0% to 7.2%), p=NR
	Hamilton-Craig, 2014 CT-COMPARE trial**	Index visit	5.3% (17/322)	2.9% (7/240)	RR 1.81 (95% CI 0.76 to 4.30) * p=0.17
UA	**CCTA vs. any functional testing**				
	Chang, 2008	1 month (30 days)	25% (28/113)	18% (24/133)	RR 1.37 (95% CI 0.85 to 2.23), p=0.2 *
	Dedic, 2016	1 month	3% (8/250)	1% (3/250)	RR 2.67 (95% CI 0.72 to 9.94), p=0.13*

	BEACON trial				
	Hoffman, 2012 ROMICAT-II trial	28 days	0.2% (1/501)	0.4% (2/499)	RR 0.50 (95% CI 0.05 to 5.47), p=0.56*
	Linde 2013, 2015 CATCH Trial	4 months (120 days)	0.4% (1/285)	0% (0/291) p=NR	(NC)‡
		Median 18.7 months	1% (3/285)	2% (5/291), p=0.72	RR 0.61 (95% CI 0.15 to 2.54), p=0.50*
	CCTA vs. SPECT				
	Goldstein, 2011 CT-STAT trial	Index visit	0.8% (3/361)	0.9% (3/338)	RR 0.94 (95% CI 0.19 to 4.60), p=0.91*
		Between discharge and 6 months	0% (0/330)	0% (0/297), p=NA	(NC)‡
	Goldstein, 2007	Between discharge and 6 months	0% (0/99)	0% (0/98), p=NA	(NC)‡
	CCTA vs. ECHO				
	Uretsky 2017, PERFECT trial	12 months	0.5% (1/206)	0% (0/205), p=NA	(NC)‡
	CCTA vs. ETT (ECG)				
	Hamilton-Craig, 2014 CT-COMPARE trial	Index visit	3.4% (11/322)	1.7% (4/240)	RR 2.05 (95% CI 0.66 to 6.36), p=0.20*

ABBREVIATIONS: ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ED = emergency department; ETT = exercise treadmill testing; F/U = follow-up period; NA = not applicable; NC = not calculable; N = number; NR = not reported; RR = relative risk; SPECT = single photon emission computed tomography; UA = unstable angina; vs = versus

*Calculated unless otherwise indicated. (RR and p-values calculated using Rothman Episheet.)
†**Dedic, 2016:** ACS defined as either unstable angina pectoris or myocardial infarction
‡ Relative risk not calculated because n=0, undefined estimate calculated but not reported.
§ **Linde, 2013, 2015:** ACS includes acute myocardial infarction composite data
** **Hamilton-Craig, 2014**: ACU includes Any Acute Coronary Syndrome

Appendix Table O31. Cumulative Frequency of Stroke, Cardiac Arrest, Continued chest pain, Recurrent ischemia, in trials comparing CCTA with functional testing in stable outpatients with suspected CAD

Outcome	Author (year) Trial name	F/U	CCTA % (n/N)	COMPARATOR % (n/N)	Risk Ratio (95% CI)*
Stroke (nonfatal)	**CCTA vs. any functional testing**				
	Douglas, 2015** PROMISE trial	Within 72 hours of index test	0.0002% (1/4996)	0.0004% (2/5007)	RR 0.50 (95% CI 0.05 to 5.52), p=0.65*
	CCTA vs. SPECT				
	Stillman, 2020 RESCUE trial	16.2 months	Overall: 0.001% (1/1047)†, p=NR		NA
	CCTA vs. ETT (ECG)				
	The SCOT-HEART Investigators, 2015 SCOT-HEART trial	Median 1.7 years	0.1% (5/2073)	0.2% (7/2073)	RR 0.71 (95% CI 0.23 to 2.25), p=0.56* adj. HR 0.727 (95% CI 0.228 to 2.315), p=0.59§
	The SCOT-HEART Investigators, 2018 SCOT-HEART trial	Median 4.8 years	0.7% (15/2073)	1.0% (20/2073)	RR 0.75 (95% CI 0.40 to 1.46), p=0.40* adj. HR 0.74 (95 % CI 0.38 to 1.44), p=NR §
Cardiac arrest	**CCTA vs. any functional testing**				
	No Studies				
Continued chest pain	**CCTA vs. ETT (ECG)**				
	McKavanagh, 2015 CAPP Trial	12 Months	3.3% (8/243)	13.1% (32/245)	RR 0.25 (95% CI 0.12 to 0.54), p=0.0001*
		12 Months	0.82% (2/243)	6.9% (17/245)	RR 0.12 (95% CI 0.03 to 0.51), p=0.0005*
	The SCOT-HEART Investigators, 2018 SCOT-HEART trial	Median 1.7 years	3.7% (76/2073)	3.3% (69/2073)	RR 1.10 (95% CI 0.80 to 1.52), p=0.60* adj. HR 1.11 (95% CI 0.81 to 1.55), p=0.513 §
Recurrent ischemia	**CCTA vs. SPECT**				
	Karthikeyan, 2017 IAEA-SPECT/CTA trial	12 months	0.7% (1/152)	1.3% (2/151)	RR 0.50 (95% CI 0.05 to 5.42), p=0.56*

ABBREVIATIONS: ACS = acute coronary syndrome; adj. = adjusted; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; CTA = computed tomography angiography; ECG = electrocardiogram; ETT = exercise treadmill testing; F/U = follow-up period; HR = hazard ratio; ICA = invasive coronary angiography; NA = not applicable; NC = not calculable; N = number; NR = not reported; RR = relative risk; SPECT = single photon emission computed tomography; UA = unstable angina; vs = versus

Stillman, 2020: Only reports overall cases (not by testing arm); not enough information to calculate an effect estimate (95% CI) or p-value for the comparison of interest, p-value provided by the authors. Only reports HR for MACE.

*Calculated unless otherwise indicated. (Risk Ratio/Relative Risk and p-values calculated using Rothman Episheet.)

† **Stillman 2020:** Only reports overall % of cases (not by testing arm).

‡ Relative risk not calculated because n=0, undefined estimate calculated but not reported.

§ HR reported by the studies adjusted for the following:

- **The SCOT-HEART Investigators, 2018:** adjusted for the variables in the minimization algorithm (per protocol) The hazard ratios were determined with the use of adjusted Cox regression models. The confidence intervals have not been adjusted for multiplicity, so intervals should not be used to infer definitive treatment effects.
- **Chang, 2019:** Only reports adj. HR for MACE
- **Dewey, 2016:** Only reports adj. HR for MACE and revascularization
- **Levsky, 2015:** Only reports HR for cardiac catheterization

- **Douglas, 2015:** All hazard ratios were adjusted for age, sex, CAD risk equivalent (history of either diabetes, peripheral arterial disease, or cerebrovascular disease), and the pre-specification of the intended functional test if randomized to the functional testing arm.

Appendix Table O32. Cumulative Frequency of Stroke, Cardiac Arrest, Continued chest pain, Recurrent ischemia, in trials evaluating CCTA in patients with suspected ACS presenting to the ED

Outcome	Author (year) Trial name	F/U	CCTA % (n/N)	COMPARATOR % (n/N)	Risk Ratio (95% CI)*
Stroke (nonfatal)	**CCTA vs. any functional testing or ETT**				
	No Studies				
	CCTA vs. SPECT				
	Levsky 2009, 2015 PROSPECT trial	12 months	0% (0/200)	1% (2/200)	(NC) ‡
	CCTA vs. ECHO				
	Levsky 2014, 2018	2 years	0.5% (1/201)	2.0% (3/199)	RR 0.33 (95% CI 0.35 to 3.15), p=0.31*
Cardiac arrest	**CCTA vs. any functional testing, SPECT or ETT**				
	No Studies				
	CCTA vs. ECHO				
	Levsky 2014, 2018	2 years	0.5% (1/201)	0% (0/199)	(NC) ‡
Continued chest pain	**CCTA vs. any functional testing**				
	Linde 2013, 2015 CATCH Trial§	4 months (120 days)	2% (7/285)	4% (11/291)	RR 0.65 (95% CI 0.26 to 1.65), p=0.36*
	CCTA vs. SPECT				
	Goldstein, 2007	6 months	6.1% (6/99)	6.1% (6/98)	RR 0.99 (95% CI 0.33 to 2.97), p=0.10*
	Nabi, 2016	Median 6.5 months	2.8% (8/283)	1.7% (5/300)	Outpatient visit RR 1.70 (95% CI 0.56 to 5.12), p=0.34*
			8.5% (24/283)	9.0% (27/300)	Hospital readmission (chest pain) RR 0.94 (95% CI 0.56 to 1.60), p=0.82*
			9.9% (28/283)	12.3% (37/300)	Emergency department visit RR 0.80 (95% CI 0.50 to 1.28), p=0.35*
	CCTA vs. ECHO				
	Levsky 2014, 2018	1 month	28% (54/201)	19% (36/199)	RR 1.49 (95% CI 1.02 to 2.16), p=0.04*
	Pineiro-Portela, 2021	12 months	4% (4/100)	2.9% (3/103)	RR 1.37 (95% CI 0.32 to 5.98), p=0.67*
		4.7 years	12% (12/100)	8.7% (9/103)	RR 1.37 (95% CI 0.61 to 3.12), p=0.45*
	CCTA vs. ETT (ECG)				
	No Studies				
Recurrent ischemia	**CCTA vs. any functional testing**				
	Linde 2013, 2015/CATCH Trial	4 months (120 days)	NR†	10% (29/284)	NA

ABBREVIATIONS: ACS = acute coronary syndrome; adj. = adjusted; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiogram; ECHO = echocardiogram; ED = emergency department; ETT = exercise treadmill testing; F/U = follow-up period; HR = hazard ratio; ICA = invasive coronary angiography; NA = not applicable; NC = not calculable; N = number; NR = not reported; RR = relative risk; SPECT = single photon emission computed tomography; vs = versus

*Calculated unless otherwise indicated.

† **Linde 2013, 2015:** Only reports control group data for ischemia.

‡ Relative risk not calculated because n=0, undefined estimate calculated but not reported.

§ Defined as readmitted for chest pain

Appendix Table O33. SAQ in trials comparing CCTA with functional testing in stable outpatients with suspected CAD

SAQ Domain†	Author (year) Trial name	F/U	CCTA Mean (SD)	COMPARATOR Mean (SD)	Mean difference (95% CI) *
Physical limitation	**CCTA vs. any functional testing**				
	Douglas, 2015 ‡ PROMISE trial	6 months	93.6 (14.6)	94.0 (13.9)	MD –0.4 (95% CI –1.2 to 0.4), p=NR
		12 months	94.3 (14.1)	95.0 (12.4)	MD –0.8 (95% CI –1.6 to -0.0), p=NR
		24 months	95.3 (12.1)	94.8 (13.2)	MD –0.7 (95% CI –1.5 to 0.1), p=NR
	CCTA vs. SPECT				
	Min, 2012	<2 months (Mean 55 days)	Δ from baseline: 2.5 (21.3)	Δ from baseline: 4.1 (19.0)	MD in change scores: -1.60 (95% CI -7.54 to 4.34) *
	CCTA vs. ETT (ECG)				
	The SCOT-HEART Investigators, 2015 (Williams, 2017) SCOT-HEART trial	6 weeks	Δ from baseline: −0.5 (0.5)	Δ from baseline −0.0 (0.5)	MD in change scores: −0.72 (95% CI −2.08 to 0.63), p=0.2957
		6 months	Δ from baseline: 1.6 (0.6)	Δ from baseline: 3.0 (0.6)	MD in change scores: −1.74 (95% CI −3.34 to −0.14), p=0.0329
	McKavanagh, 2015 CAPP trial	3 months	NR	NR	MD in change scores: 20.54 (95% CI -4.3 to 3.3), p=0.779
		12 months	NR	NR	MD in change scores: 0.33 (95% CI -4.3 to 5.0), p=0.889
Angina stability	**CCTA vs. any functional testing**				
	Douglas, 2015 PROMISE trial	6 months	54.4 (16.5)	53.7 (15.5)	MD 0.7 (95% CI –0.1 to 1.6), p=NR
		12 months	52.2 (14.5)	52.8 (14.8)	MD –0.7 (95% CI –1.5 to 0.1), p=NR
		24 months	95.0 (12.9)	51.3 (12.0)	MD –0.1 (95% CI –0.8 to 0.6), p=NR
	CCTA vs. SPECT				
	Min, 2012	<2 months (Mean 55 days)	Δ from baseline: 30.0 (37.0)	Δ from baseline: 22.9 (30.1)	MD in change scores: 7.10 (95% CI -2.834 to 17.03) *
	CCTA vs. ETT (ECG)				
	The SCOT-HEART Investigators, 2015 (Williams, 2017) SCOT-HEART trial	6 weeks	Δ from baseline: 16.7 (0.9)	Δ from baseline: 15.8 (0.9)	MD in change scores: 1.03 (95% CI −0.61 to 2.68), p=0.2184
		6 months	Δ from baseline: 13.4 (0.9)	Δ from baseline: 12.5 (0.9)	MD in change scores: 1.27 (95% CI −0.27 to 2.80), p=0.1059
	McKavanagh, 2015 CAPP trial	3 months	NR	NR	MD in change scores: -11.1 (95% CI -17.4 to -4.8), p=0.001
		12 months	NR	NR	MD in change scores: -6.8 (95% CI -12.8 to -0.7), p=0.028
Angina frequency	**CCTA vs. any functional testing**				
	Douglas, 2015 PROMISE trial	6 months	93.1 (12.1)	92.9 (13.1)	MD 0.2 (95% CI –0.4 to 0.9), p=NR
		12 months	94.0 (11.8)	94.1 (11.6)	MD –0.1 (95% CI –0.7 to 0.5), p=NR
		24 months	95.0 (11.2)	95.1 (10.8)	MD –0.2 (95% CI –0.8 to 0.4), p=NR
	CCTA vs. SPECT				

	Min, 2012	<2 months (Mean 55 days)	Δ from baseline: 10.2 (16.4)	Δ from baseline: 7.6 (14.8)	MD in change scores: 2.6 (95% CI -1.998 to 7.198)*
	CCTA vs. ETT (ECG)				
	The SCOT-HEART Investigators, 2015 (Williams, 2017) SCOT-HEART trial	6 weeks	Δ from baseline: 11.2 (0.6)	Δ from baseline: 11.8 (0.6)	MD in change scores: −0.84 (−2.20 to 0.54), p=0.2277
		6 months	Δ from baseline: 18.3 (0.6	Δ from baseline: 19.2 (0.6)	MD in change scores: −1.55 (95% CI −2.85 to −0.25), p=0.0198
	McKavanagh, 2015 CAPP trial	3 months	NR	NR	MD in change scores: -2.7 (-6.8 to 1.3), p=0.184
		12 months	NR	NR	MD in change scores: -1.9 (95% CI -6.0 to 2.2), p=0.365
Treatment satisfaction	**CCTA vs. any functional testing**				
	Douglas, 2015 PROMISE trial	6 months	89.4 (18.6)	88.2 (20.9)	MD 1.4 (95% CI 0.3 to 2.4), p=NR
		12 months	89.4 (18.4)	88.7 (20.0)	MD 1.0 (95% CI –0.1 to 2.1), p=NR
		24 months	89.8 (17.6)	89.4 (18.6)	MD 1.0 (95% CI –0.1 to 2.1), p=NR
	CCTA vs. SPECT				
	Min, 2012	<2 months (Mean 55 days)	Δ from baseline: 4.5 (17.8)	Δ from baseline: 0.6 (18.2)	MD in change scores: 3.9 (95% CI -1.395 to 9.195) *
	CCTA vs. ETT (ECG)				
	The SCOT-HEART Investigators, 2015 (Williams, 2017) SCOT-HEART trial	6 weeks	Δ from baseline: −7.0 (0.4)	Δ from baseline: −7.0 (17.1)	MD in change scores: 0.03 (95% CI −1.07 to 1.14), p=0.9525
		6 months	Δ from baseline: −5.0 (0.4)	Δ from baseline: −4.3 (0.4)	MD in change scores: −0.97 (95% CI−2.14 to 0.21), p=0.1060
	McKavanagh, 2015 CAPP trial	3 months	NR	NR	MD in change scores: -2.12 (95% CI -5.3 to 1.2), p=0.213
		12 months	NR	NR	MD in change scores: -1.4 (95% CI -5.2 to 2.3), p=0.446
	CCTA vs. ICA				
	No Studies				
QOL	**CCTA vs. any functional testing**				
	Douglas, 2015 PROMISE trial	6 months	Mean, (SD) 80.4 (19.7)	Mean, (SD) 80.6 (20.1)	MD –0.2 (95% CI –1.2 to 0.9), p=NR
		12 months	81.7 (19.1)	82.4 (18.8)	MD –0.5 (95% CI –1.5 to 0.6), p=NR
		24 months	82.8 (18.8)	83.0 (18.6)	MD –0.2 (95% CI –1.3 to 0.9), p=NR
	CCTA vs. SPECT				
	Min, 2012	<2 months (Mean 55 days)	Δ from baseline: 13.5 (22.6)	Δ from baseline: 11.6 (19.0)	MD in change scores: 1.900 (95% CI -4.248 to 8.048) *
	CCTA vs. ETT (ECG)				
	The SCOT-HEART Investigators, 2015 (Williams, 2017)	6 weeks	Δ from baseline: 8.7 (0.5)	Δ from baseline: 9.9 (0.6)	MD in change scores: −1.31 (95% CI −2.66 to 0.05), p=0.0585

	SCOT-HEART trial	6 months	Δ from baseline: 15.5 (0.6)	Δ from baseline: 18.6 (0.6)	MD in change scores: −3.48 (95% CI −4.95 to −2.01), p<0.0001
	McKavanagh, 2015 CAPP trial	3 months	NR	NR	MD in change scores: -5.7 (95% CI -10.3 to -1.2), p=0.014
		12 months	NR	NR	MD in change scores: (95% CI) -4.8 (95% CI -9.6 to -0.19), p=0.041

ABBREVIATIONS: Δ = change; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiogram; ETT = exercise treadmill testing; F/U = follow-up period; ICA = invasive coronary angiography; MD = mean difference; N = number; NR = not reported; QOL = quality of life; SAQ = Seattle Angina Questionnaire; SD= standard deviation; SPECT = single photon emission computed tomography; vs. = versus

*Calculated unless otherwise indicated.
†Scores range from 0 to 100: Physical Limitation (9 items), Angina Stability (1 item), Angina Frequency (2 items), Treatment Satisfaction (4 items), and Quality of Life (3 items). QOL scale (scale 0-100; higher=increased QOL) with higher scores indicating fewer symptoms and better health status.
‡**Douglas 2015 (Mark, 2016 Table 3) PROMISE Trial:** Diagnostic testing strategy groups are as randomized. 95% confidence intervals on treatment differences were calculated as CTA minus functional testing.

Appendix Table O34. Included studies using trial names and associated publications: Primary evidence base for efficacy and safety

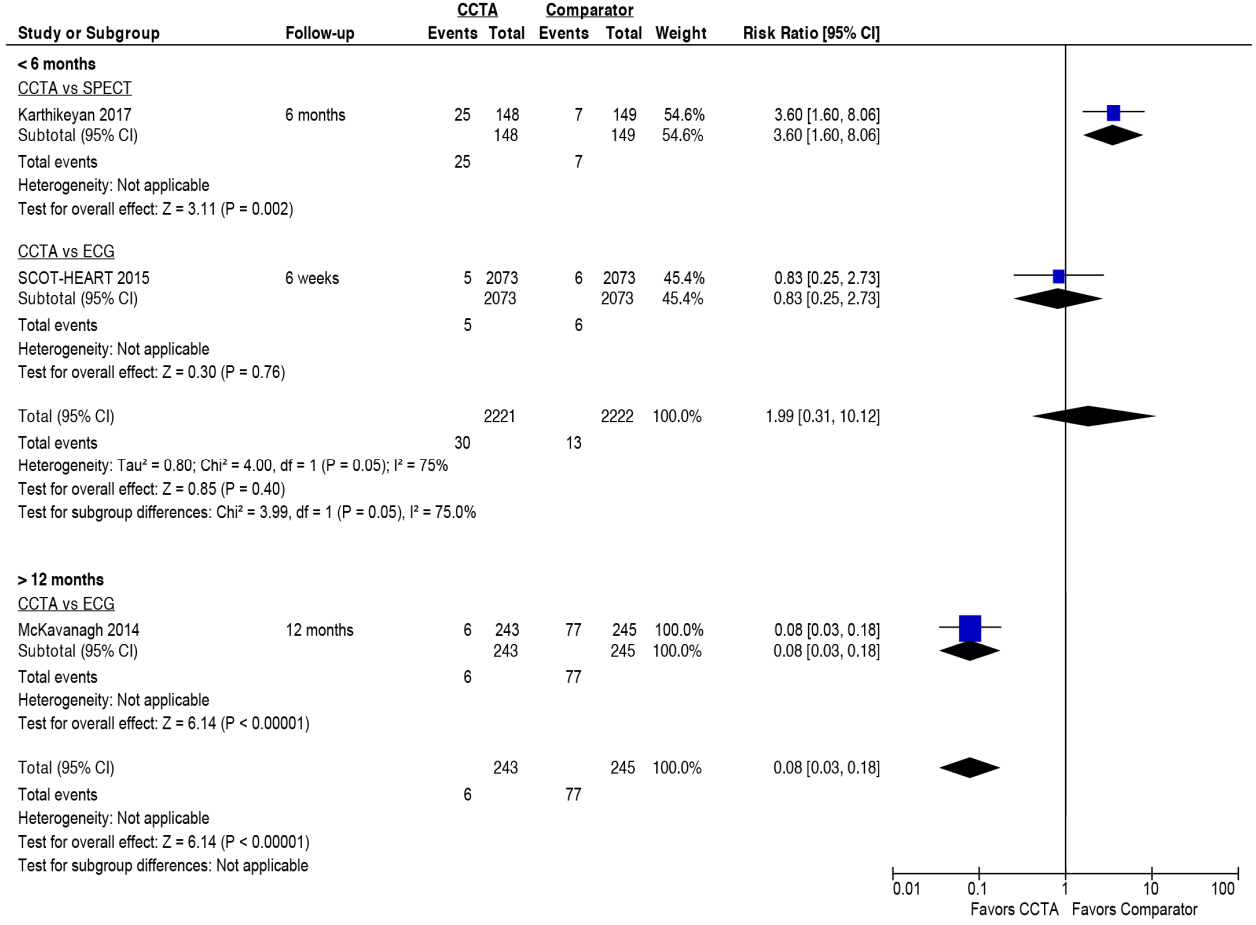
	Trial name	Index publication	Additional associated publications
CCTA			
1.	ACRIN-PA trial[32,46]	Litt, 2012	Hollander, 2016
2.	BEACON trial[12]	Dedic, 2016	None.
3.	CAD-Man trial[15]	Dewey, 2016	None.
4.	CAPP trial[52]	McKavanagh, 2015	None.
5.	CATCH trial[44,45]	Linde, 2013	Linde, 2015
6.	CT-STAT trial[23]	Goldstein, 2011	None.
7.	CT-COMPARE trial[29]	Hamilton-Craig, 2014	None.
8.	CONSERVE trial[10]	Chang, 2019	None.
9.	IAEA-SPECT/CTA trial[36]	Karthikeyan, 2017	None.
10.	PERFECT trial[89]	Uretsky, 2017	None.
11.	PROMISE trial[17,18,37,47,49-51,64,65,77,78]	Douglas, 2015a	Douglas, 2014 Ladapo, 2016 Lu, 2017 Lowenstern, 2020 Mark, 2016 Pagidipati, 2016 Pagidipati, 2019 Litwin, 2019 Sharma, 2017 Sharma, 2019
12.	PROSPECT trial[22,41,42]	Levsky, 2015	Levsky, 2009 Goldman, 2020
13.	RESCUE trial[84,85]	Stillman, 2016	Stillman, 2020
14.	ROMICAT-II trial[31,72,87,88]	Hoffman, 2012	Truong, 2013 Truong, 2016 Reinhardt, 2018
15.	SCOT-HEART trial[2,60,61,76,91,92]	The SCOT-HEART Investigators, 2015	Newby, 2012 Newby, 2018 Williams, 2017 Williams, 2018 Adamson, 2018
16.	N/A[39,40]	Levsky, 2014	Levsky, 2018
17.	N/A[11]	Chang, 2008	None.
18.	N/A[55]	Miller, 2011	None.
19.	N/A[24]	Goldstein, 2007	None.
20.	N/A[67]	Pineiro-Portela, 2021	None.
21.	N/A[57]	Min, 2012	None.
22.	N/A[59]	Nabi, 2016	None.
CCTA FFR			
1.	PLATFORM study[16,19] (prospective cohort)	Douglas, 2015b	Douglas, 2016
SPECT-MPI			
1.	CE-MARC 2 trial[25]	Greenwood, 2016	None.
2.	WOMEN trial[53,54,80]	Mieres, 2011	Mieres, 2009

	Trial name	Index publication	Additional associated publications
			Shaw, 2011
3.	CECaT trial[79,86]*	Sharples, 2007	Thom, 2014
4.	N/A[43]	Lim, 2013	None.
5.	N/A[73]	Sabharwal, 2007	None.
6.	N/A[74]	Salame, 2018	None.
PET			
1.	N/A[58]	Mullani, 2000	None.
2.	N/A[66]	Patel, 2019	None.
Stress Echocardiography			
1.	ASSENCE trial[6,62]	Nucifora, 2009	Badano, 1999
2.	COSTAMI-II trial[13]	Desideri, 2005	None.
3.	CECaT trial[79,86]*	Sharples, 2007	Thom, 2014
4.	N/A[34]	Jeetley, 2006	None.
5.	N/A[26,93]	Zacharias, 2017	Gurunathan, 2018
6.	N/A[75]	Sanfilippo, 2005	None.

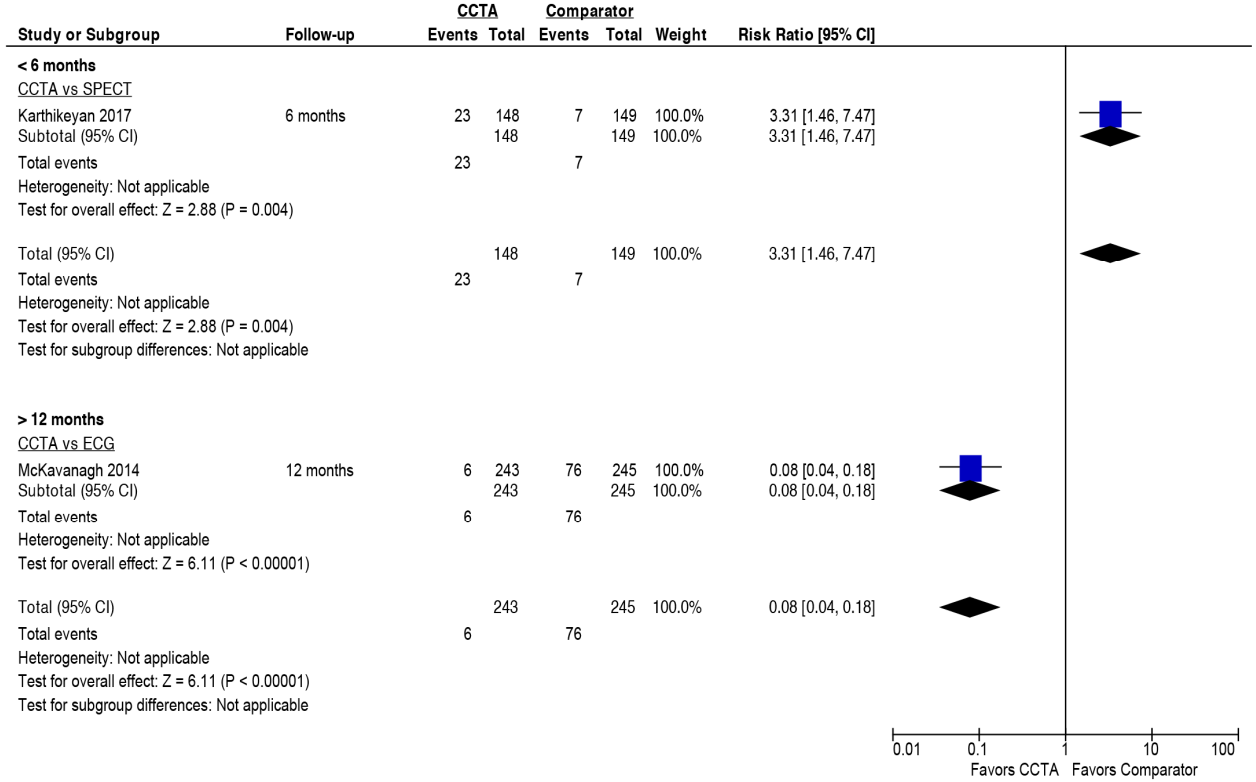
CCTA = coronary computed tomography angiography, FFR = fractional flow reserve, MPI = myocardial perfusion imaging, N/A = not applicable, PET = positron emission tomography, SPECT = single photon emission tomography.
* The CECaT trial provides data for both SPECT-MPI and stress echocardiography and is therefore listed twice under each test type.

APPENDIX P. Supplemental summary figures

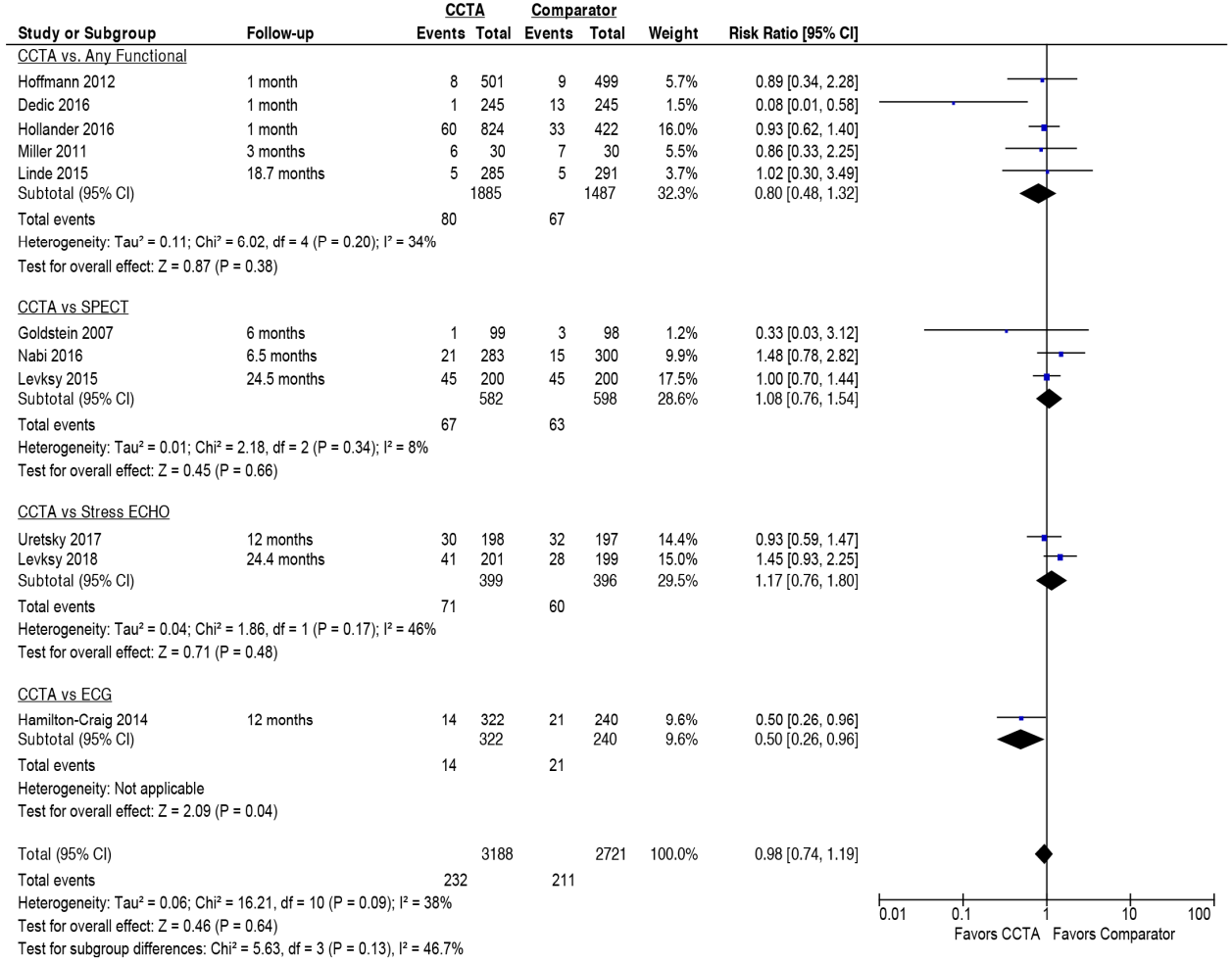
Appendix Figure P1. Figure of any additional non-invasive testing among outpatients with suspected CAD in trials assessing CCTA



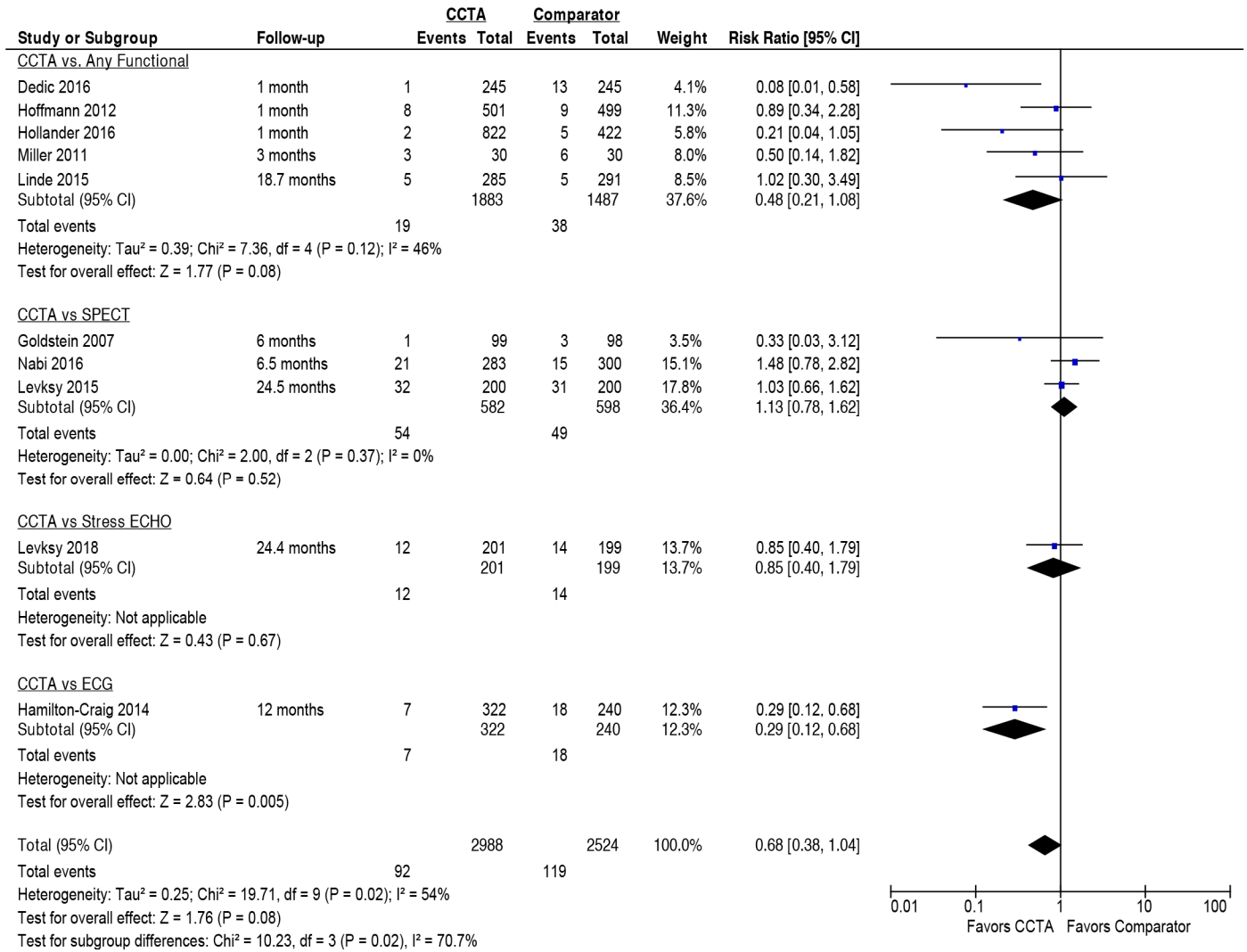
Appendix Figure P2. Figure of additional non-invasive testing involving radiation among outpatients with suspected CAD in trials assessing CCTA



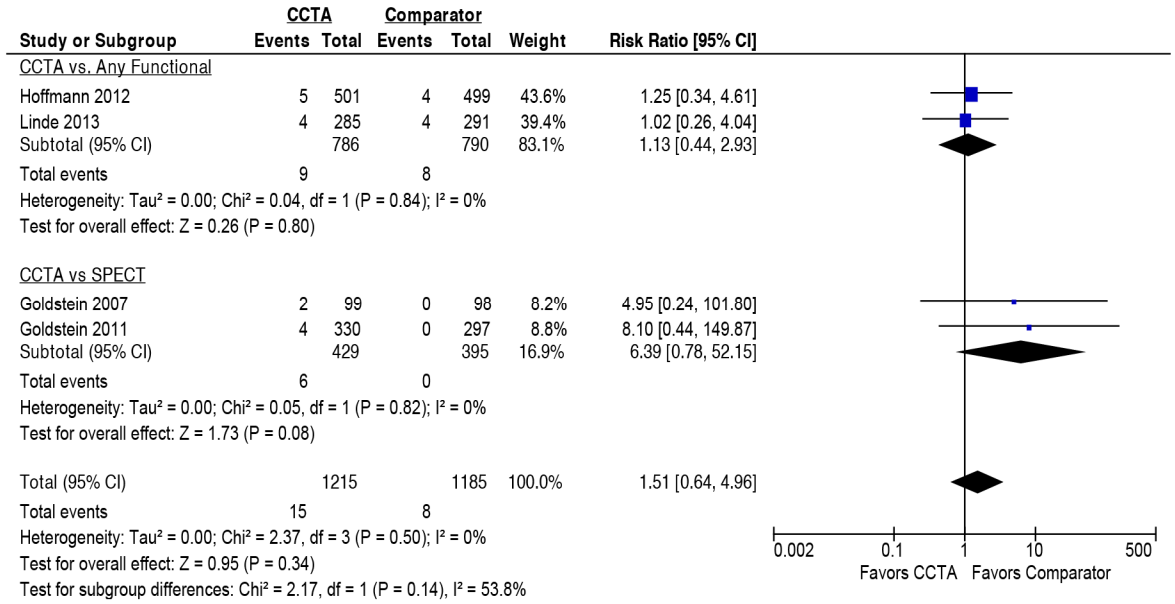
Appendix Figure P3. Figure of additional non-invasive testing among outpatients with suspected ACS in trials assessing CCTA



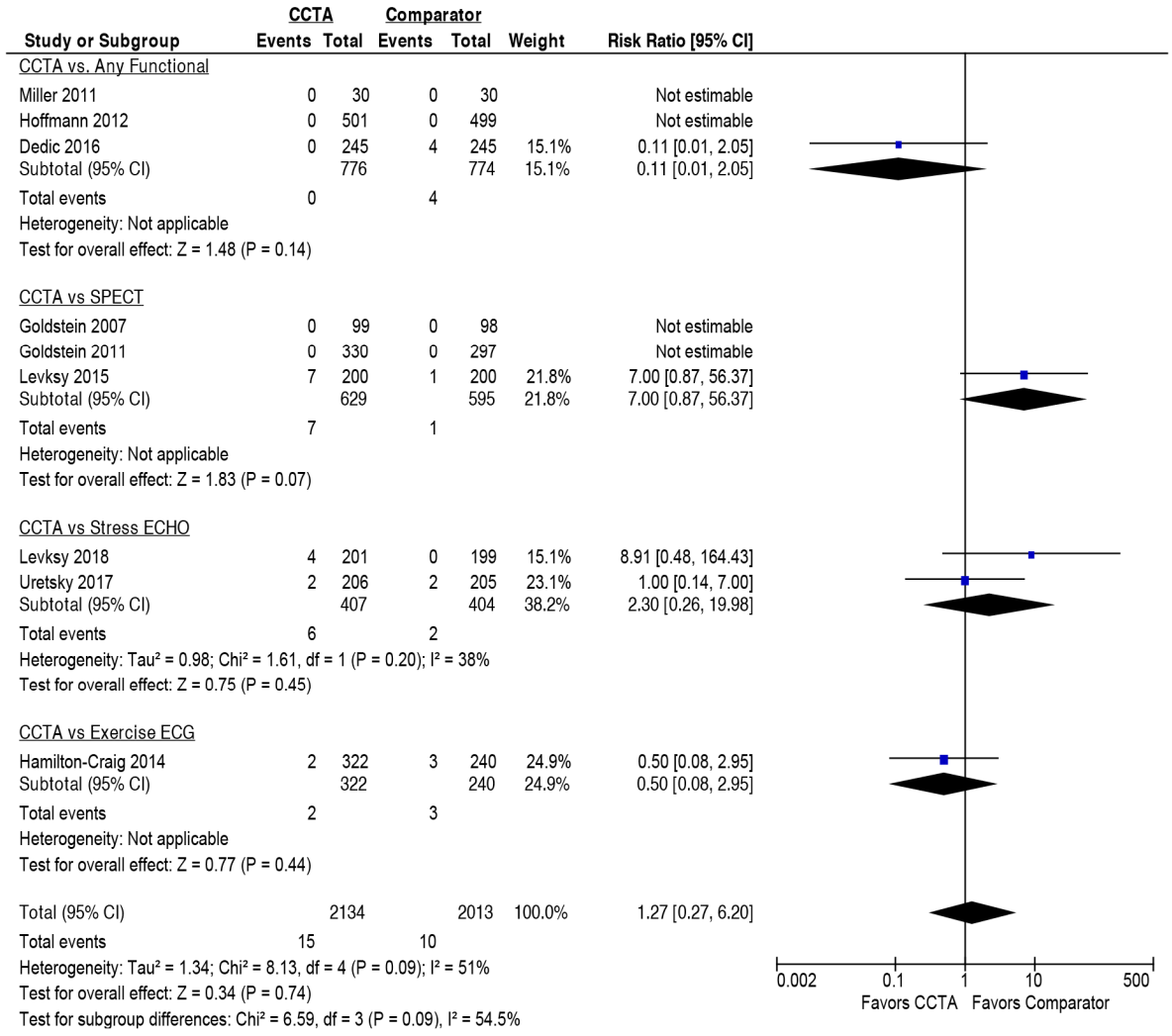
Appendix Figure P4. Figure of additional non-invasive testing involving radiation among outpatients with suspected ACS in trials assessing CCTA



Appendix Figure P5. Figure of the proportion of patients requiring CABG at index visit among outpatients with suspected CAD in trials assessing CCTA



Appendix Figure P6. Figure of the proportion of patients requiring CABG after > 1 month among outpatients with suspected CAD in trials assessing CCTA



Appendix Q. Summary Tables of Included Studites (Table 1s)

Appendix Table Q1. Demographics for included RCTs comparing CCTA versus any functional testing in populations with suspected CAD (no known history of CAD) and stable chest pain

Author, year (trial)		Douglas 2015 (PROMISE)	
Test **Sample size**		CCTA (n=4996)	Any functional testing (n=5007)
Index test received, % (n)	CCTA	92% (4589)	0.9% (47)‡
	CACS only	2% (97)	
	Nuclear stress imaging	2% (104)	63% (3159)
	Stress Echocardiography	0.5% (27)	21% (1056)
	Exercise ECG	0.3% (14)	10% (477)
	ICA	0.2% (9)	0.4% (20)
	No test	3% (156)	5% (246)
Patient demographics	Female, % (n)	51.9% (2593)	53.4% (2673)
	Age (years); mean ± SD	60.7 ± 8.3	60.9 ± 8.3
	Race, % (n)	Racial or ethnic minority: 23.5%	Racial or ethnic minority: 21.8%
	Pretest risk, % (n)†	Pre-test probability of CAD§: Low: 2.5% IM: 92.6% High: 4.9%	Pre-test probability of CAD§: Low: 2.5% IM: 92.6% High: 4.9%
	Subgroup	None	None
Cardiac risk factors, % (n)	Chest pain	73.6% (3673/4992)	71.9% (3599/5004)
	Typical angina	11.8% (590)	11.5% (576)
	Atypical angina	77.5% (3873)	77.9% (3900)
	Unstable angina	NR	NR
	Nonanginal pain	10.7% (533)	10.6% (531)
	Other primary presenting symptom**	12.2% (607/4992)	12.5% (627/5004)
	Dyspnea on exertion	14.3% (712/4992)	15.5% (778/5004)
	Prior MI	0% (0)	0% (0)
	Prior revascularization	0% (0)	0% (0)
	Known CAD	0% (0)	0% (0)
	Peripheral arterial or cerebrovascular disease	5.3% (263)	5.8% (289)
	Hypertension	65% (3247)	65% (3254)
	Diabetes	21.3% (1065)	21.5% (1079)
	Hyperlipidemia	67.4% (3365/4995)	67.9% (3402)

Author, year (trial)		Douglas 2015 (PROMISE)	
	Current smoker	50.7% (2533/4994)	51.4% (2571/5006)
Test details	CT images (slice)	≥64-slice	NA
	CACS performed	No	NA
	Type of stressor	NR	NR
	Contrast (dose)	NR	NR
Study characteristics	Setting	Outpatient	Outpatient
	Followup period % completed followup (n)	Median 25 months (IQR 18-34 months, 93.5% (9350/10,003)	Median 25 months (IQR 18-34 months, 93.5% (9350/10,003)
	Study Design	RCT	RCT
	Study Quality	Good	Good

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

*p<0.05 for between group difference

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies.

‡CCTA or Calcium scoring; authors do not present data separately for the functional testing arm.

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

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

Appendix Table Q2. Demographics for included RCTs comparing CCTA versus any functional testing in populations with suspected ACS (no known history of CAD)

Author, Year (trial)		Chang 2008		Dedic 2016 (BEACON)		Hoffman 2012 (ROMICAT-II)		Linde 2013 (CATCH)	
Test Sample size		CCTA (n=133)	Any Functional testing (n=133)	CCTA (n=250)	Any functional testing (n=250)	CCTA (n=501)	Any functional testing (n=499)	CCTA (n= 299)‡	Any functional testing (n= 301)‡
Index test received, % (n)	CCTA	100% (250)	0% (0)	97% (243)	2% (7)	94% (473)	0% (0)	95% (272)§	0% (0)
	ETT	0% (0)	39% (32)	0% (0)	0% (0)	0% (0)	29% (147)	0% (0)	76% (221)
	SPECT MPI	0% (0)	8% (11)	0% (0)	0% (0)	0% (0)	25% (124)	0% (0)	22% (63)
	Stress echocardiography	0% (0)	3% (4)	0% (0)	0% (0)	0% (0)	20% (102)	0% (0)	0% (0)
	Serial ECGs and Cardiac Biomarkers only	0% (0)	50% (67)	0% (0)	100% (250)	0% (0)	0% (0)	0% (0)	0% (0)
	No test performed	0% (0)	0% (0)	3% (7)	0% (0)	0% (0)	22% (109)	0% (0)	2% (7)
	Type of test NR	0% (0)	0% (0)	0% (0)	0% (0)	6% (28)	3% (17)	0% (0)	0% (0)
	Functional test (NOS)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	5% (13)	0% (0)
Patient demographics	Female, % (n)	39% (52)	38% (51)	49% (123)	45% (113)	47.9% (240)	46.1 (230)	44% (125/285)	42% (122/291)
	Age (years); mean ± SD	57 ± 14	58 ± 14	55 ± 10	53 ± 9	54±8	54±8	56 ± 12	55 ± 12
	Race, % (n)	NR	NR	NR	NR	White: 65.9% (330) Black: 28.1% (141) Asian: 3.6% (18) Other: 2.4% (12)	White: 66.1% (330) Black: 28.3% (141) Asian: 2.6% (13) Other: 3.6% (18)	NR	NR

Author, Year (trial)		Chang 2008		Dedic 2016 (BEACON)		Hoffman 2012 (ROMICAT-II)		Linde 2013 (CATCH)	
	Pretest risk, % (n)†	Low: 37.6% (50) IM: 41.4% (55) High: 21.1% (28)	Low: 36.8% (49) IM: 42.1% (56) High: 21.1% (28)	Low: 84% (211) IM: 12% (31) High: 3% (8)	Low 83% (208) IM: 16% (39) High: 1% (3)	Intermediate	Intermediate	Low: 21.4% (61/285) IM: 69.1% (197/285) High: 9.5% (27/285)	Low: 21.3% (62/291) IM: 69.1% (201/291) High: 9.5% (28/291)
	Subgroup	NR	NR	None	None	NR	NR	None	None
Cardiac risk factors, % (n)	Chest pain	100% (133)	100% (133)	100% (250)	100% (250)	100% (501)	100% (499)	100% (285/285)	100% (291/291)
	Typical angina	NR	NR	NR	NR	89.0% (446)	91.0% (454)	12% (34/285)	12% (35/291)
	Atypical angina	NR	NR	NR	NR	11.0% (55)	9.0% (45)	39% (111/285)	40% (116/291)
	Unstable angina	NR	NR	NR	NR	NR	NR	NR	NR
	Nonanginal chest pain	NR	NR	NR	NR	NR	NR	49% (140/285)	49% (143/291)
	Dyspnea	NR	NR	NR	NR	1.4% (7)	2.0% (10)	NR	NR
	Prior MI	NR	NR	NR	NR	0% (0)	0% (0)	NR	NR
	Prior revascularization	NR	NR	NR	NR	0% (0)	0% (0)	NR	NR
	Known CAD	12% (16)	17% (23)	NR	NR	0% (0)	0% (0)	15% (43/285)	12% (35/291)
	Hypertension	46% (61)	41% (55)	17% (43)	17% (43)	53.7% (269)	54.5% (272)	36% (103/285)	47% (137/291)
	Diabetes	16% (21)	19% (25)	NR	NR	17.2% (86)	17.4% (87)	12% (34/285)	10% (29/291)
	Hyperlipidemia	29% (39)	25% (33)	NR	NR	45.9% (230)	44.9% (224)	41% (117/285)	35% (102/291)
	Smoker (past or current)	17% (23)	23% (31)	37% (93)	31% (78)	49.7% (249)	48.7% (243)	15% (43/285)	12% (35/291)
Test details	CT images (slice)	64	NA	≥64	NA	≥64	NA	320	NA
	CACS performed	No	NR	No	NA	Yes	NA	No	NA

Author, Year (trial)		Chang 2008		Dedic 2016 (BEACON)		Hoffman 2012 (ROMICAT-II)		Linde 2013 (CATCH)	
	Type of stressor	NA	NA	NA	NR	NA	exercise or pharmacologic stress	NA	Dipyridamole (SPECT only)
	Contrast (dose)	Lomeprol (80mL lomeron 400; Bracco, Milan, Italy)	NA	NR	NR	NR (iodinated contrast agent)	NA	NR	NR
Study characteristics	Setting	ED	ED	ED	ED	ED	ED	OP	OP
	Followup period % completed followup (n)	30 days	30 days	30 days 98% (490/500)		28 days 99.2% (497)	28 days 98.2% (490)	120 days 96% (576/600)	
	Study Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Good	Good	Fair	Fair	Fair	Fair

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

*p<0.05 for between group difference

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies.

‡Demographic data only provided for those with follow-up data; n values reported here are total number randomized.

§39 of these 272 patients also had a functional test at index that was used to determine their treatment strategy.

Appendix Table Q3. Demographics for included RCTs comparing CCTA versus any functional testing in populations with suspected ACS (no known history of CAD)

Author, Year (trial)		Litt 2012 (ACRIN-PA)		Miller 2011	
Test **Sample size**		CCTA (n=908)‡	Any functional testing (n=462)‡	CCTA + Usual Care (n=30)	Any functional testing (n=30)
Index test received, % (n)	CCTA	84% (767)	6% (26)	100% (30)	0% (0)
	Stress testing (w/ or w/o imaging)	14% (124)	58% (267)	0% (0)	0% (0)
	ICA	4% (37)	4% (18)	0% (0)	0% (0)
	No test	9% (80)	36% (167)	0% (0)	0% (0)
	ECG and cardiac biomarkers	0% (0)	0% (0)	0% (0)	100% (30)
Patient demographics	Female, % (n)	51.2% (465)	56.3% (260)	57% (17)	43% (13)
	Age (years); mean ± SD	49±9	50±10	51±10	51±10
	Race, % (n)	White: 39.8% (361) Black: 57.8% (525) Asian: 1.2% (11) Other: 1.8% (16)	White: 35.1% (162) Black: 62.3% (288) Asian: 1.5% (7) Other: 2.2% (10)	White: 23.3% (7) Black: 46.7% (14) Asian: 0% (0) Hispanic: 30.0% (9)	White: 13.3% (4) Black: 46.7% (14) Asian: 3.3% (1) Hispanic: 36.7% (11)
	Pretest risk, % (n)†	Low-to-intermediate (%NR)	Low-to-intermediate (%NR)	Low-to-intermediate (%NR)	Low-to-intermediate (%NR)
	Subgroup	NR	NR	NR	NR
Cardiac risk factors, % (n)	Chest pain	100% (908)	100% (462)	100% (30)	100% (30)
	Typical angina	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR
	Unstable angina	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR
	Prior MI	1% (10)	1% (6)	NR	NR
	Prior revascularization	NR	NR	0% (0)	0% (0)
	Known CAD	NR	NR	0% (0)	0% (0)
	Hypertension	51.0% (463)	50.2% (232)	NR	NR
	Diabetes	14.3% (130)	13.9% (64)	NR	NR
	Hyperlipidemia	27.4% (249)	25.5% (118)	NR	NR
	Smoker (past or current)	32.0% (291)	33.8% (156)	NR	NR
Test details	CT images (slice)	≥64	NA	64	NA

Author, Year (trial)		Litt 2012 (ACRIN-PA)		Miller 2011	
	CACS performed	Yes	NA	Yes	NA
	Type of stressor	NA	exercise or pharmaco-logic	NA	NR
	Contrast (dose)	NR	NA	NR	NA
Study characteristics	Setting	ED	ED	ED	ED
	Followup period % completed followup (n)	30 days 98.9% (898)	30 days 98.9% (457)	90 days 100% (30)	90 days 100% (30)
	Study Design	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Poor	Poor

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

*p<0.05 for between group difference

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies.

‡According to how the author's reported their data, patients could have received more than one single test at their index visit

Appendix Table Q4. Demographics for included RCTs comparing CCTA versus SPECT in populations with suspected CAD (no known history of CAD) and stable chest pain

Author, year (trial)		Karthikeyan 2017 (IAEA-SPECT/CTA)		Min 2012		Stillman 2020 (RESCUE)	
Test Sample size		CCTA (n= 152)	SPECT (n= 151)	CCTA (n=91)	SPECT (n=89)	CCTA (n= 516)	SPECT (n= 531)
Index test received, % (n)	CCTA	93% (142)	0% (0)	100% (91)	0% (0)	92% (473)	0% (0)
	CACS	3% (4)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	No test	4% (6)	5% (8)	0% (0)	0% (0)	8% (43)	13% (67)
	SPECT	0% (0)	95% (146)	0% (0)	100% (89)	0% (0)	87% (464)
Patient demographics	Female, % (n)	51% (78)	54% (82)	41.8% (38)*	57.3% (51)*	45% (232)	46% (244)
	Age (years); mean ± SD	60 ± 11	60 ± 12	55.9 ± 10*	58.9 ± 9.5*	57 ± 9	58 ± 9
	Race, % (n)	Race Caucasian 73% (111) Indian 5% (8) African 1% (2) Other 0% (0) Ethnicity Hispanic 25% (38)	Race Caucasian 69% (104) Indian 5% (8) African 1% (2) Other 1% (2) Ethnicity Hispanic 20% (30)	NR	NR	American Indian or Alaskan Native 2% (10) Asian 2% (10) Black or African American 14% (72) Native Hawaiian or other <1% (<5) White 78% (402) Multiple races 2% (10) Unknown 2% (10)	American Indian or Alaskan Native 1% (5) Asian 3% (16) Black or African American 15% (80) Native Hawaiian or other <1% (<5) White 78% (414) Multiple races 1% (5) Unknown 2% (11)
	Pretest risk, % (n)†	All patients considered to be at intermediate to high risk based on the Framingham criteria		Intermediate-to-high Low 4.1% (4) IM: 62.6% (57) High: 33.0% (30)	Intermediate-to-high Low: 9.0% (8) IM: 67.4% (60) High: 23.6% (21)	NR	NR

Author, year (trial)		Karthikeyan 2017 (IAEA-SPECT/CTA)		Min 2012		Stillman 2020 (RESCUE)	
	Subgroup	None	None	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	80% (122)	80% (121)	NR	NR	100% (516)	100% (531)
	Typical angina	NR	NR	31.9% (29)	22.5% (20)	NR	NR
	Atypical angina	NR	NR	23.1% (21)	24.7% (22)	NR	NR
	Unstable angina	NR	NR	NR	NR	NR	NR
	Nonanginal chest pain	NR	NR	27.5% (25)	24.7% (22)	NR	NR
	Dyspnea	10% (15)	9% (14)	NR	NR	NR	NR
	Prior MI	0% (0)	0% (0)	0% (0)	0% (0)	NR	NR
	Prior revascularization	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	Known CAD	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	Hypertension	64% (97)	64% (97)	61.5% (56)	68.5% (61)	62% (320)	60% (319)
	Diabetes	28% (43)	29% (44)	23.1% (21)	21.3% (19)	20% (103)	21% (112)
	Hyperlipidemia	59% (90)	55% (83)	52.7% (48)	60.7% (54)	NR	NR
	Current smoker	24% (36)	17% (26)	58.2% (53)	42.7% (38)	14% (72)	16% (85)
Test details	CT images (slice)	≥64	NA	64	NA	≥64	NA
	CACS performed	3% (4)	NA	No	NA	No	NA
	Type of stressor	NA	Exercise treadmill: 33% (50) Exercise bike: 25% (38) Dipyridamole: 34% (51) Adenosine: 3% (5)	NA	Exercise (treadmill) or pharmacologic (adenosine)	NA	NR
	Contrast (dose)	Used, but type NR	NR	Iodinated contrast	Tc-99m sestamibi (some had dual isotope imaging thallium-201)	80 mL iodinated contrast	NR
	Setting	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient

Author, year (trial)		Karthikeyan 2017 (IAEA-SPECT/CTA)		Min 2012		Stillman 2020 (RESCUE)	
Study characteristics	Followup period % completed followup (n)	6 months: 98% (297/303) 12 months: % followed (NR)	6 months: 98% (297/303) 12 months: % followed (NR)	mean 55 ± 34 days Overall: 96.1% (173/180)	mean 55 ± 34 days Overall: 96.1% (173/180)	Mean (SD) 16.2 ± 7.9 months follow up time, % followed (NR)	
	Study Design	Multi-centered (6 sites)	Multi-Centered (6 sites)	RCT	RCT	Multi-center (44 sites)	Multi-center (44 sites)
	Study Quality	Good	Good	Poor	Poor	Good	Good

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

*p<0.05 for between group difference

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies.

Appendix Table Q5. Demographics for included RCTs comparing CCTA versus SPECT in populations with suspected ACS (no known history of CAD)

Author, Year (trial)		Goldstein 2011 (CT-STAT)		Goldstein 2007		Levsky 2015 (PROSPECT)		Nabi 2016	
Test Sample size		CCTA (n=375)‡	SPECT (n=374)‡	CCTA (n=99)	SPECT (n=98)	CCTA (n=200)	SPECT (n=200)	CCTA (n= 288)	SPECT (n= 310)
Index test received, % (n)	CCTA	96% (361)	0% (0)	100% (99)	0% (0)	94% (187)	0% (0)	99% (284)	0% (0)
	SPECT	0% (0)	90% (338)	0% (0)	100% (98)	4% (7)	95% (189)	1% (4)	100% (310)
	No test	0% (0)	0% (0)	0% (0)	0% (0)	2% (4)	5% (11)	0% (0)	0% (0)
Patient demographics	Female, % (n)	54.8% (198)	53.0% (179)	58% (57)	43% (42)	63.0% (126)	62.5% (125)	55%	56%
	Age (years); mean ± SD	50±10	50±10	48±11	51±12	56.8 ± 11.8	56.3 ± 10.5	54 ± 13	53 ± 12
	Race, % (n)	NR	NR	NR	NR	White: 4.0% (8) Hispanic: 52.5% (108) Black: 39.0% (78) Asian: 3.5% (7) Other: 0.5% (1)	White: 5.0% (10) Hispanic: 54.0% (108) Black: 33.5% (67) Asian: 5.5% (11) Other: 1.0% (2)	Black 27% (78) White 56% (161) Hispanic 14% (40) Asian 2% (6) Other 1% (3)	Black 33% (102) White 56% (174) Hispanic 10% (31) Asian <1% (<3) Other 2% (6)
	Pretest risk, % (n)†	Low-to-intermediate	Low-to-intermediate	Very low-to-low	Very low-to-low	Intermediate	Intermediate	Low 76% (219) Intermediate 19% (55) High 5% (14)	Low 77% (239) Intermediate 18% (56) High 5% (16)
	Subgroup	None	None	None	None	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	100% (361)	100% (338)	100% (99)	100% (98)	100% (200)	100% (200)	100% (288)**	100% (310)**
	Typical angina	NR	NR	NR	NR	38.5% (77)§	41.5% (83)§	NR	NR
	Atypical angina	NR	NR	NR	NR	NR	NR	NR	NR
	Unstable angina	0.8% (3)	0.9% (3)	NR	NR	NR	NR	NR	NR
	Nonanginal chest pain	NR	NR	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR	NR	NR
	Prior MI	0.3% (1)	1.5% (5)	NR	NR	NR	NR	NR	NR

Author, Year (trial)		Goldstein 2011 (CT-STAT)		Goldstein 2007		Levsky 2015 (PROSPECT)		Nabi 2016	
	Prior revascularization	NR	NR	NR	NR	NR	NR	NR	NR
	Known CAD	NR	NR	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	Hypertension	35.5% (128)	38.8% (131)	39% (38)	38% (37)	70.5% (141)	73.5% (147)	50% (144)	51% (158)
	Diabetes	5.5% (20)	8.3% (28)	8% (8)	12% (12)	33.0% (66)	30.5% (61)	15% (43)	15% (47)
	Hyperlipidemia	31.0% (112)	36.1% (122)	34% (33)	38% (37)	48.5% (97)	54.5% (109)	39% (112)	37% (115)
	Smoker (past or current)	25.2% (91)	30.5% (103)	15% (15)	20% (20)	16.5% (33)	13.0% (26)	26% (75)	27% (84)
Test details	CT images (slice)	64–320	NA	64	NA	64	NA	64	NA
	CACS performed	Yes	NA	Yes	NA	Yes	NA	Yes	NA
	Type of stressor	NA	Exercise (treadmill) or pharmacologic (adenoside or dipyridamole)‡	NA	Exercise (type NR)	NA	Treadmill (preferred); if patient unable to exercise then pharmacologic stress (adenosine or regadenoson) was used ± low-level exercise	NA	Pharmacologic stress testing: 73% (223) Adenosine: 24% (74) Regadenoson: 48% (148) Dobutamine <1% (1) Treadmill exercise stress testing 27% (84)
	Contrast (dose)	Ultravist 300	Tc-99m sestamibi	Visipaque	Tc-99m sestamibi	Iodixanol-320	201 TI rest/99m-Tc-sestamibi stress OR 99m-TC-sestamibi rest/stress	Visapaque	NR
Study characteristics	Setting	ED	ED	ED	ED	Inpatient (telemetry unit)	Inpatient (telemetry unit)	SPECT/CT department	SPECT/CT department

Author, Year (trial)		Goldstein 2011 (CT-STAT)		Goldstein 2007		Levsky 2015 (PROSPECT)		Nabi 2016	
	Followup period % completed followup (n)	6 months 88.0% (330)	6 months 79.4% (297)	6 months Overall: 97.0% (197/203)	6 months Overall: 97% (197/203)	≥12 months, 95.0% (190); 6-12 months symptoms: 88.5% (177)	≥12 months, 95.5% (191); 6-12 months symptoms: 90.0% (180)	Median follow-up 6.5 months 99.2% (593/598)	Median follow-up 6.5 months 99.2% (593/598)
	Study Design	RCT	RCT	RCT	RCT	RCT	RCT	Single Center	Single Center
	Study Quality	Good	Good	Fair	Fair	Fair	Fair	Fair	Fair

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

*p<0.05 for between group difference

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies.

‡Demographics reported only for those who completed the protocol and did not withdraw consent (Goldstein 2011).

§6% of the CCTA patients and 5% of the SPECT patients had severe angina within the last 24 hours.

**Described in study as "exertional pain".

Appendix Table Q6. Demographics for included RCTs comparing CCTA versus stress echocardiography in populations with suspected ACS (no known history of CAD)

Author, year (trial)		Uretsky 2017 (PERFECT trial)		Pineiro-Portela 2021		Levsky 2018	
Test **Sample size**		CCTA (n= 206)	Stress Echo (n= 205)	CCTA (n= 100)	Stress Echo (n= 103)	CCTA (n= 201)	Stress Echo (n=199)
Index test received, % (n)	CCTA	90% (185)	2% (3)	100% (100)	0% (0)	94% (189)	3% (5)
	CACS only	1% (2)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	Stress test (NOS)	5% (10)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	Stress SPECT	0% (0)	4% (9)	0% (0)	0% (0)	0% (0)	0% (0)
	ICA	0.5% (1)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	No test	3.5% (8)	6% (13)	0% (0)	0% (0)	2% (5)	3% (6)
	Stress echo	0% (0)	88% (180)	0% (0)	100% (103)	3% (7)	94% (188)
Patient demographics	Female, % (n)	54% (111)	53% (109)	50% (50)	50% (52)	43% (86)	42% (83)
	Age (years); mean ± SD	59 ± 10	60 ± 10	64 ± 11	64 ± 11	55 ± 9	54 ± 10
	Race, % (n)	Hispanic 41% (84) African-American 39% (80) Caucasian 14% (29) Asian 3% (6) Other 4% (8)	Hispanic 40% (82) African-American 33% (68) Caucasian 20% (41) Asian 3% (6) Other 4% (8)	NR	NR	Hispanic 46% (92) African-American 32% (64) Caucasian 12% (24) Asian 5% (10) Other 4% (8)	Hispanic 45% (90) African-American 32% (64) Caucasian 13% (26) Asian 6% (12) Other 5% (10)
	Pretest risk, % (n)†	NR	NR	TIMI I 68% (138/203) TIMI II 32% (65/203)		All patients were at low to intermediate risk	
	Subgroup	All patients were determined to need hospitalization for further examination		None	None	None	None
Cardiac risk factors, % (n)	Chest pain	100% (206)	100% (205)	100% (100)	100% (103)	100% (201)	100% (199)

Author, year (trial)		Uretsky 2017 (PERFECT trial)		Pineiro-Portela 2021		Levsky 2018	
	Typical angina	NR	NR	56% (56)	64% (66)	NR	NR
	Atypical angina	NR	NR	44% (44)	32% (33)	NR	NR
	Unstable angina	NR	NR	NR	NR	NR	NR
	Nonanginal chest pain	NR	NR	0% (0)	4% (4)	NR	NR
	Dyspnea	49% (101)	49% (100)	NR	NR	NR	NR
	Prior MI	NR	NR	NR	NR	NR	NR
	Prior revascularization	NR	NR	NR	NR	NR	NR
	Known CAD	0% (0)	0% (0)	NR	NR	0% (0)	0% (0)
	Hypertension	68% (140)	69% (141)	71% (71)	70% (72)	54% (109)	60% (119)
	Diabetes	24% (49)	33% (68)	27% (27)	29% (30)	29% (58)	28% (56)
	Hyperlipidemia	43% (89)	53% (109)	NR	NR	45% (90)	43% (86)
	Current smoker	45% (93)	46% (94)	39% (39)	34% (35)	25% (50)	24% (48)
Test details	CT images (slice)	64	NA	64	NA	64	NA
	CACS performed	1% (2)	NA	No	NA	No	NA
	Type of stressor	NA	Stress Echo: 88% (180) SPECT: 4% (9) CCTA: 2% (3) No Test: 6% (13)	NA	None used	NA	Treadmill (Bruce protocol), if unable to exercise then dobutamine/atropine infusion 16% (32)
	Contrast (dose)	Iodinated contrast	Not necessary for any patients	Iodinated contrast	Echocardiography contrast was not necessary for any patient	NR	Left Ventricular
Study characteristics	Setting	ED	ED	Chest Pain Unit	Chest Paint Unit	ED	ED
	Followup period % completed followup (n)	1 month (NR) 6 months (NR)	1 month (NR) 6 months (NR) 1 year 96% (395/411)	Mean (SD) follow up of 4.7 (2.7) Years: 100% (203/203)		1 month 100% (400/400) 12 months	1 month 100% (400/400) 12 months 97% (387/400)

Author, year (trial)		Uretsky 2017 (PERFECT trial)		Pineiro-Portela 2021		Levsky 2018	
		1 year 96% (395/411)				97% (387/400)	
	Study Design	RCT	RCT	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Fair	Fair	Fair	Fair

*p<0.05 for between group difference

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies.

Appendix Table Q7. Demographics for included RCTs comparing CCTA versus exercise ECG in populations with suspected CAD (no known history of CAD) and stable chest pain, and suspected ACS (no known history of CAD)

		Suspected CAD, stable				Suspected ACS	
Author, year (trial)		**McKavanagh 2014 (CAPP)**		**SCOT-HEART 2015**		**Hamilton-Craig 2014 (CT-COMPARE)**	
Test Sample size		CCTA (n=250)‡	Exercise ECG (n=250)‡	CCTA (n=2073)	Exercise ECG (n=2073)	CCTA (n=322)	Exercise ECG (n=240)
Index test received, % (n)	CCTA	98% (246)	2% (5)	86% (1778)	0.2% (3)	100% (322)	0% (0)
	Exercise ECG	0% (0)	0% (0)	14% (295)	99.8% (2070)	0% (0)	100% (240)
	Other test (not specified)	2% (4)	98% (245)	0% (0)	0% (0)	0% (0)	0% (0)
Patient demographics	Female, % (n)	43.2% (105)	46.5% (114)	44% (912)	44% (912)	43.5% (140)	41.6% (100)
	Age (years); mean ± SD	57.8 ± 10.0	58.9 ± 10.2	57 ± 10	57 ± 10	52.2±10.7	52.3±9.8
	Race, % (n)	NR	NR	NR	NR	NR	NR
	Pretest risk, % (n)†	Low: 41.6% (101) IM: 21.8% (53) High: 36.6% (89)	Low: 43.7% (107) IM 25.3% (62) High: 31.0% (76)	Estimated pre-test probability (according to NICE 2010 guideline criteria) <10%: 11% (415/3770) 10%-29%: 19% (716/3770) 30%-59%: 26% (980/3770) 60%-89%: 25% (942/3770) >90%: 19% (716/3770)		Low-to-intermediate (% NR)	Low-to-intermediate (% NR)
	Subgroup	None	None	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	100% (243)	100% (245)	100% (2073)	100% (2073)	100% (322)	100% (240)
	Typical angina	34.6% (84)	27.8% (68)	36% (746)	35% (726)	NR	NR
	Atypical angina	6.6% (16)	8.2% (20)	24% (498)	23% (477)	NR	NR
	Unstable angina	NR	NR	NR	NR	NR	NR
	Nonanginal chest pain	NR	NR	40% (829)	41% (850)	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR
	Prior MI	NR	NR	NR	NR	NR	NR

		Suspected CAD, stable				Suspected ACS	
	Prior revascularization	NR	NR	NR	NR	NR	NR
	Known CAD	0% (0)	0% (0)	NR	NR	0% (0)	0% (0)
	Hypertension	31.7% (77)	29.8% (73)	34% (705)	33% (684)	30.7% (99)	30.8% (74)
	Diabetes	5.8% (14)	4.9% (12)	11% (228)	11% (228)	7.1% (23)	6.3% (15)
	Hyperlipidemia	NR	NR	NR	NR	25.2% (81)	23.8% (57)
	Current smoker	18.9% (46)	19.2% (47)	53% (1099)	53% (1099)	23.9% (77)	22.9% (55)
Test details	CT images (slice)	64	NA	64 & 320	NA	64 to 128	NA
	CACS performed	Yes	NA	Yes	NA	No	NA
	Type of stressor	NA	Treadmill (Bruce protocol)	NA	Exercise	NA	Treadmill (Bruce protocol)
	Contrast (dose)	Opitray (ioversol) (dose NR)	NA	Iodinated contrast	NR	Iomeron 350	NA
Study characteristics	Setting	Rapid Access Chest Pain Clinics	Rapid Access Chest Pain Clinics	Cardiology chest pain clinics	Cardiology chest pain clinics	ED	ED
	Followup period % completed followup (n)	12 months 97.2% (243/250)	12 months 98.0% (245/250)	6 weeks: (NR) 5 years: 98% (4080/4146)	6 weeks: (NR) 5 years: 98% (4080/4146)	12 months Overall: 100%	12 months Overall: 100%
	Study Design	RCT	RCT	Multi-center	Multi-center	RCT	RCT
	Study Quality	Fair	Fair	Good	Good	Fair	Fair

*p<0.05 for between group difference

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies.

‡Demographic data are only reported for those patients that received their allocated test and had complete follow-up (N=243 for CCTA and 245 for Exercise ECG).

Appendix Table Q8. Demographics for included RCTs comparing CCTA versus ICA in populations with suspected CAD (no known history of CAD) and stable chest pain

Author, year (trial)		CAD-Man trial		CONSERVE trial	
Test **Sample size**		CCTA (n= 168)‡	ICA (n= 172)‡	CCTA (n= 823)§	ICA (n= 808)§
Index test received, % (n)	CCTA	98% (165)	94% (162)	95% (784)	0% (0)
	ICA	1.2% (2)	6% (10)	0% (0)	89% (719)
	No test	0.6% (1)	0% (0)	5% (39)	11% (89)
Patient demographics	Female, % (n)	53% (88)	48% (78)	48% (395)	44% (316)
	Age (years); mean ± SD	60 ± 11	60 ± 11	60 ± 12	61 ± 12
	Race, % (n)	NR	NR	Asian: 86% (671) White: 13% (103) African American: <1% (4) Hispanic: <1% (4) Unknown: <1% (2)	Asian: 84% (604) White: 14% (102) African American: 1% (10) Hispanic: <1% (3) Unknown: 0% (0)
	Pretest risk, % (n)†	<10%: 11% (19) 10-60%: 74% (124) >60%: 14% (24)	<10%: 15% (25) 10-60%: 61% (98) >60%: 24% (39)	Mean(SD) probability of CAD: 51% (30%)	Mean(SD) probability of CAD: 52% (30%)
	Subgroup	None	None	Stable patients	Stable patients
Cardiac risk factors, % (n)	Chest pain	100% (167)	100% (162)	73% (576)	70% (504)
	Typical angina	NR	NR	31% (243)	30% (216)
	Atypical angina	39% (65)	49% (79)	40% (315)	39% (278)
	Unstable angina	NR	NR	NR	NR
	Nonanginal chest pain	58% (97)	49% (80)	2% (18)	1% (10)
	Asymptomatic	0% (0)	0% (0)	12% (90)	11% (76)
	Dyspnea	NR	NR	14% (106)	18% (127)

Author, year (trial)		CAD-Man trial		CONSERVE trial	
	Prior MI	0% (0)	0% (0)	0% (0)	0% (0)
	Prior revascularization	0% (0)	0% (0)	0% (0)	0% (0)
	Known CAD	5% (9)	6% (10)	0% (0)	0% (0)
	Hypertension	NR	NR	57% (446)	59% (424)
	Diabetes	67% (113)	69% (119)	26% (203)	30% (212)
	Hyperlipidemia	57% (95)	51% (81)	33% (259)	35% (249)
	Current smoker	25% (41)	21% (34)	14% (108)	14% (98)
Test details	CT images (slice)	NR	NA	64	NA
	CACS performed	Yes	NA	No	NA
	Type of stressor	NA	NA	NA	NA
	Contrast (dose)	Iodinated contrast agents	NA	Iodinated contrast agents	NA
Study characteristics	Setting	Inpatient: 57% (194/340) Outpatient: 43% (146/340)		Outpatient, non-emergent	Outpatient, non-emergent
	Followup period % completed followup (n)	Mean 3.3 years: 97% (329/340)		6 months: 91% (1472/1611) 12 months: 79% (1278/1611)	6 months: 91% (1472/1611) 12 months: 79% (1278/1611)
	Study Design	Single-center	Single-center	Multi-center	Multi-center
	Study Quality	Good	Good	Fair	Fair

*p<0.05 for between group difference

†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies.

‡Only those with follow-up data are included in the patient demographic data (n=167 for CCTA and n=162 for ICA).

§Only those with follow-up data are included in the patient demographic data (n= 784 for CCTA and n=719 for ICA).

Appendix Table Q9. Demographics for included RCTs comparing PET versus SPECT in populations with mixed suspected or known CAD or known CAD

		Mixed suspected or known CAD		Known CAD	
Author, Year (trial)		**Mullani 2000**		**Patel 2019**	
Test Sample size		PET (n=105)	SPECT (n=105)	PET (n= 161)	SPECT (n=161)
Patient demographics	Female, % (n)	41% (43)	60% (63)	37% (60)	33% (53)
	Age (years); mean ± SD	63 ± 12	65 ± 11	67 ± 9	66 ± 10
	Race, % (n)	NR	NR	NR	NR
	Pretest risk, % (n)	NR	NR	NR	NR
	Subgroup	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	37% (78)*		84% (136)	78% (125)
	Typical angina	10% (20)* ‡		44% (60)	36% (45)
	Atypical angina	15% (32)*		29% (40)	38% (47)
	Angina at Rest	9% (19)*		NR	NR
	Noncardiac angina	NR		NR	NR
	Nonanginal	NR		27% (36)	26% (33)
	Silent ischemia	NR		NR	NR
	Dyspnea	16% (33)*		66% (106)	71% (114)
	Prior MI	11% (23)*		NR	NR
	Prior revascularization	NR		NR	NR
	Prior CABG/PCI	NR		NR	NR
	Known CAD	30% (31)	30% (32)	100% (161)	100% (161)
	Chest pain frequency	NR		NR	NR
	Hypertension	NR		86% (139)	93% (150)
	Diabetes	NR		27% (43)	29% (46)
	Hyperlipidemia	NR		99% (160)	99% (160)
	Smoker (past or current)	NR		17% (27)	20% (32)
	Family history of CAD	19% (40)*		41% (66) [CVD]	46% (74) [CVD]
	Cerebrovascular accident	NR		15% (24)	16% (25)
	Peripheral vascular disease	NR		27% (43)	27% (43)
	Atrial Fibrillation	NR		20% (32)	12% (19)
Test details	Radioactive tracer	Rb-chloride	Tl-chloride, Tc-labeled Sestamibi	Tc-99m Sestamibi, RB-82	Tc-99m Sestamibi, RB-82
	Type of stressor	Dipyridamole	Dipyridamole Dobutamine	Dipyridamole Regadenoson	
Index test received, % (n)	PET	100% (105)	0% (0)	100% (165; evaluable scans n=161) §	0% (0)

		Mixed suspected or known CAD		Known CAD	
Author, Year (trial)		**Mullani 2000**		**Patel 2019**	
	SPECT	0% (0)	100% (105)	0%(0)	100% (165; evaluable scans n=161)§
	Stress Echocardiography	NR	NR	NR	NR
	Exercise ECG	NR	NR	NR	NR
	ICA	NR	NR	NR	NR
	No test	NR	NR	NR	NR
Study characteristics	Setting	Outpatient		Outpatient	
	Followup period % completed followup (n)	9 months† 87% (182)*		3 months 98% (322)* 6 months 95% (314)* 12 months 95% (314)*	
	Study Design	RCT	RCT	RCT	RCT
	Study Quality	Poor	Poor	Good	Good

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

* Reported for entire population not treatment arms.

† Reported mean follow-up time; range 6-12 months.

‡Reported stress angina and exertional angina separately. Combined to represent individuals with a history of typical angina.

§ A total of n=330 patients were randomized. However, only patients with an evaluable scan at baseline were followed for up to 1 year and included in the analytic cohort. Eight patients (n=4 in each group A and group B) did not have an evaluable scan at baseline. Patient characteristics and follow-up are described out of persons with an evaluable scan at baseline (n=322).

Appendix Table Q10. Demographics for included RCTs comparing SPECT VS ECHO and SPECT VS ICA in Suspected CAD or known CAD populations.

Author, Year (trial)		**Sharples 2007, Thom 2014**		**Sharples 2007, Thom 2014**	
Test Sample size		SPECT (n= 224)	ECHO (n=226)	SPECT (n= 224)	ICA (n=222)
Patient demographics	Female, % (n)	30% (67)	29% (66)	30% (67)	33% (73)
	Age (years); mean ± SD	62 ± 10	62 ± 10	62 ± 10	61 ± 9
	Race, % (n)	NR	NR	NR	NR
	Pretest risk, % (n)	Low-risk: 31% (69)* High risk: 69% (155)	31% (70) 69% (156)	ow-risk: 31% (69)* High risk: 69% (155)	31% (69) 69% (153)
	Subgroup	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	NR	NR	NR	NR
	Typical angina	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR
	Unstable angina	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR
	Nonanginal	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR
	Prior MI	23% (52)	26% (59)	23% (52)	28% (63)
	Prior revascularization	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR
	Known CAD	NR	NR	NR	NR
	Chest pain frequency	NR	NR	NR	NR
	Hypertension	Treated 59% (132)	Treated 57% (129)	Treated 59% (132)	Treated 53% (117)
	Diabetes	12% (26)	12% (27)	12% (26)	12% (28)
	Hyperlipidemia	Treated 76% (171)	Treated 79% (179)	Treated 76% (171)	Treated 74% (164)
	Smoker (past/never)	58% (130)	56% (127)	58% (130)	53% (113)
	Smoker (current)	42% (94)	43% (99)	42% (94)	47% (104)
	Family history of CAD	25% (55)	26% (59)	25% (55)	27% (60)
	Cerebrovascular accident	6% (13)	5% (12)	6% (13)	5% (10)
	Peripheral vascular disease	9% (21)	8% (18)	NR	NR
	Atrial Fibrillation	NR	NR	NR	NR
Test details	Radioactive tracer (SPECT) or contrast (Echo)	99mTc-sestamibi, 99mTc MIBI	Yes (microspheres, NOS)	99mTc-sestamibi, 99mTc MIBI	NR

Author, Year (trial)		**Sharples 2007, Thom 2014**		**Sharples 2007, Thom 2014**	
	Type of stressor	Pharmacological, adenosine	Dobutamine	Pharmacological, adenosine	NR
Index test received, % (n)	PET	NR	NR	NR	NR
	SPECT	98% (220)	0% (0)	98% (220)	0% (0)
	Stress Echocardiography	0% (0)	96% (218)	0% (0)	0% (0)
	Exercise ECG	NR	NR	NR	NR
	ICA	1% (3)	3% (6)	1% (3)	98% (218)
	No test	<1% (1)	<1% (2)	<1% (1)	2% (4)
Study characteristics	Setting	OP	OP	OP	OP
	Followup period % completed followup (n)	6 Months 83%(187) 18 Months 88% (198)	91% (206) 84% (190)	83% (187) 88% (198)	88% (195) 84% (187)
	Study Design	RCT	RCT	RCT	RCT
	Study Quality	Good	Good	Good	Good

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

* Represents patient population

Appendix Table Q11. Demographics for included RCTs comparing Suspected ACS & Chest Pain patients

		Suspected ACS		Suspected or known Chest Pain	
Author, Year (trial)		**Lim** 2013		**Salame 2018**	
Test Sample size		SMPI (n=1004)	CA (n= 504)	SPECT MPI (n= 116)	Stress Echocardiography (n= 113)
Patient demographics	Female, % (n)	40% (405)	43% (219)	55% (64)	53% (60)
	Age (years); mean ± SD	52 ± 12	52 ± 13	58 ± 10	55 ± 9
	Race, % (n)	Chinese 70% (703) Malay 11% (105) Indian 18% (179) Other 2% (16)	Chinese 68% (343) Malay 13% (64) Indian 17% (87) Other 2% (10)	Black/African-American 19% (22) Other Race 5% (6) White 76% (88)	Black/African-American 21% (24) Other Race 7% (8) White 72% (81)
	Pretest risk, % (n)	NR	Low risk 82% (415) Intermediate or High risk 18% (89)	NR	NR
	Subgroup			None	None
Cardiac risk factors, % (n)	Chest pain	NR	NR	100% (116)	100% (113)
	Typical angina	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR
	Unstable angina	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR
	Nonanginal	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR
	Prior MI	1% (10)	2% (8)	15% (17)	16% (18)
	Prior revascularization	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR
	Known CAD	4% (40)	4% (20)	27% (31)	21% (24)
	Chest pain frequency	NR	NR	NR	NR
	Hypertension	43% (434)	39% (198)	77% (89)	75% (85)
	Diabetes	18% (180)	18% (90)	39% (45)	39% (44)
	Hyperlipidemia	NR	NR	47% (55)	49% (55)
	Smoker (past or current)	33% (331)	31% (155)	NR	NR
	COPD	NR	NR	11% (13)	9% (10)
	Family history of CAD	NR	NR	NR	NR
	Cerebrovascular disease	NR	NR	8% (9)	8% (9)
	Peripheral artery disease	NR	NR	1% (1)	0% (0)
	Atrial Fibrillation	NR	NR	NR	NR

		Suspected ACS		Suspected or known Chest Pain	
Author, Year (trial)		**Lim** 2013		**Salame 2018**	
Test details	Radioactive tracer (SPECT) or contrast (Echocardiography)	Tc-99m tetrofosmin,	NA	technetium Tc-99m sestamibi	Optison
	Type of stressor	Exercise Bruce protocol (preferred), dipyridamole, or dobutamine	NA	Dipyridamole (73%) or Exercise treadmill (27%),	Dobutamine (58%) or exercise stress test (42%)
Index test received, % (n)	PET	NR	NR	NR	NR
	SPECT	99.9 (1003)	NR	97% (116)	NR
	Stress Echocardiography	NR	NR	NR	94% (113)
	Exercise ECG	NR	NR	NR	NR
	ICA	NR	NR	NR	NR
	No test	>0.1 (1)	0%% (0)	3% (4)	6% (7)
Study characteristics	Setting	ED	ED	ED	ED
	Followup period % completed followup (n)	30 days (100%)* 1-Year NR		30 days 97% (116/120)	30 days 94% (113/120)
	Study Design	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Fair	Fair

CA= clinical assessment protocol, CABG=coronary artery bypass graft, CACS=coronary artery calcium score, CAD=coronary artery disease, CCTA=coronary computed tomography angiogram, ECG=electrocardiogram, ED=emergency department, ICA = Invasive coronary angiogram; MI=myocardial infarction, NA=not applicable, NR=not reported, PCI=percutaneous coronary intervention, RCT=randomized controlled trial, SMPI=stress myocardial perfusion imaging, SPECT=single-photon emission computed tomography.

* Mean Population

† For all patients undergoing pharmacologic stress

Appendix Table Q12. Demographics for included RCTs looking at comparing SPECT with ETT or NICE GDC in populations with suspected CAD (no known CAD).

		Suspected CAD population					
Author, Year (trial)		**Mieres 2009 & 2011, Shaw 2011 (WOMEN)§§**		**Sabharwal 2007**		**Greenwood 2016**	
Test Sample size		SPECT (n=412)	ETT (n=412)	SPECT (n=250)	ETT (n=207)	SPECT (n= 481)	NICE GDC (n= 240)
Patient demographics	Female, % (n)	100% (384)	100% (388)	44% (111)	43% (88)	47% (225)	47% (112)
	Age (years); mean ± SD	63 (59-68) *†		60 ± 12	59 ± 11	56 ± 9	57 ± 9
	Race, Ethnicity % (n)	Ethnicity: Black 7% (54/824) Hispanic 3% (24/824) Asian 2% (16/824) Caucasian 87% (717/824)		Origin: Caucasian 52% (258) * Indian-subcontinent origin 40% (236) *		Nonwhite 8% (38)	Nonwhite 8% (19)
	Pretest risk, % (n)	Intermediate-High risk (NR)		Low 11% (27) Intermediate 71% (178) High 18% (45)	Low 21% (44) Intermediate 49% (102) High 29% (61)	10-29‡ 26% (125) 30-60‡ 38% (183) 61-90‡ 36% (173)	10-29‡ 25% (61) 30-60‡ 37% (88) 61-90‡ 38% (91)
	Subgroup	None	None	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	90% (346) ††	89% (347) ††	100% (250)	100% (207)	NR	NR
	Typical angina	60% (230)	61% (237)	NR	NR	32% (156)	34% (82)
	Atypical angina	9% (35)	9% (35)	NR	NR	68% (325)	66% (158)
	Unstable angina	NR	NR	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR
	Nonangina	NR	NR	NR	NR	NR	NR
	Nonspecific angina	28% (108)	27% (105)	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR	NR
	Dyspnea	48% (184)	54% (210)	NR	NR	NR	NR
	Prior MI	0% (0)	0% (0)	NR	NR	0% (exclusion criteria)	
	Prior revascularization	0% (0)	0% (0)	NR	NR	0% (exclusion criteria)	
	Prior CABG/PCI	NR	NR	NR	NR	0% (exclusion criteria)	
	Known CAD	0% (0)	0% (0)	0% (0)	0% (0)	NR	NR

		Suspected CAD population					
Author, Year (trial)		**Mieres 2009 & 2011, Shaw 2011 (WOMEN)§§**		**Sabharwal 2007**		**Greenwood 2016**	
	Chest pain frequency	Almost daily: 19% ≥3 episodes/ week: 26%	Almost daily: 16% ≥3 episodes/ week: 29%	NR	NR	NR	NR
	Hypertension	52% (200)	55% (213)	53% (133)	46% (96)	38% (182)	41% (99)
	Diabetes	14% (54)	13% (50)	19% (48)	15% (30)	15% (73)	10% (24)
	Hyperlipidemia	54% (208)	55% (213)	NR	NR	NR	NR
	Dyslipidemia	NR	NR	NR	NR	41% (198)	41% (99)
	Smoker (past or current)	42% (161)	49% (190)	13% (32)	16% (34)	56% (271)	61% (147)
	Family history of CAD	46% (177)	47% (182)	43% (102)	46% (96)	54% (259)	58% (140)
	Esophageal reflux	40% (154	37% (144)				
	Cerebrovascular disease	NR		NR	NR	4 (17)	3 (8)
	Peripheral vascular disease	NR		NR	NR	2% (9)	4% (10)
	Atrial Fibrillation	NR		NR	NR	0% (exclusion criteria)	
Test details	Radioactive tracer	Tc-99m tetrofosmin	NA	Tc-99m Sestamibi	NA	Tc-99m tetrofosmin or sestamibi	NA
	Type of stressor	Exercise stress testing Bruce protocol*		Exercise treadmill 62% (155) Dipyridamole or doubtamine 38% (95)**	Symptom-limited Bruce, Modified Bruce	Treadmill exercise or adenosine	SPECT: see SPECT group Cardiac CT: none, but iodinated contrast used Stress echo: dobutamine
Index test received, % (n)	CMR	NR	NR	NR	NR	1% (4)	<1% (1)
	SPECT	NR	NR	100% (250)	NR	93% (446)	36% (86)
	Stress Echocardiography	NR	NR	NR	NR	1% (5) §	<1% (1)
	Exercise ECG	100% (412)	100% (412)	NR	98% (204)	NR	NR
	ICA	NR	NR	NR	NR	1% (5)	35% (85)
	No test	0% (0)	0% (0)	0% (0)	1% (3)	4% (21)	5% (11)
	Setting	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient

		Suspected CAD population					
Author, Year (trial)		**Mieres 2009 & 2011, Shaw 2011 (WOMEN)§§**		**Sabharwal 2007**		**Greenwood 2016**	
Study characteristics	Followup period % completed followup (n)	24 months, 93% (384/412)	24 months, 94% (388/412)	Mean of 20 ± 6 months, 98% (447/457)		Median 15.8 (IQR 12.1 to 24.2) months (12 month minimum), 97% (468/481)	Median 15.8 (IQR 12.1 to 24.2) months (12 month minimum), 98% (234/240)
	Study Design	RCT	RCT	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Fair	Fair	Good	Good

CABG=coronary artery bypass graft, CACS=coronary artery calcium score, CAD=coronary artery disease, CCTA=coronary computed tomography angiogram, ECG=electrocardiogram, ED=emergency department, GDC= guideline directed care, ICA = invasive coronary angiogram, ;MI=myocardial infarction, NA=not applicable, NICE= National institute for health and care experience, NR=not reported, PCI=percutaneous coronary intervention, RCT=randomized controlled trial, SPECT=single-photon emission computed tomography.

* Patient population

† Median and interquartile range measurements

‡ Categories use to decide stratification in the NICE guidelines group

§Reported in the same value

**dipyridamole with or without treadmill or dobutamine infusion

†† Author reports all women had Angina or Dyspnea

‡‡ Pretest likelihood %

§§ With the exception of race/ethnicity, demographics out of the those followed/analyzed (384 vs. 388)

Appendix Table Q13. Demographics for included RCTs comparing ECHO versus Exercise ECG and versus Standard Care in the ED or Hospital Setting

		Suspected ACS			Suspected or Known CAD			
Author, Year (trial)		Nucifora 2009 (ASSENCE)			Jeetley 2006		Desideri 2005 (COSTAMI-II)	
Test Sample size		**ECHO (n= 110) ‡**	**Exercise ECG (n= 89) ‡**	**Standard care† (n =91) ‡**	ECHO (n= 148)	Exercise ECG (n= 154)	ECHO (n= 132)	Exercise ECG (n= 130)
Patient demographics	Female, % (n)	47% (36/77)	32% (24/75)	45% (25/55)	43% (64)	44% (67)	12% (16)	15% (19)
	Age (years); mean ± SD	52 ± 10	50 ± 10	56 ± 14	61 ± 13	60 ± 13	58 ± 10	59 ± 11
	Race, Ethnicity % (n)	NR	NR	NR	Caucasian 51% (75) South Asian 41% (60)	Caucasian 45% (69) South Asian 47% (72)	NR	NR
	Pretest risk, % (n)	Low (NR)§	Low (NR)§	Low (NR)§	Low 20% (30) Intermediate 72% (107) High 9% (13)	21% (32) 65% (100) 14% (22)	NR - Presenting with uncomplicated acute MI‡‡	
	Subgroup	None	None	None	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	65% (50/77)**	71% (53/75)**	69% (38/55)**	NR	NR	NR	NR
	Typical angina	77% (59/77)	76% (57/75)	85% (47/55)	NR	NR	NR	NR
	Atypical angina	23% (18/77)	24% (18/75)	15% (8/55)	NR	NR	NR	NR
	Unstable angina	NR	NR	NR	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR	NR
	Nonanginal	NR	NR	NR	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR	NR
	Prior angina	NR	NR	NR	NR	NR	20% (27)	22% (29)
	Prior unstable angina	1% (1/77)	4% (3/75)	2% (1/55)	NR	NR	NR	NR
	Prior MI	3% (2/77)	3% (2/75)	2% (1/55)	12% (18)	18% (27)	6% (8)	11% (14)
	Prior revascularization (any)	2% (2/77)	3% (2/75)	5% (3/55)	18% (26)	32% (49)	4% (5)	5% (7)
	Prior PCI	1% (1/77)	3% (2/75)	5% (3/55)	9% (13)	19% (29)	NR	NR
	Prior CABG	1% (1/77)	0% (0/75)	0% (0/55)	9% (13)	13% (20)	NR	NR
	Known CAD	NR	NR	NR	23% (34) (IHD)	31% (48) (IHD)	NR	NR
	Chest pain frequency	NR††	NR††	NR††	NR	NR	NR	NR
	Hypertension	38% (29/77)	35% (26/75)	49% (27/55)	70% (103)	62% (95)	43% (57)	41% (54)
	Diabetes	12% (9/77)	7% (5/75)	11% (6/55)	23% (34)	25% (39)	17% (23)	16% (21)
	Hyperlipidemia	NR	NR	NR	55% (81)	65% (100)	NR	NR

		Suspected ACS			Suspected or Known CAD			
Author, Year (trial)		**Nucifora 2009 (ASSENCE)**			**Jeetley 2006**		**Desideri 2005 (COSTAMI-II)**	
	Smoker (past or current)	48% (37/77)	44% (33/75)	49% (27/55)	38% (56)	49% (76)	65% (85)	61% (79)
	Family history of CAD	NR	NR	NR	48% (71)	47% (73)	NR	NR
	Cerebrovascular accident	NR	NR	NR	NR	NR	NR	NR
	Peripheral vascular disease	NR	NR	NR	NR	NR	NR	NR
	Atrial Fibrillation	NR	NR	NR	NR	NR	NR	NR
Test details	Type of stressor	Dobutamine-atropine	Exercise	NA	Dobutamine-atropine or treadmill exercise	Exercise Bruce/modified Bruce protocol	Dobutamine	Treadmill stress
Index test received, % (n)	PET	NR	NR	NR	NR	NR	NR	NR
	SPECT	NR	NR	NR	NR	NR	NR	NR
	Stress Echocardiography	100% (77/77)	NR	11% (6/55)	100% (148)	NR	100% (132)	NR
	Exercise ECG	NR	100% (75/75)	13% (7/55)	NR	100% (154)	NR	100% (130)
	ICA	NR	NR	NR	NR	NR	NR	NR
	No test	NR	NR	71% (39/55)	NR	NR	NR	NR
Study characteristics	Setting	ED	ED	ED	ED	ED	ED	ED
	Followup period % completed followup (n)	2 Months 70% (77/110)	2 months 84% (75/89)	2 months 60% (55/91)	8.5 ± 4.9 months, 96% (142/148)	8.5 ± 4.9 months, 98% (151/154)	6-month 100% (262) 12-month 100% (262)	
	Study Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT
	Study Quality	Poor	Poor	Poor	Poor	Poor	Fair	Fair

CABG=coronary artery bypass graft, CACS=coronary artery calcium score, CAD=coronary artery disease, CCTA=coronary computed tomography angiogram, DASE= dobutamine-atropine stress echocardiography, EET= electrocardiogram exercise testing ECG=electrocardiogram, ED=emergency department, ICA = invasive coronary angiography, MI=myocardial infarction, NA=not applicable, NR=not reported, PCI=percutaneous coronary intervention, RCT=randomized controlled trial, SPECT=single-photon emission computed tomography.

† The final diagnosis was achieved using clinical judgement only without performing additional diagnostic examinations.

‡The test sample size reported based on the randomized population (n= 290), the data reported those who followed up in the 2 months after (n= 207).

§Because of nondiagnostic ECG and negative myocardial injury biomarker

**On admisison

††Last ACP attack:

0-3 hours: 47% (36) vs. 56% (42) vs. 55% (30)

3-6 hours: 21% (16) vs. 23% (17) vs. 25% (14)

6-12 23% (18) vs. 15% (11) vs. 13% (7)

‡‡ (1) no recurrent ischaemic chest pain (with documented ECG changes) lasting five minutes or longer and occurring at least 24 hours after hospital admission; (2) no clinical or radiographic evidence of heart failure; (3) no major arrhythmias; and (4) echocardiographic left ventricular ejection fraction at rest. 40% on day 3.

Appendix Table Q14. Demographics for included RCTs comparing ECHO versus ECG, and versus ICA in the outpatient setting

		Suspected stable CAD				Mixed Suspected or Known Stable CAD	
Author, Year (trial)		**Zacharias 2017, Gurunathan 2018**		**Sanfilippo 2005**		**Sharples 2007, Thom 2014 (CECaT trial)**	
Test Sample size		ECHO (n=191)	Exercise ECG (n=194)	ECHO (n= 104)	Exercise ECG (n= 54)	ECHO (n= 226)	ICA (n= 222)
Patient demographics	Female, % (n)	30% (58)	34% (65)	100% (104)	100% (54)	29% (66)	33% (73)
	Age (years); mean ± SD	55 ± 11	54 ± 11	55 ± 11	53 ± 10	62 ± 10	61 ± 9
	Race, % (n)	NR	NR	Caucasian 97% (101)	Caucasian 100% (54)	NR	NR
	Pretest risk, % (n)	Low 41% (79) Intermediate 31% (59) High 28% (53)	Low 40% (78) Intermediate 38% (73) High 22% (43)	NR	NR	Low 31% (70) High 69% (156)	Low 31% (69) High 69% (153)
	Subgroup	None	None	Women	Women	None	None
Cardiac risk factors, % (n)	Chest pain	100% (191)	100% (194)	NR	NR	NR	NR
	Typical angina	NR	NR	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR	NR	NR
	Unstable angina	0% (0)	0% (0)	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR
	Nonanginal	NR	NR	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR
	Prior MI	0% (0)	0% (0)	NR	NR	26% (59)	28% (63)
	Prior revascularization	0% (0)	0% (0)	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR	NR	NR
	Known CAD	0% (0) (Exclusion)	0% (0) (Exclusion)	0% (0) (Exclusion)	0% (0) (Exclusion)	NR	NR
	Chest pain frequency	NR	NR	NR	NR	NR	NR
	Hypertension	21% (40)	16% (31)	54% (56)	39% (21)	57% (129) (treated)	53% (117) (treated)
	Diabetes	7% (14)	9% (17)	11% (11)	7% (4)	12% (27)	12% (28)
	Hyperlipidemia	NR	NR	41% (43)	43% (23)	79% (179) (treated)	74% (164) (treated)

		Suspected stable CAD				Mixed Suspected or Known Stable CAD	
Author, Year (trial)		**Zacharias 2017, Gurunathan 2018**		**Sanfilippo 2005**		**Sharples 2007, Thom 2014 (CECaT trial)**	
	Smoker (past or current)	7% (14)	9% (18)	18% (19)	26% (14)	43% (99)	47% (104)
	Family history of CAD	12% (24)	14% (27)	23% (24)	24% (13)	26% (59)	27% (60)
	Cerebrovascular accident	NR	NR	NR	NR	5% (12)	5% (10)
	Peripheral vascular disease	NR	NR	3% (3)	4% (2)	8% (18)	9% (20)
	Atrial Fibrillation	NR	NR	NR	NR	NR	NR
	Postmenopausal	NR	NR	75% (78)	78% (42)		
Test details	Type of stressor	Treadmill exercise Bruce protocol*		Dobutamine 45% (47) Treadmill exercise 55% (57)	Treadmill exercise	Dobutamine	NA
Index test received, % (n)	PET	NR	NR	NR	NR	NR	NR
	SPECT	NR	NR	NR	NR	0% (0)	0% (0)
	Stress Echocardiography	100% (191)	0% (0)	100% (104)	0% (0)	96% (218)	0% (0)
	Exercise ECG	0% (0)	100% (194)	0% (0)	100% (54)	NR	NR
	ICA	NR	NR	NR	NR	3% (6)	98% (218)
	No test	NR	NR	NR	NR	<1% (2)	2% (4)
Study characteristics	Setting	OP	OP	OP	OP	OP	OP
	Followup period % completed followup (n)	Mean 21 ± 5 months, 100% (385/385); 79% (303/385) contacted by telephone 21% (82/385) collected via PCP or records search		Mean 28 ± 14.2 months 100% (158) *		6 Months 91% (206) 18 Months 84% (190) 36 months 84% (190)	88% (195) 84% (187) 84% (187)
		Mean 3 ± 0.7 years, 98% (188/191)	Mean 3 ± 0.7 years, 98% (190/194)				
	Study Design	RCT	RCT	RCT	RCT	RCT	RCT
	Study Quality	Good	Good	Poor	Poor	Good	Good

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

* Not reported separately by test

Appendix Table Q15. Demographics for included comparative cohort comparing CCTA FFR versus any noninvasive testing, and versus ICA in the outpatient setting

Author, Year (trial)		Douglas 2015 & 2016 (PLATFORM study)			
Test **Sample size**		CCTA FFR (n=104)	Any non-invasive test (n=100)	CCTA FFR (n=193)	ICA (n=187)
Index test received, % (n)	CCTA	100% (104)	0% (0)	100% (193)	0% (0)
	FFR	64% (67)	0% (0)	69% (134)	0% (0)
	ICA	0% (0)	0% (0)	0% (0)	100% (187)
	Other non-invasive test†	0% (0)	100% (100)	0% (0)	0% (0)
Patient demographics	Female, % (n)	34%	42%	38%	42%
	Age (years); mean ± SD	59.5 ± 9.3	57.9 ± 10.7	60.7 (10.2)*	63.4 (10.9)*
	Racial/ethnic minority, % (n)	0% (0)	5% (5)	0.5% (1)	1.1% (2)
	Pretest risk, %	45%	45%	49%	52%
	Subgroup	Patients who had originally been planned to receive non-invasive testing		Patients who had originally been planned to receive ICA	
Cardiac risk factors, % (n)	Chest pain	100% (104)	100% (100)	100% (193)	100% (187)
	Typical angina	17% (18)	8% (8)	23% (45)	28% (
	Atypical angina	77% (80)	91% (91)	74% (142)	65%
	Non-cardiac chest pain	6% (6)	1% (1)	3% (5)	7%
	Dyspnea	NR	NR	NR	NR
	Prior MI	NR	NR	NR	NR
	Prior revascularization	NR	NR	NR	NR
	Known CAD	0% (0)	0% (0)	0% (0)	0% (0)
	Hypertension	55% (57)*	38% (38)	58% (111)	59% (111)
	Diabetes	6% (6)	8% (8)	16% (30)	19% (36)
	Hyperlipidemia	27% (28)	22% (22)	40% (77)	41% (76)
	Smoker (past or current)	57% (59)	52% (52)	52% (101)	55% (103)
Test details	CT images (slice)	≥64	≥64	≥64	NA
	CACS performed	No	No	No	No
	Type of stressor	NA	NR	NA	NR
	Contrast (dose)	NR	NR	NR	NR
Study characteristics	Setting	Outpatient	Outpatient	Outpatient	Outpatient
	Followup period % completed followup (n)	12 months 96.4% (581)			
	Study Design	Prospective comparative cohort			
	Study Quality	Good			

APPENDIX R. List of on-going trials

Appendix Table R1. List of on-going RCTs from clinicaltrials.gov

Title	Intervention vs. comparator	Anticipated Enrollment	Anticipated Completion Date	NCT Number
Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease	CCTA vs. ICA	3546	3/1/2022	NCT02400229
Computed Tomography Coronary Angiography for the Prevention of Myocardial Infarction (The SCOT-HEART 2 Trial)	CCTA vs. Assign score only	6000	4/1/2027	NCT03920176
CArdiac cT in the Treatment of Acute CHest Pain 2 - Myocardial CT Perfusion	CCTA vs. CCTA + CT myocardial perfusion	600	6/1/2022	NCT02014311
CCTA, CACS and ECG Stress Testing in Patients With Suspected CAD: Precision Phenotyping and Financial Evaluation	CCTA vs. ECG stress testing vs. ECG stress testing + CACS	900	12/31/2023	NCT04424121
CT Stress Myocardial Perfusion, Fractional Flow Reserve and Angiography in Patients With Stable Chest Pain Syndromes	CCTA vs. FFR CT vs. Stress MPI	2000	5/1/2031	NCT04709900
Randomised Controlled Trial to Assess Whether Computed Tomography Cardiac Angiography Can Improve Invasive Coronary Angiography in Bypass Surgery Patients	CCTA vs. ICA	688	6/8/2022	NCT03736018
Coronary CT Angiography in Non ST-elevation Myocardial Infarction	CCTA vs. ICA	300	10/1/2023	NCT04537741
Angiographic Control vs. Ischemia-driven Management of Patients Treated With PCI on Left Main With Drug-eluting Stents	CCTA vs. ischemic management only	550	10/15/2022	NCT04144881
Troponin in Acute Chest Pain to Risk Stratify and Guide EffecTive Use of Computed Tomography Coronary Angiography	CCTA vs. usual care	2270	11/1/2023	NCT03952351
Coronary Computed Tomographic Angiography in Intermediate-risk Chest Pain Patients	CCTA vs. usual care (any non-invasive test)	3500	12/1/2025	NCT04748237
Impact of Stress CT Myocardial Perfusion on Downstream Resources and Prognosis	CCTA vs. usual care (any non-invasive test)	2000	10/1/2022	NCT03976921
Role of On-site CT-derived FFR in the Management of Suspect CAD Patients	CCTA w/ FFR CT vs. usual care (any non-invasive test)	1216	12/1/2021	NCT03901326

Title	Intervention vs. comparator	Anticipated Enrollment	Anticipated Completion Date	NCT Number
The PRECISE Protocol: Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization	CCTA w/ selective FFR CT vs. usual care (any non-invasive test)	2103	4/1/2022	NCT03702244
The MATCH Investigation: CT Myocardial Perfusion and CT-FFR vs PET MPI	FFR CT vs. CT-MPI vs. PET-MPI	30	12/1/2022	NCT04316676
Follow-up With CT-FFR in CHD Patients After DCB	FFR CT vs. ICA	92	6/30/2022	NCT04664439
Safety and Cost-efficiÃ«ncy of New Imaging Techniques in Patients Suspected of Coronary Artery Disease	FFR CT vs. ICA FFR	825	4/1/2025	NCT04939207
Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain	FFR CT vs. usual care	1400	12/1/2020	NCT03187639
Stress Echocardiography Versus Exercise ECG (ExECG) in Women With Chest Pain	Stress echocardiography vs. Exercise ECG	416	12/1/2020	NCT02346565
Alternative Imaging Modalities in Ischemic Heart Failure (AIMI-HF) Project I-A of Imaging Modalities to Assist With Guiding Therapy and the Evaluation of Patients With Heart Failure (IMAGE-HF)	PET/CT or CMR vs. SPECT	1511	6/30/2022	NCT01288560
Evaluation of a Strategy Guided by Imaging Versus Systematic Coronary Angiography in Elderly Patients With Ischemia: a Multicentric Randomized Non Inferiority Trial.	SPECT vs. ICA	1759	12/1/2023	NCT03289728
Assessment of Patients With suspeCted Coronary Artery Disease by Coronary calciUm fiRst strATegy vErsus Usual Care Approach.	PET vs. non-PET medical management	2500	11/1/2027	NCT03972774

CACS = coronary artery calcium scoring, CCTA = coronary computed tomography, CHD = coronary heart disease, CMR = cardiac magnetic resonance, CT = computed tomography, ECG = electrocardiogram, FFR = fractional flow reserve, ICA = invasive coronary angiogram, MPI = myocardial perfusion imaging, NCT = National Clinical Trial, PCI = percutaneous coronary intervention, PET = positron emission tomography, SPECT = single photon emission computed tomography.

APPENDIX S. Clinical Expert Peer Review

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APPENDIX T. Appendix References

1. Guidelines for the management of acute coronary syndromes 2006. Med J Aust 2006;184:S1-s32.
2. Adamson PD, Hunter A, Williams MC, et al. Diagnostic and prognostic benefits of computed tomography coronary angiography using the 2016 National Institute for Health and Care Excellence guidance within a randomised trial. Heart (British Cardiac Society) 2018;104:207-14.
3. Agency for Healthcare Research and Quality. Methods guide for Effectiveness and Comparative Effectiveness Reviews. Rockville MD: Agency for Healthcare Research and Quality. AHRQ publication No. 10(13)-EHC063-EF; 2013.
4. Agus A, McKavanagh P, Lusk L, et al. The cost-effectiveness of cardiac computed tomography for patients with stable chest pain. Heart (British Cardiac Society) 2016;102:356-62.
5. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. Jama 2000;284:835-42.
6. Badano LP, Gregori D, Slavich G, Gremese E, Ghidina M, Fioretti PM. ASSENCE (assessment of cost-effectiveness of several strategies of early diagnosis in patients with acute chest pain and non-conclusive electrocardiogram). Giornale Italiano di Cardiologia 1999;29:1291-301.
7. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of clinical epidemiology 2011;64:401-6.
8. Bertoldi EG, Stella SF, Rohde LEP, Polanczyk CA. Cost-effectiveness of anatomical and functional test strategies for stable chest pain: public health perspective from a middle-income country. BMJ open 2017;7:e012652.
9. Campeau L. Letter: Grading of angina pectoris. Circulation 1976;54:522-3.
10. Chang HJ, Lin FY, Gebow D, et al. Selective Referral Using CCTA Versus Direct Referral for Individuals Referred to Invasive Coronary Angiography for Suspected CAD: A Randomized, Controlled, Open-Label Trial. JACC Cardiovascular imaging 2019;12:1303-12.
11. Chang SA, Choi SI, Choi EK, et al. Usefulness of 64-slice multidetector computed tomography as an initial diagnostic approach in patients with acute chest pain. American heart journal 2008;156:375-83.
12. Dedic A, Lubbers MM, Schaap J, et al. Coronary CT Angiography for Suspected ACS in the Era of High-Sensitivity Troponins: Randomized Multicenter Study. Journal of the American College of Cardiology 2016;67:16-26.
13. Desideri A, Fioretti PM, Cortigiani L, et al. Pre-discharge stress echocardiography and exercise ECG for risk stratification after uncomplicated acute myocardial infarction: results of the COSTAMI-II (cost of strategies after myocardial infarction) trial. Heart (British Cardiac Society) 2005;91:146-51.
14. Dettori JR, Skelly AC, Brodt ED. Critically low confidence in the results produced by spine surgery systematic reviews: an AMSTAR-2 evaluation from 4 spine journals. Global spine journal 2020;10:667-73.
15. Dewey M, Rief M, Martus P, et al. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. BMJ (Clinical research ed) 2016;355:i5441.
16. Douglas PS, De Bruyne B, Pontone G, et al. 1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: The PLATFORM Study. Journal of the American College of Cardiology 2016;68:435-45.
17. Douglas PS, Hoffmann U, Lee KL, et al. PROspective Multicenter Imaging Study for Evaluation of chest pain: rationale and design of the PROMISE trial. American heart journal 2014;167:796-803 e1.
18. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. The New England journal of medicine 2015a;372:1291-300.

19. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. Eur Heart J 2015b;36:3359-67.
20. Goehler A, Mayrhofer T, Pursnani A, et al. Long-term health outcomes and cost-effectiveness of coronary CT angiography in patients with suspicion for acute coronary syndrome. Journal of cardiovascular computed tomography 2020;14:44-54.
21. Goldman L, Cook EF, Johnson PA, Brand DA, Rouan GW, Lee TH. Prediction of the need for intensive care in patients who come to emergency departments with acute chest pain. The New England journal of medicine 1996;334:1498-504.
22. Goldman LH, Lerer R, Shabrang C, Travin MI, Levsky JM. Clinical significance of incidental findings on coronary CT angiography: Insights from a randomized controlled trial. Journal of Nuclear Cardiology 2020;27:2306-15.
23. Goldstein JA, Chinnaiyan KM, Abidov A, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. Journal of the American College of Cardiology 2011;58:1414-22.
24. Goldstein JA, Gallagher MJ, O'Neill WW, Ross MA, O'Neil BJ, Raff GL. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. Journal of the American College of Cardiology 2007;49:863-71.
25. Greenwood JP, Ripley DP, Berry C, et al. Effect of Care Guided by Cardiovascular Magnetic Resonance, Myocardial Perfusion Scintigraphy, or NICE Guidelines on Subsequent Unnecessary Angiography Rates: the CE-MARC 2 Randomized Clinical Trial. JAMA 2016;316:1051-60.
26. Gurunathan S, Zacharias K, Akhtar M, et al. Cost-effectiveness of a management strategy based on exercise echocardiography versus exercise electrocardiography in patients presenting with suspected angina during long term follow up: A randomized study. International journal of cardiology 2018;259:1-7.
27. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology 2011;64:383-94.
28. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. Journal of clinical epidemiology 2011;64:380-2.
29. Hamilton-Craig C, Fifoot A, Hansen M, et al. Diagnostic performance and cost of CT angiography versus stress ECG--a randomized prospective study of suspected acute coronary syndrome chest pain in the emergency department (CT-COMPARE). International journal of cardiology 2014;177:867-73.
30. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2011.
31. Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. The New England journal of medicine 2012;367:299-308.
32. Hollander JE, Gatsonis C, Greco EM, et al. Coronary Computed Tomography Angiography Versus Traditional Care: Comparison of One-Year Outcomes and Resource Use. Annals of emergency medicine 2016;67:460-8 e1.
33. Jafari P, Goudarzi R, Amiresmaeili M, Rashidinejad H. The optimal diagnostic strategies for patient with coronary artery diseases and stable chest pain syndrome: a cost-effectiveness analysis. The Egyptian Heart Journal 2020;72:1-9.
34. Jeetley P, Burden L, Senior R. Stress echocardiography is superior to exercise ECG in the risk stratification of patients presenting with acute chest pain with negative Troponin. European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology 2006;7:155-64.

35. Karády J, Mayrhofer T, Ivanov A, et al. Cost-effectiveness analysis of anatomic vs functional index testing in patients with low-risk stable chest pain. JAMA network open 2020;3:e2028312-e.
36. Karthikeyan G, Guzic Salobir B, Jug B, et al. Functional compared to anatomical imaging in the initial evaluation of patients with suspected coronary artery disease: An international, multi-center, randomized controlled trial (IAEA-SPECT/CTA study). J Nucl Cardiol 2017;24:507-17.
37. Ladapo JA, Hoffmann U, Lee KL, et al. Changes in Medical Therapy and Lifestyle After Anatomical or Functional Testing for Coronary Artery Disease. J Am Heart Assoc 2016;5.
38. Lee SP, Jang EJ, Kim YJ, et al. Cost-effectiveness of coronary CT angiography in patients with chest pain: Comparison with myocardial single photon emission tomography. Journal of cardiovascular computed tomography 2015;9:428-37.
39. Levsky JM, Haramati LB, Spevack DM, et al. Coronary Computed Tomography Angiography Versus Stress Echocardiography in Acute Chest Pain: A Randomized Controlled Trial. JACC Cardiovascular imaging 2018;11:1288-97.
40. Levsky JM, Haramati LB, Taub CC, et al. Rationale and design of a randomized trial comparing initial stress echocardiography versus coronary CT angiography in low-to-intermediate risk emergency department patients with chest pain. Echocardiography (Mount Kisco, NY) 2014;31:744-50.
41. Levsky JM, Spevack DM, Travin MI, et al. Coronary Computed Tomography Angiography Versus Radionuclide Myocardial Perfusion Imaging in Patients With Chest Pain Admitted to Telemetry: A Randomized Trial. Annals of internal medicine 2015;163:174-83.
42. Levsky JM, Travin MI, Spevack DM, et al. Rationale and design of a randomized controlled trial comparing stress myocardial perfusion imaging with coronary CT angiography as the initial imaging study for intermediate-risk patients admitted with chest pain. Journal of cardiovascular computed tomography 2009;3:264-71.
43. Lim SH, Anantharaman V, Sundram F, et al. Stress myocardial perfusion imaging for the evaluation and triage of chest pain in the emergency department: A randomized controlled trial. Journal of Nuclear Cardiology 2013;20:1002-12.
44. Linde JJ, Hove JD, Sørgaard M, et al. Long-Term Clinical Impact of Coronary CT Angiography in Patients With Recent Acute-Onset Chest Pain: The Randomized Controlled CATCH Trial. JACC Cardiovascular imaging 2015;8:1404-13.
45. Linde JJ, Kofoed KF, Sørgaard M, et al. Cardiac computed tomography guided treatment strategy in patients with recent acute-onset chest pain: results from the randomised, controlled trial: CArdiac cT in the treatment of acute CHest pain (CATCH). International journal of cardiology 2013;168:5257-62.
46. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. The New England journal of medicine 2012;366:1393-403.
47. Litwin SE, Coles A, Pagidipati N, et al. Effects of obesity on noninvasive test results in patients with suspected cardiac ischemia: Insights from the PROMISE trial. Journal of Cardiovascular Computed Tomography 2019;13:211-8.
48. Lorenzoni V, Bellelli S, Caselli C, et al. Cost-effectiveness analysis of stand-alone or combined non-invasive imaging tests for the diagnosis of stable coronary artery disease: results from the EVINCI study. The European Journal of Health Economics 2019;20:1437-49.
49. Lowenstern A, Alexander KP, Hill CL, et al. Age-Related Differences in the Noninvasive Evaluation for Possible Coronary Artery Disease: Insights From the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) Trial. JAMA Cardiol 2020;5:193-201.
50. Lu MT, Douglas PS, Udelson JE, et al. Safety of coronary CT angiography and functional testing for stable chest pain in the PROMISE trial: A randomized comparison of test complications, incidental findings, and radiation dose. Journal of cardiovascular computed tomography 2017;11:373-82.

51. Mark DB, Anstrom KJ, Sheng S, et al. Quality-of-Life Outcomes With Anatomic Versus Functional Diagnostic Testing Strategies in Symptomatic Patients With Suspected Coronary Artery Disease: Results From the PROMISE Randomized Trial. Circulation 2016;133:1995-2007.
52. McKavanagh P, Lusk L, Ball PA, et al. A comparison of cardiac computerized tomography and exercise stress electrocardiogram test for the investigation of stable chest pain: the clinical results of the CAPP randomized prospective trial. European heart journal cardiovascular Imaging 2015;16:441-8.
53. Mieres JH, Heller GV, Hendel RC, et al. Signs and symptoms of suspected myocardial ischemia in women: results from the What is the Optimal Method for Ischemia Evaluation in WomeN? Trial. Journal of women's health (2002) 2011;20:1261-8.
54. Mieres JH, Shaw LJ, Hendel RC, Heller GV. The WOMEN study: what is the optimal method for ischemia evaluation in women? A multi-center, prospective, randomized study to establish the optimal method for detection of coronary artery disease (CAD) risk in women at an intermediate-high pretest likelihood of CAD: study design. J Nucl Cardiol 2009;16:105-12.
55. Miller AH, Pepe PE, Peshock R, et al. Is coronary computed tomography angiography a resource sparing strategy in the risk stratification and evaluation of acute chest pain? Results of a randomized controlled trial. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 2011;18:458-67.
56. Min JK, Gilmore A, Jones EC, et al. Cost-effectiveness of diagnostic evaluation strategies for individuals with stable chest pain syndrome and suspected coronary artery disease. Clinical imaging 2017;43:97-105.
57. Min JK, Koduru S, Dunning AM, et al. Coronary CT angiography versus myocardial perfusion imaging for near-term quality of life, cost and radiation exposure: a prospective multicenter randomized pilot trial. Journal of cardiovascular computed tomography 2012;6:274-83.
58. Mullani NA, Caras D, Ahn C, et al. Fewer women than men have positive SPECT and PET cardiac findings among patients with no history of heart disease. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2000;41:263-8.
59. Nabi F, Kassi M, Muhyieddeen K, et al. Optimizing Evaluation of Patients with Low-to-Intermediate-Risk Acute Chest Pain: A Randomized Study Comparing Stress Myocardial Perfusion Tomography Incorporating Stress-Only Imaging Versus Cardiac CT. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2016;57:378-84.
60. Newby DE, Adamson PD, Berry C, et al. Coronary CT Angiography and 5-Year Risk of Myocardial Infarction. The New England journal of medicine 2018;379:924-33.
61. Newby DE, Williams MC, Flapan AD, et al. Role of multidetector computed tomography in the diagnosis and management of patients attending the rapid access chest pain clinic, The Scottish computed tomography of the heart (SCOT-HEART) trial: study protocol for randomized controlled trial. Trials 2012;13:184.
62. Nucifora G, Badano LP, Sarraf-Zadegan N, et al. Effect on quality of life of different accelerated diagnostic protocols for management of patients presenting to the emergency department with acute chest pain. The American journal of cardiology 2009;103:592-7.
63. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. Journal of Managed Care Pharmacy 2003;9:53-61.
64. Pagidipati NJ, Coles A, Hemal K, et al. Sex differences in management and outcomes of patients with stable symptoms suggestive of coronary artery disease: Insights from the PROMISE trial. American heart journal 2019;208:28-36.
65. Pagidipati NJ, Hemal K, Coles A, et al. Sex Differences in Functional and CT Angiography Testing in Patients With Suspected Coronary Artery Disease. Journal of the American College of Cardiology 2016;67:2607-16.

66. Patel KK, Al Badarin F, Chan PS, et al. Randomized Comparison of Clinical Effectiveness of Pharmacologic SPECT and PET MPI in Symptomatic CAD Patients. JACC Cardiovascular imaging 2019;12:1821-31.
67. Piñeiro-Portela M, Peteiro-Vázquez J, Bouzas-Mosquera A, et al. Comparison of two strategies in a chest pain unit: stress echocardiography and multidetector computed tomography. Revista Espanola de Cardiologia 2021;74:59-64.
68. Powell ES, Patterson BW, Venkatesh AK, Khare RK. Cost-effectiveness of a novel indication of computed tomography of the coronary arteries. Critical pathways in cardiology 2012;11:20-5.
69. Priest VL, Scuffham PA, Hachamovitch R, Marwick TH. Cost-effectiveness of coronary computed tomography and cardiac stress imaging in the emergency department: a decision analytic model comparing diagnostic strategies for chest pain in patients at low risk of acute coronary syndromes. JACC: Cardiovascular Imaging 2011;4:549-56.
70. Pryor DB, Shaw L, McCants CB, et al. Value of the history and physical in identifying patients at increased risk for coronary artery disease. Annals of internal medicine 1993;118:81-90.
71. Reilly BM, Evans AT, Schaider JJ, et al. Impact of a clinical decision rule on hospital triage of patients with suspected acute cardiac ischemia in the emergency department. Jama 2002;288:342-50.
72. Reinhardt SW, Babatunde A, Novak E, Brown DL. Effect of Race on Outcomes Following Early Coronary Computed Tomographic Angiography or Standard Emergency Department Evaluation for Acute Chest Pain. Ethnicity & disease 2018;28:517-24.
73. Sabharwal NK, Stoykova B, Taneja AK, Lahiri A. A randomized trial of exercise treadmill ECG versus stress SPECT myocardial perfusion imaging as an initial diagnostic strategy in stable patients with chest pain and suspected CAD: cost analysis. J Nucl Cardiol 2007;14:174-86.
74. Salame G, Juselius WE, Burden M, et al. Contrast-Enhanced Stress Echocardiography and Myocardial Perfusion Imaging in Patients Hospitalized With Chest Pain: A Randomized Study. Critical pathways in cardiology 2018;17:98-104.
75. Sanfilippo AJ, Abdollah H, Knott TC, Link C, Hopman W. Stress echocardiography in the evaluation of women presenting with chest pain syndrome: a randomized, prospective comparison with electrocardiographic stress testing. The Canadian journal of cardiology 2005;21:405-12.
76. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet (London, England) 2015;385:2383-91.
77. Sharma A, Coles A, Sekaran NK, et al. Stress Testing Versus CT Angiography in Patients With Diabetes and Suspected Coronary Artery Disease. Journal of the American College of Cardiology 2019;73:893-902.
78. Sharma A, Sekaran NK, Coles A, et al. Impact of Diabetes Mellitus on the Evaluation of Stable Chest Pain Patients: Insights From the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) Trial. J Am Heart Assoc 2017;6.
79. Sharples L, Hughes V, Crean A, et al. Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial. Health Technol Assess 2007;11:iii-iv, ix-115.
80. Shaw LJ, Mieres JH, Hendel RH, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. Circulation 2011;124:1239-49.
81. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ (Clinical research ed) 2017;358.
82. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. Jama 2011;306:2128-36.

83. Skelly AC, Hashimoto R, Buckley DI, et al. Noninvasive Testing for Coronary Artery Disease. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016.
84. Stillman AE, Gatsonis C, Lima JA, et al. Rationale and design of the Randomized Evaluation of patients with Stable angina Comparing Utilization of noninvasive Examinations (RESCUE) trial. American heart journal 2016;179:19-28.
85. Stillman AE, Gatsonis C, Lima JAC, et al. Coronary Computed Tomography Angiography Compared With Single Photon Emission Computed Tomography Myocardial Perfusion Imaging as a Guide to Optimal Medical Therapy in Patients Presenting With Stable Angina: The RESCUE Trial. J Am Heart Assoc 2020;9:e017993.
86. Thom H, West NE, Hughes V, et al. Cost-effectiveness of initial stress cardiovascular MR, stress SPECT or stress echocardiography as a gate-keeper test, compared with upfront invasive coronary angiography in the investigation and management of patients with stable chest pain: mid-term outcomes from the CECaT randomised controlled trial. BMJ open 2014;4:e003419.
87. Truong QA, Hayden D, Woodard PK, et al. Sex differences in the effectiveness of early coronary computed tomographic angiography compared with standard emergency department evaluation for acute chest pain: the rule-out myocardial infarction with Computer-Assisted Tomography (ROMICAT)-II Trial. Circulation 2013;127:2494-502.
88. Truong QA, Schulman-Marcus J, Zakroysky P, et al. Coronary CT Angiography Versus Standard Emergency Department Evaluation for Acute Chest Pain and Diabetic Patients: Is There Benefit With Early Coronary CT Angiography? Results of the Randomized Comparative Effectiveness ROMICAT II Trial. J Am Heart Assoc 2016;5:e003137.
89. Uretsky S, Argulian E, Supariwala A, et al. Comparative effectiveness of coronary CT angiography vs stress cardiac imaging in patients following hospital admission for chest pain work-up: The Prospective First Evaluation in Chest Pain (PERFECT) Trial. Journal of Nuclear Cardiology 2017;24:1267-78.
90. Versteylen MO, Kietselaer BL, Dagnelie PC, et al. Additive value of semiautomated quantification of coronary artery disease using cardiac computed tomographic angiography to predict future acute coronary syndrome. Journal of the American College of Cardiology 2013;61:2296-305.
91. Williams MC, Hunter A, Shah A, et al. Symptoms and quality of life in patients with suspected angina undergoing CT coronary angiography: a randomised controlled trial. Heart (British Cardiac Society) 2017;103:995-1001.
92. Williams MC, Hunter A, Shah ASV, et al. Impact of noncardiac findings in patients undergoing CT coronary angiography: a substudy of the Scottish computed tomography of the heart (SCOT-HEART) trial. European radiology 2018;28:2639-46.
93. Zacharias K, Ahmed A, Shah BN, et al. Relative clinical and economic impact of exercise echocardiography vs. exercise electrocardiography, as first line investigation in patients without known coronary artery disease and new stable angina: a randomized prospective study. European heart journal cardiovascular Imaging 2017;18:195-202.