Appendix A. Search Strategy

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to October Week 2 2014>

Search Strategy:

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

36	3 and 35
37	exp Magnetic Resonance Imaging/
38	3 and 37
39	9 or 12 or 13 or 15 or 20 or 22 or 33 or 36 or 38
40	limit 39 to english language
41	limit 39 to abstracts
42	40 or 41

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 2014>

Search Strategy:

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

33	(heart$ or cardia$ or cardio$ or myocard$ or coronar$).mp. [mp=title, abstract, full text, keywords, caption text]
34	32 and 33
35	(non-invasiv$ adj5 (imag$ or procedur$ or interven$ or scan$ or test$ or diagno$ or radiogra$ or x-ray$)).mp. [mp=title, abstract, full text, keywords, caption text]
36	("not " adj invasiv$ adj5 (imag$ or procedur$ or interven$ or scan$ or test$ or diagno$ or radiogra$ or x-ray$)).mp.
37	35 or 36
38	4 and 37
39	12 or 14 or 16 or 18 or 23 or 28 or 34 or 38

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <October 2014>

Search Strategy:

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

	mesh headings, heading words, keyword]
34	32 and 33
35	(non-invasiv$ adj5 (imag$ or procedur$ or interven$ or scan$ or test$ or diagno$ or radiogra$ or x-ray$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
36	("not " adj invasiv$ adj5 (imag$ or procedur$ or interven$ or scan$ or test$ or diagno$ or radiogra$ or x-ray$)).mp.
37	37 35 or 36
38	4 and 37
39	12 or 14 or 16 or 18 or 23 or 28 or 34 or 38

Database: EBM Reviews - Health Technology Assessment <4th Quarter 2014>

Search =

1	(coronary adj5 (diseas$ or occlus$ or occlud$ or block$ or stenos$ or stenotic$ or arterioscler$ or atheroscler$ or vasospas$ or aneurysm$)).mp. [mp=title, text, subject heading word]
2	(coronary adj5 (circulat$ or ((blood adj3 flow$) or supply$ or supplie$))).mp.
3	((stable adj2 angina$) or (chest adj2 pain$)).mp. [mp=title, text, subject heading word]
4	1 or 2 or 3
5	((Exercis$ or treadmill$ or bicycl$ or step or steps or stress$) adj3 (echocardiogra$ or electrocardiogra$ or ekg or ecg)).mp.
6	((Exercis$ or treadmill$ or bicycl$ or step or steps or stress$) adj3 Test$).mp.
7	(Electrocardiogra$ or ekg or ecg).mp.
8	Echocardiogra$.mp.
9	7 or 8
10	6 and 9
11	5 or 10
12	4 and 11
13	(spect or (single adj3 photon$ adj5 (emit$ or emission$) adj7 tomogra$)).mp.
14	4 and 13
15	((pet adj2 scan$) or (Positron$ adj3 (emit$ or emission$) adj7 tomogra$)).mp.
16	4 and 15
17	(radionuclid$ adj5 scintigra$).mp.
18	4 and 17
19	vasodilator$.mp.
20	dobutamine.mp.
21	19 or 20
22	(mri or (magnet$ adj3 resonan$ adj3 imag$)).mp.
23	4 and 21 and 22
24	cine ct.mp.
25	((x-ray$ or spiral$ or multidetector$ or cone beam$ or electron beam$) adj5 (comput$ adj3 tomogra$)).mp.
26	((x-ray$ or spiral$ or multidetector$ or cone beam$ or electron beam$) adj5 ((cat or ct) adj scan$)).mp.
27	24 or 25 or 26
28	4 and 27
29	(comput$ adj5 assist$ adj7 (imag$ adj5 process$)).mp. [mp=title, text, subject heading word]
30	(calcium or ca++ or ca ion$ ca2+ or ca+2).mp. [mp=title, text, subject heading word]
31	29 and 30
32	4 and 31
33	(heart$ or cardia$ or cardio$ or myocard$ or coronar$).mp. [mp=title, text, subject heading word] (1374)
34	32 and 33

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

Appendix B. List of Included Studies

1. Buchsbaum M, Marshall E, Levine B, et al. Emergency department evaluation of chest pain using exercise stress echocardiography. Acad Emerg Med. 2001 Feb;8(2):196-9. PMID: 11157301.
2. Chang SA, Choi SI, Choi EK, et al. Usefulness of 64-slice multidetector computed tomography as an initial diagnostic approach in patients with acute chest pain. Am Heart J. 2008 Aug;156(2):375-83. PMID: 18657674.
3. Cheezum MK, Hulten EA, Taylor AJ, et al. Cardiac CT angiography compared with myocardial perfusion stress testing on downstream resource utilization. J Cardiovasc Comput Tomogr. 2011 Mar-Apr;5(2):101-9. PMID: 21256102.
4. Cho I, Shim J, Chang HJ, et al. Prognostic value of multidetector coronary computed tomography angiography in relation to exercise electrocardiogram in patients with suspected coronary artery disease. J Am Coll Cardiol. 2012 Nov 20;60(21):2205-15. PMID: 23103039.
5. Colon PJ, 3rd, Guarisco JS, Murgo J, et al. Utility of stress echocardiography in the triage of patients with atypical chest pain from the emergency department. Am J Cardiol. 1998 Nov 15;82(10):1282-4, A10. PMID: 9832109.
6. Dedic A, Genders TS, Ferket BS, et al. Stable angina pectoris: head-to-head comparison of prognostic value of cardiac CT and exercise testing. Radiology. 2011 Nov;261(2):428-36. PMID: 21873254.
7. Dodi C, Cortigiani L, Masini M, et al. The incremental prognostic value of pharmacological stress echo over exercise electrocardiography in women with chest pain of unknown origin. Eur Heart J. 2001 Jan;22(2):145-52. PMID: 11161916.
8. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease. The New England journal of medicine. 2015 Mar 14PMID: 25773919.
9. Elhendy A, Shub C, McCully RB, et al. Exercise echocardiography for the prognostic stratification of patients with low pretest probability of coronary artery disease. Am J Med. 2001 Jul;111(1):18-23. PMID: 11448656.
10. Ferrara N, Leosco D, Abete P, et al. Dipyridamole echocardiography as a useful and safe test in the assessment of coronary artery disease in the elderly. J Am Geriatr Soc. 1991 Oct;39(10):993-9. PMID: 1918787.
11. Fine NM, Pellikka PA, Scott CG, et al. Characteristics and outcomes of patients who achieve high workload (>10 metabolic equivalents) during treadmill exercise echocardiography. Mayo Clin Proc. 2013 Dec;88(12):1408-19. PMID: 24290114.
12. Gentile R, Vitarelli A, Schillaci O, et al. Diagnostic accuracy and prognostic implications of stress testing for coronary artery disease in the elderly. Ital Heart J. 2001 Jul;2(7):539-45. PMID: 11501963.
13. Goldstein JA, Chinnaiyan KM, Abidov A, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. J Am Coll Cardiol. 2011 Sep 27;58(14):1414-22. PMID: 21939822.
14. Goldstein JA, Gallagher MJ, O'Neill WW, et al. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. J Am Coll Cardiol. 2007 Feb 27;49(8):863-71. PMID: 17320744.
15. Gruettner J, Fink C, Walter T, et al. Coronary computed tomography and triple rule out CT in patients with acute chest pain and an intermediate cardiac risk profile. Part 1: impact on patient management. Eur J Radiol. 2013 Jan;82(1):100-5. PMID: 22749769.
16. Hachamovitch R, Berman DS, Kiat H, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. Circulation. 1996 Mar 1;93(5):905-14. PMID: 8598081.
17. Hachamovitch R, Nutter B, Hlatky MA, et al. Patient management after noninvasive cardiac imaging results from SPARC (Study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease). J Am Coll Cardiol. 2012 Jan 31;59(5):462-74. PMID: 22281249.

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

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

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

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

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

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

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

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

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

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

28. 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 Apr 12;366(15):1393-403. PMID: 22449295.

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

30. Mazeika PK, Nadazdin A, Oakley CM. Prognostic value of dobutamine echocardiography in patients with high pretest likelihood of coronary artery disease. Am J Cardiol. 1993 Jan 1;71(1):33-9. PMID: 8420233.

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

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

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

34. Min JK, Shaw LJ, Berman DS, et al. Costs and clinical outcomes in individuals without known coronary artery disease undergoing coronary computed tomographic angiography from an analysis of Medicare category III transaction codes. Am J Cardiol. 2008 Sep 15;102(6):672-8. PMID: 18773986.Nabi F, Chang SM, Pratt CM, et al. Coronary artery calcium scoring in the emergency department: identifying which patients with chest pain can be safely discharged home. Ann Emerg Med. 2010 Sep;56(3):220-9. PMID: 20138399.

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

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

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

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

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

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

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

42. Shaw LJ, Mieres JH, Hendel RH, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. Circulation. 2011 Sep 13;124(11):1239-49. PMID: 21844080.

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

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

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

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

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

1-47

Appendix C. List of Excluded Studies with Rationale

1. Abdelmoneim SS, Bernier M, Hagen ME, et al. A multicenter, prospective study to evaluate the use of contrast stress echocardiography in early menopausal women at risk for coronary artery disease: trial design and baseline findings. J Womens Health (Larchmt). 2013 Feb;22(2):173-83. PMID: 23398128. **Wrong population.**
2. Abdelmoneim SSD, A.;Bernier, M.;Erwin, P. J.;Korosoglou, G.;Senior, R.;Moir, S.;Kowatsch, I.;Xian-Hong, S.;Muro, T.;Dawson, D.;Vogel, R.;Wei, K.;West, C. P.;Montori, V. M.;Pellikka, P. A.;Abdel-Kader, S. S.;Mulvagh, S. L. Quantitative myocardial contrast echocardiography during pharmacological stress for diagnosis of coronary artery disease: a systematic review and meta-analysis of diagnostic accuracy studies. Eur J Echocardiogr. 2009 Oct;10(7):813-25. PMID: 19549700. **Wrong population, wrong intervention.**
3. Abdulla JA, C.;Kofoed, K. F. Prognostic value of absence or presence of coronary artery disease determined by 64-slice computed tomography coronary angiography a systematic review and meta-analysis. Int J Cardiovasc Imaging. 2011 Mar;27(3):413-20. PMID: 20549366. **Wrong population.**
4. Aggarwal NR, Knickelbine T, Tande A, et al. Noncalcified plaque: relationship between results of multislice computed tomography, risk factors, and late clinical outcome. Catheter Cardiovasc Interv. 2011 Dec 1;78(7):1116-24. PMID: 21542104. **Wrong population.**
5. Amemiya S, Takao H. Computed tomographic coronary angiography for diagnosing stable coronary artery disease: a cost-utility and cost-effectiveness analysis. Circ J. 2009 Jul;73(7):1263-70. PMID: 19436120. **Wrong outcomes.**
6. Arruda AM, Das MK, Roger VL, et al. Prognostic value of exercise echocardiography in 2,632 patients > or = 65 years of age. J Am Coll Cardiol. 2001 Mar 15;37(4):1036-41. PMID: 11263605. **Wrong population.**
7. Arruda-Olson AM, Juracan EM, Mahoney DW, et al. Prognostic value of exercise echocardiography in 5,798 patients: is there a gender difference? J Am Coll Cardiol. 2002 Feb 20;39(4):625-31. PMID: 11849861. **Wrong population.**
8. Ayaram DB, M. F.;Murad, M. H.;Laack, T. A.;Sadosty, A. T.;Erwin, P. J.;Hollander, J. E.;Montori, V. M.;Stiell, I. G.;Hess, E. P. Triple rule-out computed tomographic angiography for chest pain: a diagnostic systematic review and meta-analysis. Acad Emerg Med. 2013 Sep;20(9):861-71. PMID: 24050793. **Wrong population, wrong intervention.**
9. Bamberg FS, W. H.;Hoffmann, V.;Achenbach, S.;Nikolaou, K.;Conen, D.;Reiser, M. F.;Hoffmann, U.;Becker, C. R. Meta-analysis and systematic review of the long-term predictive value of assessment of coronary atherosclerosis by contrast-enhanced coronary computed tomography angiography. J Am Coll Cardiol. 2011 Jun 14;57(24):2426-36. PMID: 21658564. **Wrong outcomes.**
10. Banerjee AN, D. R.;Van den Bruel, A.;Heneghan, C. Diagnostic accuracy of exercise stress testing for coronary artery disease: a systematic review and meta-analysis of prospective studies. Int J Clin Pract. 2012 May;66(5):477-92. PMID: 22512607. **Wrong intervention.**
11. Biagini E, Shaw LJ, Poldermans D, et al. Accuracy of non-invasive techniques for diagnosis of coronary artery disease and prediction of cardiac events in patients with left bundle branch block: a meta-analysis. Eur J Nucl Med Mol Imaging. 2006 Dec;33(12):1442-51. PMID: 16847655. **Wrong population, systematic review or meta-analysis, original data used instead.**
12. Bigi R, Desideri A, Cortigiani L, et al. Stress echocardiography for risk stratification of diabetic patients with known or suspected coronary artery disease. Diabetes Care. 2001 Sep;24(9):1596-601. PMID: 11522705. **Wrong population.**
13. Bikiri E, Mereles D, Voss A, et al. Dobutamine stress cardiac magnetic resonance versus echocardiography for the assessment of outcome in patients with suspected or known coronary artery disease. Are the two imaging modalities comparable? Int J Cardiol. 2014 Feb 1;171(2):153-60. PMID: 24342416. **Wrong population.**
14. Bingham SE, Hachamovitch R. Incremental prognostic significance of combined cardiac magnetic resonance imaging, adenosine stress perfusion, delayed enhancement, and left ventricular function over preimaging information for the prediction of adverse events. Circulation. 2011 Apr 12;123(14):1509-18. PMID: 21444886. **Wrong population.**

15. Bobbio M, Pollock BH, Cohen I, et al. Comparative accuracy of clinical tests for diagnosis and prognosis of coronary artery disease. Am J Cardiol. 1988 Nov 1;62(13):896-900. PMID: 3177237. **Wrong intervention.**
16. Bodi V, Sanchis J, Lopez-Lereu MP, et al. Prognostic and therapeutic implications of dipyridamole stress cardiovascular magnetic resonance on the basis of the ischaemic cascade. Heart. 2009 Jan;95(1):49-55. PMID: 18381373. **Wrong population.**
17. Bodi V, Sanchis J, Lopez-Lereu MP, et al. Prognostic value of dipyridamole stress cardiovascular magnetic resonance imaging in patients with known or suspected coronary artery disease. J Am Coll Cardiol. 2007 Sep 18;50(12):1174-9. PMID: 17868810. **Wrong population.**
18. Bouzas-Mosquera A, Peteiro J, Alvarez-Garcia N, et al. Prognostic value of exercise echocardiography in patients with left bundle branch block. JACC Cardiovasc Imaging. 2009 Mar;2(3):251-9. PMID: 19356568. **Wrong population.**
19. Bouzas-Mosquera A, Peteiro J, Broullon FJ, et al. Effect of atrial fibrillation on outcome in patients with known or suspected coronary artery disease referred for exercise stress testing. Am J Cardiol. 2010 May 1;105(9):1207-11. PMID: 20403467. **Wrong population.**
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48-296

Appendix D. Sample Data Extraction Elements

- Author, year
- Study design
    - RCT
    - Prospective cohort
    - Retrospective cohort
    - Administrative database
- Country, number of centers (multicenter / single center), setting (inpatient, outpatient, emergency department, etc), funding source
- Inclusion criteria
- Exclusion criteria
- Number enrolled, randomized, analyzed, complete followup (%, months)
- Followup time points
    - Note if followup was assessed in-person
    - Note any separate followup studies
- Tests evaluated (number of patients evaluated by each test)
- Test details
    - Type of stressor (specific modality- drug, type of exercise, etc.)
    - Contrast
    - Other pertinent details
- Definition of a positive test (as reported in text)
- Demographics
    - Age (mean)
    - % female
    - Race
    - Note any pertinent subgroups
- Baseline risk for CAD (e.g. very low, low, intermediate to high, high)
    - ACC pre-test likelihood (%)
    - Framingham
    - TIMI score
- Cardiovascular characteristics (%)
    - Chest pain
        - Typical angina
        - Atypical angina
        - Nonspecific chest pain
    - Dyspnea
    - Prior myocardial infarction
    - Prior revascularization
    - Known CAD
    - Chest pain frequency
    - Hypertension
    - Hyperlipidemia
    - Diabetes
- Test results (i.e., normal vs. abnormal) (%)

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

Appendix E. Evidence Tables for Comparative Studies

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

Author (year)		**Chang (2008)[2]**		**Sabharwal (2007)[35]**		**Sanfilippo (2005)[36]**		**McKavanagh (2014)[29]**	
Test Sample size		CCTA (n = 133)	Usual Care (n = 133)	SPECT (n = 250)	Exercise ECG (n = 207)	Stress Echo (n =104)	Exercise ECG (n =54)	CCTA (n = 250)*	Exercise ECG (n = 250)*
Patient demographics	Female, % (n)	39% (52)	38% (51)	44.4% (111)	42.5% (88)	100% (104)	100% (104)	43.2% (105)	46.5% (114)
	Age (years); mean ± SD	57 ± 14	58 ± 14	59.7 ± 12.2	58.9 ± 911.4	54.9†	53.2 ± 10.1	57.8 ± 10.0	58.9 ± 10.2
	Race, % (n)	NR	NR	White: 55.6% (139)	White: 46.9% (97)	97.1% (101)	100% (54)	NR	NR
	Pretest risk, % (n)‡	Low: 37.6% (50) IM: 41.4% (55) High: 21.1% (28)	Low: 36.8% (49)† IM: 42.1% (56) High: 21.1% (28)	Low: 10.8% (27) IM: 71.2% (178) High: 18.0% (45)	Low: 21.3% (44) IM: 49.3% (102) High: 29.5% (61)	Mixed	Mixed	Low: 41.6% (101) IM: 21.8% (53) High: 36.6% (89)	Low: 43.7% (107) IM 25.3% (62) High: 31.0% (76)
	Subgroup	NR	NR	None	None	Women only	Women only	None	None
Cardiac risk factors, % (n)	Chest pain	100% (133)	100% (133)	100% (250)	100% (207)	100% (104)	100% (54)	100% (243)	100% (245)
	Typical angina	NR	NR	NR	NR	NR	NR	34.6% (84)	27.8% (68)
	Atypical angina	NR	NR	NR	NR	NR	NR	6.6% (16)	8.2% (20)
	Unstable angina	NR	NR	NR	NR	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR	NR	NR	NR	NR
	Nonangina	NR	NR	NR	NR	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR	NR	NR
	Prior MI	NR	NR	0% (0)	0% (0)	NR	NR	NR	NR
	Prior revascularization	NR	NR	NR	NR	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR	NR	NR	NR	NR
	Known CAD	12% (16)	17% (23)	0% (0)	0% (0)	NR	NR	0% (0)	0% (0)
	Chest pain frequency	NR	NR	NR	NR	NR	NR	NR	NR
	Hypertension	46% (61)	41% (55)	53.2% (133)	46.3% (96)	53.7% (56)	38.9% (21)†	31.7% (77)	29.8% (73)
	Diabetes	16% (21)	19% (25)	19.2% (48)	14.5% (30)	10.5% (11)	7.4% (4)†	5.8% (14)	4.9% (12)

Author (year)		Chang (2008)[2]		Sabharwal (2007)[35]		Sanfilippo (2005)[36]		McKavanagh (2014)[29]	
	Hyperlipidemia	29% (39)	25% (33)	NR	NR	41.3% (43)†	42.6% (23)†	NR	NR
	Current smoker	17% (23)	23% (31)	12.8% (32)	16.4% (34)	18.2% (19)†	25.9% (14)†	18.9% (46)	19.2% (47)
Test details	CT images (slice)	64	NA	NA	NA	NA	NA	64	NA
	CACS performed	NR	NR	NA	NA	NA	NA	Yes	NA
	Type of stressor	NA	NA	Exercise (treadmill 62%) and/or pharmacologic stress (dipyradimole 38% [or dobutamine if contraindication])	Treadmill (Bruce protocol)	Dobutamine (n=47) or unspecified exercise (n=57)	NR	Opitray (ioversol)	NA
	Contrast (dose)	Lomeprol (80mL lomeron 400; Bracco, Milan, Italy)	NA	Radiotracer: Tc-99m sestamibi	NA	NR	NA	Opitray (ioversol)	NA
Study characteristics	Setting	ED	ED	Outpatient	Outpatient	Outpatient	Outpatient	Rapid Access Chest Pain Clinics	Rapid Access Chest Pain Clinics
	Followup period % completed followup (n)	30 days	30 days	Mean 19.6 months 96.9% (443/457)§	Mean 19.6 months 96.9% (443/457)§	28.1±14.2 months 100 (104)	28.1±14.2 months 100 (54)	12 months 97.2% (243/250)	12 months 98.0% (245/250)
	Study Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Fair	Fair	Poor	Poor	Fair	Fair

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

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

† Back calculated weighted mean.

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

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

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

	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure, Stroke	Major Adverse Cardiac Events	Unstable Angina	Stability and Frequency of Angina*	Quality of Life*
Chang, 2008[2†]	CCTA (n = 133) 30 days	NR	0% (0)	NR	NR	NR	NR	NR
	Usual Care (n = 133) 30 days	NR	0.8% (1)	NR	NR	NR	NR	NR
Sabharwal 2007[35†]	SPECT (n = 250) Mean 21.7 ± 6.4 months	0.8% (2)	0% (0)	NR	NR	NR	NR	NR
	Exercise ECG (n = 207) Mean 21.7 ± 6.4 months	0.9% (2)	0.5% (1)	NR	NR	NR	NR	NR
Sanfillippo 2005[36‡]	Stress echocardiography[§] (n = 104) Mean 28.1 ± 14.2 months	NR	NR	NR	7.7% (8)	NR	NR	NR
	Exercise ECG (n = 54) Mean 28.1 ± 14.2 months	NR	NR	NR	7.4% (4)	NR	NR	NR
McKavanagh 2014[29]	CCTA (n = 243) 12 months	0.41% (1) (noncardiac)	0.41% (1)	NR	NR	0.41% (1)	NR	NR
	Exercise ECG (n = 245) 12 months	0.41% (1) (noncardiac)	0.82% (2)	NR	NR	1.2% (3)	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography.
*Difference from baseline (95% confidence interval) between CCTA and ECG for the Seattle Angina Questionnaire subscales of "angina stability", "angina frequency", and "disease perception/quality of life outcomes"; the change in the score was significantly improved in the CT arm compared with the EST arm in the angina stability and quality-of-life domains at 3 and 12 months.
†For Chang, myocardial infarction was not reported stratified by risk group; for Sabharwal, mortality and myocardial infarction were not reported stratified by risk group. Thus, these outcomes are reported in the mixed population table.
‡Also reports noncardiac clinical outcomes (no clinical events and either resolution of chest pain or establishment of an alternative cause of chest pain, or negative results on ICA) and Indeterminate clinical outcome (continued presenting chest pain syndrome without clinical confirmatory events ([i.e., symptomatic but stable with unknown cause of chest pain])
§ Includes exercise (n = 57) and dobutamine (n = 47) stress echocardiography. Results also reported separately by type of stressor.

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

	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Revascular-ization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Stress testing with imaging	Coronary computed tomography angiography	Medical therapy	Hospitali-zation (chest pain)
Chang, 2008[2*]	CCTA (n = 133) 30 days	NR	NR	NR	NR	30 days: 10% (13)	NR	NR	NR	NR
	Usual Care (n = 133) 30 days	NR	NR	NR	NR	30 days: NR	NR	NR	NR	NR
Sabharwal 2007[35*]	SPECT (n = 250) Mean 21.7 ± 6.4 months	NR	NR	NR	NR	NR	0% (0)†	NR	NR	NR
	Exercise ECG (n = 207) Mean 21.7 ± 6.4 months	NR	NR	NR	NR	NR	23% (48)†	NR	NR	NR
Sanfillippo 2005[36]	Stress echocardiography‡ (n = 104) Mean 28.1 ± 14.2 months	NR	NR	NR	NR	NR	1.9% (2)†	NR	NR	NR
	Exercise ECG (n = 54) Mean 28.1 ± 14.2 months	NR	NR	NR	NR	NR	24.1% (13)†	NR	NR	NR
McKavanagh 2014[29**]	CCTA (n = 243) 12 months	27.2% (66)	15.2% (37)	11.9% (29)	3.3% (8)	2.5% (6)	2.5% (6)§	0% (0)	40.7% (99)	0.82% (2)
	Exercise ECG (n = 245) 12 months	20.8% (51)	7.8% (19)	4.9% (12)	2.9% (7)	31.4% (77)	24.9% (61)§	6.5% (16)	14.3% (35)	6.9% (17)

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography.
*For Chang 2008, additional noninvasive testing was reported at 30 days in the CCTA as a whole, i.e. not stratified by pretest risk; thus this outcomes is included in the mixed population table. For Sabharwal, referral for additional testing was not reported stratified by pretest risk and so is included here.
†Dobutamine stress echocardiography.
‡Includes exercise (n = 57) and dobutamine (n = 47) stress echocardiography. Results also reported separately by type of stressor.
§Includes myocardial perfusion imaging and dobutamine stress echocardiography. Rates for the CCTA group and ECG group respectively are 2.5% (n=6) and 0% versus 24.5% (n=60) and 0.4% (n=1).
**Also reports proportions of patients with 1 to 3 outpatient cardiology visits Exercise ECG (18.4% (100)) versus CCTA (10.4% (26)).

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

	Author (year)	Marwick (2003)[27]		Shreibati (2011)[39]		
Test **Sample size**		Ex Echo (n = 3860)	Ex ECG (n = 3796)	Stress Echo (n = 80604)	Ex ECG (n =61063)	Nuclear MPI (n = 132,343)
Patient demographics	Female, % (n)	40% (1544)	42% (1594)	57.5% (46,347)	49.0% (29,913)	54.5% (72,165)
	Age (years); mean ± SD	61.4 ± 12[†]	63.2 ± 12[†]	73.8 ± 5.8	73.1 ± 5.6	75.7 ± 5.9
	Race, % (n)	NR	NR	White: 89.7% (71802) Black: 5.8% (4695) Hispanic: 1.1% (863)	White: 87.2% (53,223) Black: 5.5% (3,346) Hispanic: 1.8% (1067)	White: 89.3% (118,185) Black: 6.7% (8902) Hispanic: 1.5% (1898)
	Pretest risk, % (n)[*]	Low: 11% (425) IM: 58% (2239) High: 31% (1197)	Low: 12% (456) IM: 60% (2278) High: 28% (1063)	Mixed	Mixed	Mixed
	Subgroup	No	No	Medicare population (100%)	Medicare population (100%)	Medicare population (100%)
Cardiac risk factors, % (n)	Chest pain	100% (3860)	100% (3796)	NR	NR	NR
	Typical angina	NR	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR
	Prior MI	NR	NR	0% (0)[§]	0% (0)[§]	0% (0)[§]
	Prior revascularization	NR	NR	0% (0)[§]	0% (0)[§]	0% (0)[§]
	Prior CABG/PCI	NR	NR	0% (0)[§]	0% (0)[§]	0% (0)[§]
	Known CAD	25% (965)[‡]	21% (797)[‡]	0% (0)[**]	0% (0)[**]	0% (0)[**]
	Chest pain frequency	NR	NR	NR	NR	NR
	Hypertension	48% (1853)	50% (1898)	60.2% (48,495)	57.5% (35,091)	57.5% (35,091)
	Diabetes	17% (656)	18% (683)	26.4% (21,242)	25.0% (15,249)	25.0% (15,249)
	Hyperlipidemia	NR	NR	64.6% (52056)	65.1% (39,737)	65.1% (39,737)
	Current smoker	26% (1004)	30% (1139)	2.3% (1896)	2.1% (1268)	2.1% (1268)
Test details	CT images (slice)	NA	NA	NA	NA	NA
	CACS performed	NA	NA	NA	NA	NA
	Type of stressor	Treadmill	Treadmill	NR	Exercise or pharmacologic stress (types NR)	Exercise or pharmacologic stress (types NR)
	Contrast (dose)	NR	NA	NR	NA	NA

	Author (year)	Marwick (2003)[27]		Shreibati (2011)[39]		
Study characteristics	Setting	NR	NR	Outpatient	Outpatient	Outpatient
	Followup period % completed followup (n)	38.4 ± 24 months	30 ± 24 months	6 months 100% (80,604)	6 months 100% (61,063)	6 months 100% (61,063)
	Study Design	Retro cohort	Retro cohort	Retro admin database	Retro admin database	Retro admin database
	Study Quality	Poor	Poor	Fair	Fair	Fair

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

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

†$p<0.05$

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

§ Within previous 12 months.

** Within previous 9 months.

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

Author Study design	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction, Heart Failure, Change in Angina	Major Adverse Cardiac Events	Unstable Angina	Quality of Life*
Marwick 2003[27]* Prospective cohort	Exercise Echocardiography (n = 2895) Mean 3.2 +/- 2.0 years	4.2% (122) (cardiac)	NR	8.4% (243)‡	NR	NR
	Exercise ECG (2999) Mean 2.5 +/- 2.0 years	5.2% (156) (cardiac)	NR	10.7% (321)‡	NR	NR
Shreibati 2011[39] Administrative database	Stress echocardiography (n = 80,604) 6 months	0.95% (765) (all-cause)	NR	NR	NR	NR
	Exercise ECG (n = 61,063) 6 months	0.78% (479) (all-cause)	NR	NR	NR	NR
	Nuclear MPI (n = 132,343) 6 months	1.28% (1694) (all-cause)	NR	NR	NR	NR

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

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

Author Study Design	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Revascular-ization	Percuntaneous Coronary Intervention	Coronary Artery Bypass Graft	Any Additional Noninvasive Testing	Hospitalization
Marwick 2003[27]* Prospective cohort	Exercise Echocardiography (n = 2895) Mean 3.2 +/- 2.0 years	58% (NR)	42% (NR)	31% (NR)	10% (NR)	NR	NR
	Exercise ECG (2999) Mean 2.5 +/- 2.0 years	50% (NR)	36% (NR)	24% (NR)	13% (NR)	NR	NR
Shreibati 2011[39] Administrative database	Stress Echocardiography (n = 80,604) 6 months	9.50% (7659)	4.22% (3403)	2.61% (2100)	1.69% (1365)	5.57% (4492)‡	0.32% (255) for acute MI
	Exercise ECG (n = 61,063) 6 months	9.04% (5520)	4.31% (2632)	2.57% (1569)	1.82% (1112)	19.34% (11,812)§	0.32% (195) for acute MI
	Nuclear MPI (n = 132,343) 6 months	12.13% (16,058)	4.59% (6078)	3.37% (4465)	1.29% (1709)	3.22% (4257)**	0.43% (575) for acute MI

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

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

†Death or myocardial infarction.

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

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

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

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

Author (year)		**Yamauchi (2012)[43‡]**		**Tandon (2012)[41*]**		**Min (2008)[32* †‡]**	
Test **Sample size**		CCTA (n = 635)	MPI (n =1221)	CCTA (n = 1221)	SPECT (n = 1221)	CCTA (n = 1938)	SPECT (n = 7752)
Patient demographics	Female, % (n)	46.6% (291)	43.8% (528)	49.1% (599)	49.1% (599)	43.2% (837)	43.2% (3349)
	Age (years); mean ± SD	66.0±10.3	66.2±10.6	58.1±10.9	58.1±10.9	52.1±8.7	52.1±8.7
	Race, % (n)	NR	NR	NR	NR	NR	NR
	Pretest risk, % (n)[§]	NR (NYHA class)	NR (NYHA class)	NR	NR	NR	NR
	Subgroup (%)	None	None	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	NR	NR	50.8% (620)	48.8% (596)	NR	NR
	Typical angina	NR	NR	NR	NR	NR	NR
	Atypical angina	0% (0)	0% (0)	NR	NR	NR	NR
	Unstable angina	NR	NR	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR	NR	NR
	Nonangina	NR	NR	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR
	Prior MI	0% (0)	0% (0)	NR	NR	0% (0)	0% (0)
	Prior revascularization	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	Known CAD	NR	NR	0% (0)	0% (0)	0% (0)[††]	0% (0)[††]
	Chest pain frequency	NR	NR	NR	NR	NR	NR
	Hypertension	57.8% (361)	56.4% (679)	47.9% (585)	47.5% (580)	34.8% (674)	34.8% (2698)
	Diabetes	26.6% (166)	28.1% (339)	11.4% (139)	11.9% (145)	8.6% (167)	8.6% (667)
	Hyperlipidemia	49.8% (311)[‡‡]	44.2% (532)[‡‡]	47.4% (579)[‡‡]	38.7% (472)[‡‡]	48.3% (936)	48.3% (3744)
	Smoker (current or past)	21.6% (135)	20.7% (249)	54.1% (661)	47.9% (585)	NR	NR
Test details	CT images (slice)	NR	NA	64	NA	NR	NA
	CACS performed	NR	NA	No	NA	NR	NA
	Type of stressor	NA	NR	NA	Exercise (type NR) or pharmacologic (dipyridamole)	NA	NR
	Contrast/radioisotope	NR	NR	Visapaque or Omnipaque	Tc-99m sestamibi	NR	NR
Study characteristics	Setting	NR	NR	NR	NR	NR	NR
	Followup period % completed followup (n)	Median 1.4±0.5 years; 98.4% (625/635)	Median 1.4±0.5 years; 98.7% (1205/1221)	6 months (%NR)	6 months (%NR)	9 months (%NR)	9 months (%NR)
	Study Design	Pro cohort	Pro cohort	Pro registry	Pro registry	Retro admin database	Retro admin database
	Study Quality	Fair	Fair	Poor	Poor	Fair	Fair

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

Table E7. Continued.

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

	Author (year)	Shreibati (2011)[39]			
Study characteristics	Setting	Outpatient	Outpatient	Outpatient	Outpatient
	Followup period % completed followup (n)	6 months 100 (8820)	6 months 100% (80,604)	6 months 100% (61,063)	6 months 100% (61,063)
	Study Design	Retro admin database	Retro admin database	Retro admin database	Retro admin database
	Study Quality	Fair	Fair	Fair	Fair

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

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

† Within previous 12 months.

‡ Within previous 9 months.

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

Author Study design	Test, Sample Size, Final Followup	Mortality	Myocardial infarction	Heart failure, unstable angina	Major Adverse Cardiac Events	New onset angina	Quality of Life*
Yamauchi 2012[43*] Prospective observational	CCTA (n=625) Median 17 months	NR	NR	NR	2.1% (13)	NR	NR
	Nuclear MPI (n=1205) Median 17 months	NR	NR	NR	2.6% (31)[†]	NR	NR
Tandon 2012[41] Prospective registry	CCTA[‡] (n=1221) 6 months	0.2% (3) (cardiac)	0.5% (6)	NR	NR	NR	NR
	SPECT[‡] (n=1221) 6 months	NR	NR	NR	NR	NR	NR
Min 2008[32] Administrative database	CCTA (n=1938) 9 months	NR	0.4% (8)	NR	NR	3.0% (58)	NR
	SPECT (n=7752) 9 months	NR	0.6% (43)	NR	NR	3.5% (272)	NR
Shreibati 2011[39] Administrative database	CCTA (n=8820) 6 months	1.05% (93) (all-cause)	NR	NR	NR	NR	NR
	Stress Echocardiography (n = 80,604) 6 months	0.95% (765) (all-cause)	NR	NR	NR	NR	NR
	Exercise ECG (n = 61,063) 6 months	0.78% (479) (all-cause)	NR	NR	NR	NR	NR
	Nuclear MPI (n = 132,343) 6 months	1.28% (1694) (all-cause)	NR	NR	NR	NR	NR

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

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

Author Study design	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Revascular-ization	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Any Additional Noninvasive Testing	Hospitali-zation	Cardio-vascular Outpatients Visit
Yamauchi 2012[43*] Prospective observational	CCTA (n=625) Median 17 months	31% (194)	NR[†]	NR	NR	2.0% (13)	NR	NR
	Nuclear MPI (n=1205) Median 17 months	33% (398)	NR[†]	NR	NR	1.0% (12)	NR	NR
Tandon 2012[41] Prospective registry	CCTA[‡] (n=1221) 6 months	10.6% (129)	6.2% (76)	3.9% (48)	2.3% (28)	NR	NR	NR
	SPECT[‡] (n=1221) 6 months	10.2% (125)	5.9% (72)	4.0% (49)	1.9% (23)	NR	NR	NR
Min 2008[32*§] Administrative database	CCTA (n=1938) 9 months	6.2% (120)	2.1% (41)	1.4% (27)	0.7% (14)	8.3% (161)[§]	4.2% (82) cardiac-related	17.4% (338)
	SPECT (n=7752) 9 months	9.5% (736)	1.6% (124)	1.1% (85)	0.5% (39)	2.1% (163)[**]	4.1% (320) cardiac-related	13.3% (1030)
Shreibati 2011[39] Administrative database	CCTA (n=8820) 6 months	22.94% (2023)	11.41% (1006)	7.85% (692)	3.71% (327)	4.98% (439)[††]	0.19% For acute MI	NR
	Stress Echocardiography (n = 80,604) 6 months	9.50% (7659)	4.22% (3403)	2.61% (2100)	1.69% (1365)	5.57% (4492)[‡‡]	0.32% (255) for acute MI	NR
	Exercise ECG (n = 61,063) 6 months	9.04% (5520)	4.31% (2632)	2.57% (1569)	1.82% (1112)	19.34% (11,812)[§§]	0.32% (195) for acute MI	NR
	Nuclear MPI (n = 132,343) 6 months	12.13% (16,058)	4.59% (6078)	3.37% (4465)	1.29% (1709)	3.22% (4257)[***]	0.43% (575) for acute MI	NR

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

*n's back-calculated from percent given

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

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

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

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

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

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

	Author (year)	Chang (2008)[2]		Sabharwal (2007)[35]	
Test **Sample size**		CCTA (n = 28)*	Usual Care (n = 28)*	SPECT (n = 45)*	Exercise ECG (n = 61)*
Patient demographics	Female, % (n)	39% (52)	38% (51)	44.4% (111)	42.5% (88)
	Age (years); mean ± SD	57 ± 14	58 ± 14	59.7 ± 12.2	58.9 ± 911.4
	Race, % (n)	NR	NR	White: 55.6% (139)	White: 46.9% (97)
	Pretest risk, % (n)[†]	Low: 37.6% (50) IM: 41.4% (55) High: 21.1% (28)	Low: 36.8% (49) IM: 42.1% (56) High: 21.1% (28)	Low: 10.8% (27) IM: 71.2% (178) High: 18.0% (45)	Low: 21.3% (44) IM: 49.3% (102) High: 29.5% (61)
	Subgroup	NR	NR	None	None
Cardiac risk factors, % (n)	Chest pain	100% (133)	100% (133)	100% (250)	100% (207)
	Typical angina	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR
	Unstable angina	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR
	Nonangina	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR
	Prior MI	NR	NR	0% (0)	0% (0)
	Prior revascularization	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR
	Known CAD	12% (16)	17% (23)	0% (0)	0% (0)
	Chest pain frequency	NR	NR	NR	NR
	Hypertension	46% (61)	41% (55)	53.2% (133)	46.3% (96)
	Diabetes	16% (21)	19% (25)	19.2% (48)	14.5% (30)
	Hyperlipidemia	29% (39)	25% (33)	NR	NR
	Current smoker	17% (23)	23% (31)	12.8% (32)	16.4% (34)
Test details	CT images (slice)	64	NA	NA	NA
	CACS performed	NR	NR	NA	NA
	Type of stressor	NA	NA	Exercise (treadmill 62%) and/or pharmacologic stress (dipyradimole 38% [or dobutamine if contraindication])	Treadmill (Bruce protocol)
	Contrast (dose)	Lomeprol (80mL lomeron 400; Bracco, Milan, Italy)	NA	Radiotracer: Tc-99m sestamibi	NA
Study characteristics	Setting	ED	ED	Outpatient	Outpatient
	Followup period % completed followup (n)	30 days	30 days	Mean 19.6 months 96.9% (443/457)[‡]	Mean 19.6 months 96.9% (443/457)[‡]

	Author (year)	Chang (2008)[2]		Sabharwal (2007)[35]	
	Study Design	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Fair	Fair

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

*Subgroup of high pretest risk patients; demographics represent the entire population (not reported separately for groups stratified by high risk).

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

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

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

Author, Year	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure	Stroke	Major Adverse Cardiac Events	Unstable Angina	Dysrhythmia	Quality of Life
Chang, 2008[2]*	CCTA (n = 28) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 14% (4) 30 days: NR†	NR	NR	NR	Index: 43% (12) 30 days: NR	NR	NR
	Usual Care (n = 28) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 29% (8) 30 days: NR†	NR	NR	NR	Index: 36% (10) 30 days: NR	NR	NR
Sabharwal 2007[35]*	SPECT (n = 45) Mean 21.7 ± 6.4 months	NR‡	NR‡	NR	NR	NR	NR	NR	NR
	Exercise ECG (n = 61) Mean 21.7 ± 6.4 months	NR‡	NR‡	NR	NR	NR	NR	NR	NR

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

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

†30 day myocardial infarction for both CCTA and Usual Care not reported by pretest risk, this outcome is reported in the mixed population table, Table E2.

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

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

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Re-vascularization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Medical Therapy	Outpatient cardiovascular visit
Chang, 2008[2]*	CCTA (n = 28) 30 days	Index: 75.0% (21) 30 days: NR	Index: 42.9% (12) 30 days: NR	NR	NR	Index: 0% (0) 30 days: NR	NR	NR
	Usual Care (n = 28) 30 days	Index: 92.9% (26) 30 days: NR	Index: 50.0% (14) 30 days: NR	NR	NR	Index: 0% (0)† 30 days: NR	NR	NR
Sabharwal 2007[35]*	SPECT (n = 45) Mean 21.7 ± 6.4 months	44.4% (20)	NR‡	NR	NR	0% (0) (imaging)	55.5% (25)	NR
	Exercise ECG (n = 61) Mean 21.7 ± 6.4 months	85.2% (52)	NR‡	NR	NR	4.9% (3) (imaging)	9.8% (6)	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography.
*Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the low risk group only are reported here.
†All the patients classified as having a high probability for acute coronary syndrome were admitted to the ward with no additional stress testing in the emergency department
‡Revascularization for SPECT and Ex ECG are not reported by pretest risk, these outcomes are reported in the mixed population table, Table E2.

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

Author, Year	Test, Sample Size, Final Followup	Hospitalization (any)	Hospitalization (cardiac)	Emergency Department Revisit
Chang, 2008[2]*	CCTA (n = 28) 30 days	Index: 79% (22)† 30 days: NR	Index: 57% (16)‡ 30 days: NR	NR
	Usual Care (n = 28) 30 days	Index: 100% (28)† 30 days: NR	Index: 64% (18)‡ 30 days: NR	NR
Sabharwal 2007[35]*	SPECT (n = 45) Mean 21.7 ± 6.4 months	NR§	NR§	NR§
	Exercise ECG (n = 61) Mean 21.7 ± 6.4 months	NR§	NR§	NR§

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography.
*Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the low risk group only are reported here.
†Authors also reported unnecessary admissions, for high risk for CCTA (18% (4/28)) versus Usual Care (21% (6/28)). Unnecessary admission is 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).
‡Includes hospitalization for non-ST-segment elevation myocardial infarction or unstable angina, which are also reported separately under clinical outcomes.
§ Hospitalization and ER revisit are not reported stratified by pretest risk group, these outcomes are reported in the mixed population table, Table E2.

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

Author (year)		**Min (2012)[31]**	
Test **Sample size**		CCTA (n = 91)	SPECT (n = 89)
Patient demographics	Female, % (n)	41.8% (38)*	57.3% (51)*
	Age (years); mean ± SD	55.9±10*	58.9±9.5*
	Race, % (n)	NR	NR
	Pretest risk, % (n)†	Mixed (results not stratified): Low 4.1% (4) IM: 62.6% (57) High: 33.0% (30)	Mixed (results not stratified): Low: 9.0% (8) IM: 67.4% (60) High: 23.6% (21)
	Subgroup	None	None
Cardiac risk factors, % (n)	Chest pain	NR	NR
	Typical angina	31.9% (29)	22.5% (20)
	Atypical angina	23.1% (21)	24.7% (22)
	Unstable angina	NR	NR
	Nonspecific chest pain	NR	NR
	Nonangina	NR	NR
	Noncardiac angina	27.5% (25)	24.7% (22)
	Silent ischemia	NR	NR
	Dyspnea	NR	NR
	Prior MI	0% (0)	0% (0)
	Prior revascularization	0% (0)	0% (0)
	Prior CABG/PCI	NR	NR
	Known CAD	0% (0)	0% (0)
	Chest pain frequency	NR	NR
	Hypertension	61.5% (56)	68.5% (61)
	Diabetes	23.1% (21)	21.3% (19)
	Hyperlipidemia	52.7% (48)	60.7% (54)
	Current smoker	58.2% (53)	42.7% (38)
Test details	CT images (slice)	64	NA
	CACS performed	No	NA
	Type of stressor	NA	Exercise (treadmill) or pharmacologic (adenosine)
	Contrast (dose)	Iodinated contrast	Tc-99m sestamibi (some had dual isotope imaging thallium-201)
Study characteristics	Setting	Outpatient	Outpatient
	Followup period % completed followup (n)	mean 55 ± 34 days Overall: 96.1% (173/180)	mean 55 ± 34 days Overall: 96.1% (173/180)
	Study Design	RCT	RCT
	Study Quality	Poor	Poor

CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; IM = intermediate risk; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography.
*$p<0.05$

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

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

Author, Year	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure, Stroke, MACE	Change in angina*	Quality of Life*	Invasive Coronary Angiography	Re-vascularization (any)†	Additional Noninvasive Testing (any) ‡	Hospitalization (CAD-related)
Min 2012[31‡]	CCTA (n = 91) Mean 55 ± 34 days	0% (0)	0% (0)	NR	Stability: 30.0 ± 37.0 Frequency: 10.2 ± 16.4	13.5 ± 22.6	13% (12)	8% (7)	3% (3)	12.1% (11)
	SPECT (n = 89) Mean 55 ± 34 days	0% (0)	0% (0)	NR	Stability: 22.9 ± 30.1 Frequency: 7.6 ± 14.8	11.6 ± 19.0	8% (7)	1% (1)	10% (9)	11.2% (10)

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

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

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

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

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

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

Author, Year		**Hachamovitch (2012) / Hlatky (2014)[15, 19]**	
Test **Sample size**		SPECT (n = 565)*	PET (n = 548)*
Patient demographics	Female, % (n)	51% (286)	59% (323)
	Age (years); mean ± SD	60 ± 11	63 ± 11
	Race, % (n)	White: 68% (386)	White: 80% (439)
	Pretest risk, % (n)†	Intermediate-high risk	Intermediate-high risk
	Subgroup	None	None
Cardiac risk factors, % (n)	Chest pain	NR	NR
	Typical angina	79% (449)	68% (370)
	Atypical angina	NR	NR
	Unstable angina	NR	NR
	Nonspecific chest pain	4% (23)	5% (27)
	Dyspnea	24% (136)	44% (239)
	Prior MI	NR	NR
	Prior revascularization	NR	NR
	Prior CABG/PCI	NR	NR
	Known CAD	0% (0)	0% (0)
	Chest pain frequency	NR	NR
	Hypertension	66% (371)	73% (398)
	Diabetes	31% (173)	41% (225)
	Hyperlipidemia	60% (338)	65% (356)
	Smoker (past or current)	20% (110) within 5 years	12% (64) within 5 years
Test details	Type of stressor	Exercise, pharmacologic or combination (types NR)	Pharmacologic (type NR)
	Radioisotope	NR	NR
Study characteristics	Setting	Hospital, outpatient, academic, nonacademic sites, and community and tertiary care centers	Hospital, outpatient, academic, nonacademic sites, and community and tertiary care centers
	Followup period % completed followup (n)	3 months %NR	3 months %NR
	Study Design	Prospective	Prospective
	Study Quality	Fair	Fair

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

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

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

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

	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure, Stroke, MACE, Change in Angina, QOL	Invasive coronary angiography	Revascular-ization (any)	Percutaneous coronary intervention	Coronary artery bypass graft	Additional non-invasive testing (any)	Hospital-ization (CAD-related)
Hachamovitch 2012/Hlatky 2014[15, 19‡]	PET (n = 548) 24 months	5.5% (30)	1.1% (6)	NR	3 mos: 11.5% (63) 24 mos: 15.5% (82)	3 mos: 6.2% (34) 24 mos: 7.7% (42)	3 mos: 4.6% (25) 24 mos: 5.7% (31)	3 mos: 1.6% (9) 24 mos: 2.0% (11)	NR	NR
	SPECT (n = 565) 24 months	1.6% (9)	1.2% (7)	NR	3 mos: 4.2% (24) 24 mos: 6.7% (38)	3 mos: 1.8% (10) 24 mos: 2.3% (13)	3 mos: 1.4% (8) 24 mos: 1.9% (11)	3 mos: 0.4% (2) 24 mos: 0.4% (2)	NR	NR

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

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

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

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

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

Author (year)		**Hoffman (2012)[20]**		**Chang (2008)[2]**		**Shaw (2011)[38]**		**Sabharwal (2007)[35]**	
Test Sample size		CCTA (n = 501)	Usual Care (n = 499)	CCTA (n = 55)*	Usual Care (n = 56)*	SPECT (n = 412)*	Exercise ECG (n = 412)*	SPECT (n = 178)*	Exercise ECG (n = 102)*
Patient demographics	Female, % (n)	47.9% (240)	46.1 (230)	39% (52)	38% (51)	100% (384)	100% (388)	44.4% (111)	42.5% (88)
	Age (years); mean ± SD	54±8	54±8	57 ± 14	58 ± 14	median (IQR): 62 (58–68)	median (IQR): 63 (60–69)	59.7 ± 12.2	58.9 ± 911.4
	Race, % (n)	White: 65.9% (330) Black: 28.1% (141) Asian: 3.6% (18) Other: 2.4% (12)	White: 66.1% (330) Black: 28.3% (141) Asian: 2.6% (13) Other: 3.6% (18)	NR	NR	NR	NR	White: 55.6% (139)	White: 46.9% (97)
	Pretest risk, % (n)[†]	NR	NR	Low: 37.6% (50) IM: 41.4% (55) High: 21.1% (28)	Low: 36.8% (49) IM: 42.1% (56) High: 21.1% (28)	IM: 100% (384)	IM: 100% (384)	Low: 10.8% (27) IM: 71.2% (178) High: 18.0% (45)	Low: 21.3% (44) IM: 49.3% (102) High: 29.5% (61)
	Subgroup	NR	NR	NR	NR	Women (100%)	Women (100%)	None	None
Cardiac risk factors, % (n)	Chest pain	100% (501)	100% (499)	100% (133)	100% (133)	90.0% (346)	89.4% (347)	100% (250)	100% (207)
	Typical angina	89.0% (446)	91.0% (454)	NR	NR	59.8% (230)	61.2% (237)	NR	NR
	Atypical angina	11.0% (55)	9.0% (45)	NR	NR	9.3% (36)	9.1% (35)	NR	NR
	Unstable angina	NR	NR	NR	NR	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR	27.8% (107)	27.0% (105)	NR	NR
	Nonangina	NR	NR	NR	NR	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR	NR	NR	NR
	Dyspnea	1.4% (7)	2.0% (10)	NR	NR	48.3% (185)	53.5% (208)	NR	NR
	Prior MI	0% (0) (1.6% (8) at index visit)[‡]	0% (0) (3.0% (15) at index visit)[‡]	NR	NR	NR	NR	0% (0)	0% (0)
	Prior revascularization	0% (0)[‡]	0% (0)[‡]	NR	NR	NR	NR	NR	NR
	Prior CABG/PCI	0% (0)[‡]	0% (0)[‡]	NR	NR	NR	NR	NR	NR
	Known CAD	0% (0)[‡]	0% (0)[‡]	12% (16)	17% (23)	0% (0)	0% (0)	0% (0)	0% (0)

Author (year)		Hoffman (2012)[20]		Chang (2008)[2]		Shaw (2011)[38]		Sabharwal (2007)[35]	
	Chest pain frequency	NR	NR	NR	NR	Within 4 wks Daily: 18.5% (71); ≥3 episodes/ wk: 25.9% (99)	Within 4 wks Daily: 16.3% (63); ≥3 episodes/ wk: 29.3% (114)	NR	NR
	Hypertension	53.7% (269)	54.5% (272)	46% (61)	41% (55)	52.0% (200)	55.2% (214)	53.2% (133)	46.3% (96)
	Diabetes	17.2% (86)	17.4% (87)	16% (21)	19% (25)	14.2% (55)	12.6% (49)	19.2% (48)	14.5% (30)
	Hyperlipidemia	45.9% (230)	44.9% (224)	29% (39)	25% (33)	53.7% (206)	50.0% (194)	NR	NR
	Current smoker	49.7% (249)	48.7% (243)	17% (23)	23% (31)	42.4% (163)	48.8% (189)	12.8% (32)	16.4% (34)
Test details	CT images (slice)	64+	NA	64	NA	NA	NA	NA	NA
	CACS performed	Yes	NA	NR	NR	NA	NA	NA	NA
	Type of stressor	NA	exercise or pharmacologic stress	NA	NA	Exercise (type NR)	Treadmill (Bruce protocol)	Exercise (treadmill 62%) and/or pharmacologic stress (dipyradimole 38% [or dobutamine if contraindication])	Treadmill (Bruce protocol)
	Contrast (dose)	NR (iodinated contrast agent)	NA	Lomeprol (80mL lomeron 400; Bracco, Milan, Italy)	NA	Tc-99m tetrofosmin; dual-isotope imaging with thallium 201 (n = 94)	NA	Radiotracer: Tc-99m sestamibi	NA
Study characteristics	Setting	ED	ED	ED	ED	Outpatient	Outpatient	Outpatient	Outpatient
	Followup period % completed followup (n)	28 days 99.2% (497)	28 days 98.2% (490)	30 days	30 days	24 months 94.2% (388/412)	24 months 93.2% (384/412)	Mean 19.6 months 96.9% (443/457)§	Mean 19.6 months 96.9% (443/457)§
	Study Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair

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

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

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

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

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

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

	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure	Stroke	Major Adverse Cardiac Events*	Unstable Angina	Worsening angina frequency or stability†	Angina-free	Quality of Life, Dysrhythmia
Hoffman 2012[20]	CCTA (n = 501) 28 days	Index: 0% (0) 28 days: 0% (0)	Index: 1.6% (8) 28 days: 0.2% (1)	NR	NR	28 days: 0.4% (2)	Index: 7.0% (35) 28 days: 0.2% (1)‡	NR	NR	NR
	Usual Care (n = 499) 28 days	Index: 0% (0) 28 days: 0% (0)	Index: 3.0% (15) 28 days: 0.8% (4)	NR	NR	28 days: 1.2% (6)	Index: 3.4% (17) 28 days: 0.4% (2)‡	NR	NR	NR
Chang, 2008[28]	CCTA (n = 55) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 9% (5) 30 days: NR	NR	NR	NR	Index: 27% (15) 30 days: NR	NR	NR	NR
	Usual Care (n = 56) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 9% (5) 30 days: NR	NR	NR	NR	Index: 24% (13) 30 days: NR	NR	NR	NR
Shaw 2011[38**]	SPECT (n = 384) 24 months	1.0% (4)	NR	NR	NR	2.3% (9)	NR	5% (19)	6 mos: 51.0% (196) 12 mos: 49.5% (190) 24 mos: 64.9% (249)	NR
	Exercise ECG (n = 388) 24 months	0.5% (2)	NR	NR	NR	1.7% (7)	NR	5% (19)	6 mos: 50.6% (196) 12 mos: 48.9% (190) 24 mos: 60.4% (234)	NR
Sabharwal 2007[35§‡]	SPECT (n = 178) Mean 21.7 ± 6.4 months	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Exercise ECG (n = 102) Mean 21.7 ± 6.4 months	NR	NR	NR	NR	NR	NR	NR	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; mos = months; NR = not reported; SPECT = single photon emission tomography.
*For Hoffman 2012, includes death, myocardial infarction, unstable angina, or urgent coronary revascularization; for Shaw 2011, includes death, nonfatal myocardial infarction, or hospital admission for an acute coronary syndrome or heart failure.
†As measured by the corresponding subscales of the Seattle Angina Questionnaire.
‡Requiring percutaneous coronary intervention.
§Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the intermediate risk group only are reported here.
**Shaw also reported cardiac death, myocardial infarction, and heart failure through 24 months followup but did not report events by test group; thus, for the entire population, rates were 0.1% (1/772), 0.4% (3/772), and 0.1% (1/772), respectively. The six deaths listed in the table are non-cardiac deaths.

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

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Re-vascularization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Single positron emission computed tomography	Stress echo-cardiography	Exercise electro-cardiography	Medical Therapy
Hoffman 2012[20]	CCTA (n = 501) 28 days	Index: 11% (54) 28 days: 1.0% (5)	Index: 5.8% (29) 28 days: 0.6% (3)	Index: 5.0% (24) 28 days: 0.6% (3)	Index: 1.0% (5) 28 days: 0% (0)	Index: 16.4% (82) 28 days: 3.6% (18)	Index: 10% (50) 28 days: 1.6% (8)	Index: 4% (20) 28 days: 0% (0)	Index: 2% (12) 28 days: 1.9% (10)	NR
	Usual Care (n = 499) 28 days	Index: 7% (36) 28 days: 0.8% (4)	Index: 3.6% (18) 28 days: 0.6% (3)	Index: 3% (14) 28 days: 0.6% (3)	Index: 1.0% (4) 28 days: 0% (0)	Index: 74.7% (373) 28 days: 4.8% (24)	Index: 25% (124) 28 days: 1.8% (9)	Index: 20% (102) 28 days: 0% (0)	Index: 29% (147) 28 days: 3.0% (15)	NR
Chang 2008[2*]	CCTA (n = 55) 30 days	Index: 42% (23) 30 days: NR	Index: 20% (11) 30 days: NR	NR	NR	Index: 0% (0) 30 days: NR	NR	NR	NR	NR
	Usual Care (n = 56) 30 days	Index: 46% (26) 30 days: NR	Index: 23% (13) 30 days: NR	NR	NR	Index: 50% (28) 30 days: NR	NR	NR	NR	NR
Shaw 2011[38†]	SPECT (n = 384) 24 months	65.7% (22)	2.1% (8)	NR	NR	9.4% (36)	9.1% (35)	NR	0.3% (1)	NR
	Exercise ECG (n = 388) 24 months	6.4% (25)	1.0% (4)	NR	NR	18.6% (72)	18.0% (70)	NR	0.5% (2)	NR
Sabharwal 2007[35*]	SPECT (n = 178) Mean 21.7 ± 6.4 months	10.6% (19)	NR	NR	NR	0% (0) (imaging)	NR	NR	NR	89.3% (159)
	Exercise ECG (n = 102) Mean 21.7 ± 6.4 months	43.1% (44)	NR	NR	NR	38.2% (39) (imaging)	NR	NR	NR	18.6% (19)

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

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

	Test, Sample Size, Final Followup	Hospitalization (any)	Hospitalization (cardiac)	Emergency Department Revisit
Hoffman 2012[20]	CCTA (n = 501) 28 days	Index: 21.3% (107) 28 days: 1.4% (7)	NR	28 days: 2.8% (14)
	Usual Care (n = 499) 28 days	Index: 25.1% (125) 28 days: 1.4% (7)	NR	28 days: 3.8% (19)
Chang 2008[2*]	CCTA (n = 55) 30 days	Index: 47% (26) 30 days: NR	Index: 36% (20)† 30 days: NR	NR
	Usual Care (n = 56) 30 days	Index: 55% (31) 30 days: NR	Index: 32% (18)† 30 days: NR	NR
Shaw 2011[38]	SPECT (n = 384) 24 months	43.9% (15)	43.9% (15)‡	NR
	Exercise ECG (n = 388) 24 months	3.1% (12)	3.1% (12)‡	NR
Sabharwal 2007[35§‡]	SPECT (n = 178) Mean 21.7 ± 6.4 months	NR	NR	NR
	Exercise ECG (n = 102) Mean 21.7 ± 6.4 months	NR	NR	NR

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

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

Author (year)		**Douglas (2015)[8]**	
Test Sample size		CCTA (n = 4996)	Functional testing (n = 5007) Nuclear Stress Imaging: 63.09% (3159/5007) Stress Echocardiography: 21.09% (1056/5007) Exercise ECG: 9.53% (477/5007)
Patient demographics	Female, % (n)	51.9% (2593)	53.4% (2673)
	Age (years); mean ± SD	60.7 ± 8.3	60.9 ± 8.3
	Race, % (n)	Racial or ethnic minority: 23.5%	Racial or ethnic minority: 21.8%
	Pretest risk, % (n)[*]	Pre-test probability of CAD:[†] Low: 2.5% IM: 92.6% High: 4.9%	Pre-test probability of CAD:[†] Low: 2.5% IM: 92.6% High: 4.9%
	Subgroup	None	None
Cardiac risk factors, % (n)	Chest pain	73.6% (3673/4992)	71.9% (3599/5004)
	Typical angina	11.8% (590)	11.5% (576)
	Atypical angina	77.5% (3873)	77.9% (3900)
	Unstable angina	NR	NR
	Nonspecific chest pain	NR	NR
	Nonangina	10.7% (533)	10.6% (531)
	Noncardiac angina/ other pain[‡]	12.2% (607/4992)	12.5% (627/5004)
	Silent ischemia	NR	NR
	Dyspnea on exertion	14.3% (712/4992)	15.5% (778/5004)
	Prior MI	0% (0)	0% (0)
	Prior revascularization	0% (0)	0% (0)
	Prior CABG/PCI	NR	NR
	Known CAD	0% (0)	0% (0)
	Peripheral arterial or cerebrovascular disease	5.3% (263)	5.8% (289)
	Chest pain frequency	NR	NR
	Hypertension	65% (3247)	65% (3254)
	Diabetes	21.3% (1065)	21.5% (1079)
	Hyperlipidemia	67.4% (3365/4995)	67.9% (3402)
	Current smoker	50.7% (2533/4994)	51.4% (2571/5006)
Test details	CT images (slice)	≥64-slice	NA
	CACS performed	No	NA
	Type of stressor	NR	NR
	Contrast (dose)	NR	NR
Study characteristics	Setting	Outpatient	Outpatient
	Followup period % completed followup (n)	Median 25 months (IQR 18-34 months, 93.5% (9350/10,003)	Median 25 months (IQR 18-34 months, 93.5% (9350/10,003)

Author (year)		**Douglas (2015)**[8]	
	Study Design	RCT	RCT
	Study Quality	Good	Good

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

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

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

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

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

	Test, Sample Size, Final Followup	Mortality (all-cause)	Myocardial Infarction (non-fatal)	Heart Failure	Stroke	Unstable Angina	Change in Angina	Quality of Life
Douglas 2015[8]	CCTA (n = 4996)	12 months: 0.4% (21/4996) Median 25 months: 1.5% (74/4996)	12 months: 0.4% (18/4996) Median 25 months: 0.6% (30/4996)	NR	NR	NR	NR	NR
	Functional imaging (n = 5007)	12 months: 0.6% (32/5007) Median 25 months: 1.5% (75/5007)	12 months: 0.5% (27/5007) Median 25 months: 0.8% (40/5007)	NR	NR	NR	NR	NR

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

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

	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Re-vascularization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Medical Therapy
Douglas 2015[8]	CCTA (n = 4996) 90 days	12.2% (609/4996)	6.2% (311/4996)	NR	1.4% (72/4996)	NR	NR
	Functional imaging (n = 5007) 90 days	8.1% (406/5007)*	3.2% (158/5007)	NR	0.75% (38/5007)	NR	NR

CCTA = coronary computed tomography angiography; NR = not reported.
*Also report proportion of patients with invasive catheterization showing no obstructive CAD.

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

Author, Year	Test, Sample Size, Final Followup	Hospitalization (any)	Hospitalization (unstable angina)	Emergency Department Revisit
Douglas 2015[8]	CCTA (n = 4996)	Median 25 months: 0% (0/4996)	12 months: 0.98% (49/4996) Median 25 months: 1.2% (61/4996)	NR
	Functional imaging (n = 5007)	Median 25 months: 0.10% (5/5007)	12 months: 0.68% (34/5007) Median 25 months: 0.8% (41/5007)	NR

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

Table E26. Demographics for the included observational study in populations considered to be at intermediate risk for coronary artery disease

Author, Year		**Henzler (2013)/ Gruettner (2013)[17, 229]**	
Test **Sample size**		CCTA (n = 100)	Usual Care (n = 100)
Patient demographics	Female, % (n)	48% (48)	39% (39)
	Age (years); mean ± SD	58 (range, 27-95)	66 (range, 36-87)
	Race, % (n)	NR	NR
	Pretest risk, % (n)*	Intermediate	Intermediate
	Subgroup	None	None
Cardiac risk factors, % (n)	Chest pain	100% (100)	100% (100)
	Typical angina	NR	NR
	Atypical angina	NR	NR
	Unstable angina	NR	NR
	Noncardiac angina	NR	NR
	Nonangina	NR	NR
	Noncardiac angina	NR	NR
	Silent ischemia	NR	NR
	Dyspnea	NR	NR
	Prior MI	0% (0)[229]	NR
	Prior revascularization	NR	NR
	Prior CABG/PCI	0% (0)	0% (0)
	Known CAD	9% (9)	10% (10)
	Chest pain frequency	NR	NR
	Hypertension	59% (59)	71% (71)
	Diabetes	24% (24)	29% (29)
	Hyperlipidemia	30% (30)	40% (40)
	Smoker (past or current)	54% (54)	47% (47)
Test details	CT images (slice)	320[229]	NA
	CACS performed	Yes[229]	NA
	Type of stressor	NA	NR
	Contrast (dose)	Iomeron 400[229]	NA
Study characteristics	Setting	ED	ED
	Followup period % completed followup (n)	90 days 100% (100)	90 days 87% (87)
	Study Design	Retrospective cohort	Retrospective cohort
	Study Quality	Poor	Poor

CABG = coronary artery bypass graft; CACS = coronary artery calcium scoring; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ED = emergency department; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation.
*As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.

Table E27. Clinical outcomes, clinical management outcomes, and hospital outcomes from observational studies including patients considered to be at intermediate risk for coronary artery disease

	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure	Stroke	Major Adverse Cardiac Events*	Change in angina	Invasive coronary angiography†	Hospitalization (recurrent chest pain)
Henzler/ Gruettner (2013)[17, 229]	CCTA (n = 100) 3 months	0% (0)	0% (0)	0% (0)	NR	0% (0)	NR	40% (40)	0% (0)
	Usual Care (n = 100) 3 months	0% (0)	0% (0)	0% (0)	NR	0% (0)	NR	87% (80)	3% (3)

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

*Includes (1) death, (2) acute myocardial infarction, (3) unstable angina requiring hospitalization, (4) development or progression of heart failure requiring hospitalization and (5) lethal ventricular arrhythmias requiring appropriate discharge from external or internal defibrillators.

†CCTA patients received invasive coronary angiography per study protocol if CCTA found stenosis > 50%; usual care group received invasive coronary angiography in the course of usual clinical care with no details provided.

Table E28. Demographics for included RCTs in populations considered to be at low-to-intermediate risk for coronary artery disease

Author, Year		**Litt (2012)[26]**		**Miller (2011)[30]**		**Goldstein (2011)[12]**		**Hamilton-Craig (2014)[16]**		**Goldstein (2007)[13]**	
Test **Sample size**		CCTA (n = 908)	Usual Care (n = 462)	CCTA + Usual Care (n = 30)	Usual Care (n = 30)	CCTA (n = 375)*	SPECT (n = 374)*	CCTA (n = 322)	Exercise ECG (n = 240)	CCTA (n = 99)*	SPECT (n = 98)*
Patient demographics	Female, % (n)	51.2% (465)	56.3% (260)	57% (17)	43% (13)	54.8% (198)	53.0% (179)	43.5% (140)	41.6% (100)	57.6 (57)	42.9 (42)
	Age (years); mean ± SD	49±9	50±10	51±10	51±10	50±10	50±10	52.2±10.7	52.3±9.8	48±11	51±12
	Race, % (n)	White: 39.8% (361) Black: 57.8% (525) Asian: 1.2% (11) Other: 1.8% (16)	White: 35.1% (162) Black: 62.3% (288) Asian: 1.5% (7) Other: 2.2% (10)	White: 23.3% (7) Black: 46.7% (14) Asian: 0% (0) Hispanic: 30.0% (9)	White: 13.3% (4) Black: 46.7% (14) Asian: 3.3% (1) Other: 36.7% (11)	NR	NR	NR	NR	NR	NR
	Pretest risk, % (n)†	Low-to-intermediate (%NR)	Low-to-intermediate (%NR)	Low-to-intermediate (%NR)	Low-to-intermediate (%NR)	Low-to-intermediate	Low-to-intermediate	Low-to-intermed-iate (%NR)	Low-to-intermed-iate (%NR)	Very low-to-low	Very low-to-low
	Subgroup	NR	NR	NR	NR	None	None	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	100% (908)	100% (462)	100% (30)	100% (30)	100% (361)	100% (338)	100% (322)	100% (240)	100 (99)	100 (98)
	Typical angina	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Unstable angina	NR	NR	NR	NR	0.8% (3)	0.9% (3)	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Nonangina	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Prior MI	1% (10)	1% (6)	NR	NR	0.3% (1)	1.5% (5)	NR	NR	NR	NR
	Prior revascularization	NR	NR	0% (0)	0% (0)	NR	NR	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	0% (0)	0% (0)	NR	NR	NR	NR	NR	NR
	Known CAD	NR	NR	0% (0)	0% (0)	NR	NR	0% (0)	0% (0)	0 (0)	0 (0)
	Chest pain frequency	NR	NR	NR	NR	NR	NR	NR	NR	In last 24 hrs: 77 (76)	In last 24 hrs: 65 (66)

Author, Year		Litt (2012)[26]		Miller (2011)[30]		Goldstein (2011)[12]		Hamilton-Craig (2014)[16]		Goldstein (2007)[13]	
	Hypertension	51.0% (463)	50.2% (232)	NR	NR	35.5% (128)	38.8% (131)	30.7% (99)	30.8% (74)	39 (38)	38 (37)
	Diabetes	14.3% (130)	13.9% (64)	NR	NR	5.5% (20)	8.3% (28)	7.1% (23)	6.3% (15)	8.2 (8)	12.2 (12)
	Hyperlipidemia	27.4% (249)	25.5% (118)	NR	NR	31.0% (112)	36.1% (122)	25.2% (81)	23.8% (57)	34 (33)	38 (37)
	Smoker (past or current)	32.0% (291)	33.8% (156)	NR	NR	25.2% (91)	30.5% (103)	23.9% (77)	22.9% (55)	15 (15)	20 (20)
Test details	CT images (slice)	64+	NA	64	NA	64–320	NA	64–128	NA	64	NA
	CACS performed	Yes	NA	Yes	NA	Yes	NA	No	NA	Yes	NA
	Type of stressor	NA	exercise or pharmaco-logic	NA	NR	NA	Exercise (treadmill) or pharmacologic (adenoside or dipyridamole)‡	NA	Treadmill (Bruce protocol)	NA	Exercise (type NR)
	Contrast (dose)	NR	NA	NR	NA	Ultravist 300	Tc-99m sestamibi	Iomeron 350	NA	Visipaque	Tc-99m sestamibi
Study characteristics	Setting	ED	ED	ED	ED	ED	ED	ED	ED	ED	ED
	Followup period % completed followup (n)	30 days 98.9% (898)	30 days 98.9% (457)	90 days 100% (30)	90 days 100% (30)	6 months 88.0% (330)	6 months 79.4% (297)	12 months Overall: 100%	12 months Overall: 100%	6 months Overall: 97.0% (197/203)	6 months Overall: 97% (197/203)
	Study Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Poor	Poor	Good	Good	Fair	Fair	Fair	Fair

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

*Demographics reported only for those who completed the protocol and did not withdraw consent (Goldstein 2011) or who completed followup (2007).

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

‡Rest imaging was done in all patients and stress testing was only done if the resting studies were normal

Table E29. Clinical outcomes from randomized controlled trials including patients considered to be at low-to-intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Heart Failure	Stroke	Major Adverse Cardiac Events*	Unstable Angina	Quality of Life*
Litt 2012[26]	CCTA (n = 908) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 1.0% (9) 30 days: 0.1% (1)	NR	NR	NR	Index: 3.1% (28) 30 days: NR	NR
	Usual Care (n = 462) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 0.9% (4) 30 days: 0.2% (1)	NR	NR	NR	Index: 1.5% (7) 30 days: NR	NR
Miller 2011[30]	CCTA (n = 30) 3 months	NR	NR	NR	NR	NR	NR	SF-12 PCS (n = 15): 1.0 ± 7.4 SF-12 MCS (n = 15): –0.5 ± 11.5
	Usual Care (n = 30) 3 months	NR	NR	NR	NR	NR	NR	SF-12 PCS (n = 17): –2.3 ± 13.4 SF-12 MCS (n = 17): –0.7 ± 11.9
Goldstein 2011[12]	CCTA (n = 361) 6 months	Index: 0% (0) 6 mos: 0% (0)	Index: 0.3% (1) 6 mos: 0% (0/330)	NR	NR	NR	Index: 0.8% (3) 6 mos: 0% (0/330)	NR
	SPECT (n = 338) 6 months	Index: 0% (0) 6 mos: 0% (0)	Index: 1.5% (5) 6 mos: 0% (0/297)	NR	NR	NR	Index: 10.9% (3) 6 mos: 0% (0/297)	NR
Hamiton-Craig 2014[16†]	CCTA (n = 322) 12 months	Index: NR 30 days: 0% (0) 12 mos: 0.6% (2)‡	Index: 1.9% (6) 30 days: 0% (0) 12 mos: NR	NR	NR	NR	Index: 3.4% (11) 30 days: 0% (0) 12 mos: NR	NR
	Exercise ECG (n = 240) 12 months	Index: NR 30 days: 0% (0) 12 mos: 0.4% (1)‡	Index: 1.7% (4) 30 days: 0% (0) 12 mos: NR	NR	NR	NR	Index: 1.3% (3) 30 days: 0% (0) 12 mos: NR	NR
Goldstein 2007[13]	CCTA (n = 99) 6 months	Index: 0% (0) 6 mos: 0% (0)	Index: 0% (0) 6 mos: 0% (0)	NR	NR	NR	Index: NR 6 mos: 0% (0)	NR
	SPECT (n = 98) 6 months	Index: 0% (0) 6 mos: 0% (0)	Index: 0% (0) 6 mos: 0% (0)	NR	NR	NR	Index: NR 6 mos: 0% (0)	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; mos = months; NR = not reported; SF-12 MCS: Short Form 12 Mental Component Score; SF-12 PCS: Short Form 12 Physical Component Score; SPECT = single photon emission computed tomography.

*Scores are reported as difference from baseline to final followup (3 months).

†All events were back-calculated using the percentages provided.

‡For CCTA, deaths were due to urosepsis and multi-organ failure during elective aortic valve replacement; for ECG, the one death was due to complications from cancer therapy.

Table E30. Clinical management outcomes from randomized controlled trials including patients considered to be at intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Re-vascularization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Stress testing with imaging	Stress testing without imaging	Resting echo-cardiography	Outpatient cardiology visit
Litt 2012[26]	CCTA (n = 908) 30 days	Index: 4% (37) 30 days: 0.9% (8/887)	Index: 3% (23) 30 days: 0.1% (1/893)	NR	NR	30 days: 23.1% (206/891)	30 days: 16% (140/891)	30 days: 1% (11/886)	30 days: 6% (55/888)	30 days: 7% (62/787)
	Usual Care (n = 462) 30 days	Index: 4% (18) 30 days: 0.2% (1/454)	Index: 1% (4) 30 days: 0.4% (2/457)	NR	NR	30 days: 66.4% (304/458)	30 days: 58% (264/458)	30 days: 2% (10/454)	30 days: 7% (30/454)	30 days: 4 (17/451)
Miller 2011[30]	CCTA (n = 30) 3 months	13% (4)	3.3% (1)	3.3% (1)	0% (0)	33.3% (10)	20.0% (6)*	6.7% (2)*	6.7% (2)	10.0% (3)†
	Usual Care (n = 30) 3 months	13% (4)	0% (0)	0% (0)	0% (0)	60.0% (18)	23.3% (7)*	20.0% (6)*	16.7% (5)	16.7% (5)†
Goldstein 2011[12]	CCTA (n = 361) 6 months	Index: 6.7% (24) 6 mos: 0.6% (2/330)	Index: 3.6% (13) 6 mos: 0.3% (1/330)	Index: 2.5% (9) 6 mos: 0.3% (1/330)	Index: 1.1% (4) 6 mos: 0% (0/330)	Index: 10.9% (37)‡ 6 mos: NR	Index: 10.9% (37)‡ 6 mos: NR	NR	NR	NR
	SPECT (n = 338) 6 months	Index: 6.2% (21) 6 mos: 0.3% (1/297)	Index: 2.4% (8) 6 mos: 0% (0/297)	Index: 2.4% (8) 6 mos: 0% (0/297)	Index: 0% (0) 6 mos: 0% (0/297)	Index: 1.8% (6)‡ 6 mos: NR	NR	NR	NR	NR
Hamiton-Craig 2014[16]	CCTA (n = 322) 12 months	12 mos: 9.0% (29)	12 mos: 4.3% (14)	12 mos.3.7% (12)	12 mos: 0.62% (2)	12 mos: 4.3% (14)	12 mos: 4.3% (14)§	NR	NR	NR
	Exercise ECG (n = 240) 12 months	12 mos: 4.2% (10)	12 mos: 1.3% (3)	NR	NR	12 mos: 8.8% (21)	12 mos: 8.8% (21)§	NR	NR	NR
Goldstein 2007[13]	CCTA (n = 99) 6 months	Index: 11.1% (11) 6 mos: 1.0% (1)	Index: 5.1% (5) 6 mos: 1.0% (1)	Index: 3.0% (3) 6 mos: 1.0% (1)	Index: 2.0% (2) 6 mos: 0% (0)	Index: 24.2% (24) 6 mos: 1.0% (1)	NR	NR	NR	6 mos: 2.0% (2)
	SPECT (n = 98) 6 months	Index: 3.1% (3) 6 mos: 4.1% (4)	Index: 1.0% (1) 6 mos: 0% (0)	Index: 1.0% (1) 6 mos: 0% (0)	Index: 0% (0) 6 mos: 0% (0)	Index: 24.2% (24) 6 mos: 1.0% (1)	NR	NR	NR	6 mos: 2.0% (2)

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

*For the CCTA group, stress testing with imaging consisted of stress echocardiography (10%, n=3) and nuclear perfusion (10%, n=3); for usual care, stress echocardiography (3.3%, n=1) and nuclear perfusion (20%, n=6). Stress testing without imaging consisted of exercise electrocardiography for both test groups.
†Primary care/other visits were also reported in the CCTA group (50%, n=15) and the usual care group (70%, n=21) during followup.
‡Additional testing for the CCTA group consisted of single photon emission computed tomography (SPECT) and for the SPECT group, CCTA.
§For the CCTA group, stress testing with imaging consisted of single photon emission computed tomography (2.2%, n=7) and stress echocardiography (2.2%, n=7); for the exercise electrocardiography group, single photon emission computed tomography (7.5%, n=18) and stress echocardiography (1.3%, n=3).

Table E31. Hospital and emergency department outcomes from randomized controlled trials including patients considered to be at low to intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Hospitalization (any)	Hospitalization (cardiac)	Emergency Department Revisit
Litt 2012[26]	CCTA (n = 908) 30 days	Index: 50.4% (458) 30 days: 3% (28/889)	NR	30 days: 8% (71/885)
	Usual Care (n = 462) 30 days	Index: 77.3% (357) 30 days: 2% (11/456)	NR	30 days: 8% (34/452)
Miller 2011[30]	CCTA (n = 30) 3 months	20.0% (6)	NR	16.7% (5)
	Usual Care (n = 30) 3 months	53.3% (16)	NR	33.3% (10)
Goldstein 2011[12]	CCTA (n = 361) 6 months	Index: 27.4% (99)* 6 months: NR	Index: NR 6 months: 0% (0/330)	6 months: 0.6% (2/330)
	SPECT (n = 338) 6 months	Index: 19.2% (65)* 6 months: NR	Index: NR 6 mos: 0% (0/297)	6 months: 1.3% (4/297)
Hamiton-Craig 2014[16]†	CCTA (n = 322) 12 months	12 months: 10.2% (33)	NR	12 months: 12.7% (41)‡
	Exercise ECG (n = 240) 12 months	12 months: 10.8% (26)	NR	12 months: 10.5% (25)‡
Goldstein 2007[13]	CCTA (n = 99) 6 months	Index: 11.1% (11)§ 6 months: NR	NR	6 months: 6.1% (6)
	SPECT (n = 98) 6 months	Index: 3.1% (3)§ 6 months: NR	NR	6 months: 6.1% (6)

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography.
*Authors reported the number of patients discharged home after index visit; we inferred that those not discharged were admitted or kept for observation.
†All events back-calculated using percentages provided.
‡For chest pain/symptoms.
§Authors reported the number of patients who were discharged to home; we reported the difference as those who were hospitalized or kept for observation at index.

Table E32. Demographics for included observational studies in populations considered to be at low-to-intermediate risk for coronary artery disease

Author, Year		Cheezum (2011)[3*]		Nielsen (2011)[33]	
Test **Sample size**		CCTA (n = 252)	SPECT (n = 241)	CCTA (n = 251)	Exercise ECG (n = 247)
Patient demographics	Female, % (n)	44% (111)	45% (108)	51.0% (128)	46.6% (115)
	Age (years); mean ± SD	53±10	53±11	55±11	56±12
	Race, % (n)	NR	NR	NR	NR
	Pretest risk, % (n)[†]	Low: 16% (40) IM: 84% (212)	Low: 19% (46) IM: 81% (195)	Low: 27% (68) IM: 69% (173) High: 4% (10)	Low: 28% (68) IM: 69% (171) High: 3% (8)
	Subgroup (%)	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	90% (227)	8%8 (212)	100% (251)	100% (247)
	Typical angina	0% (0)	0% (0)	5.6% (14)	5.7% (14)
	Atypical angina	NR	NR	18.7% (47)	21.9% (54)
	Unstable angina	NR	NR	NR	NR
	Nonangina	NR	NR	75.7% (190)	72.5% (179)
	Noncardiac angina	NR	NR	NR	NR
	Dyspnea	10% (25)	12% (29)	NR	NR
	Prior MI	NR	NR	NR	NR
	Prior revascularization	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR
	Known CAD	NR	NR	0% (0)	0% (0)
	Chest pain frequency	NR	NR	NR	NR
	Hypertension	60.3% (152)	62.7	59.4% (149)	53.0% (131)
	Diabetes	11% (28)	11 (27)	8.4% (21)	9.7% (24)
	Hyperlipidemia	NR	NR	80.9% (203)	84.2% (208)
	Smoker (current or past)	17% (43)	14 (34)	51.0% (128)	44.5% (110)
Test details	CT images (slice)	64	NA	64	NA
	CACS performed	Yes	NA	NR	NA
	Type of stressor	NA	Exercise (treadmill 72%); pharmacologic (persantine 25%, adenosine 3%)	NA	Bicycle ergometer
	Contrast/radioisotope	Visapaque	Tc-99m sestamibi	NR (iodinated contrast)	NA
Study characteristics	Setting	Outpatient; Inpatient (9.5%),	Outpatient; Inpatient (10.4%)	Outpatient	Outpatient
	Followup period % completed followup (n)	Mean 29±7 months; 96.8% (244/252)	Mean 30±8 months 97.5% (235/241)	12 months 100% (251)	12 months 100% (247)
	Study Design	Retro cohort	Retro cohort	Retro cohort	Retro cohort
	Study Quality	Fair	Fair	Fair	Fair

CABG = coronary artery bypass graft; CAD = coronary artery disease; ECG = electrocardiogram; IM = intermediate; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; Retro = retrospective; SD = standard deviation; SPECT = single photon emission computed tomography.

*One group of patients were selected through patient matching: CCTA

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

Table E33. Clinical outcomes from retrospective observational studies including patients considered to be at low to intermediate risk for coronary artery disease[**]

Author, Year	Test, Sample Size, Final Followup	Mortality[*]	Myocardial Infarction	Major Adverse Cardiac Events	Unstable Angina	Heart Failure	Stroke
Cheezum 2011[3]	CCTA (n = 244) Mean 30 ± 7 months	2.4% (1)	NR	0.4% (1)[†]	NR	NR	NR
	SPECT (n = 235) Mean 30 ± 7 months	2.4% (1)	NR	0.9% (2)[†]	NR	NR	NR
Nielsen 2011[33]	CCTA (n = 251) 12 months	0% (0)	0% (0)	NR	NR	NR	NR
	Exercise ECG (n = 247) 12 months	0% (0)	1.2% (3)	NR	NR	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography.
*The two death reported are both due to unknown causes and identified on review of medical records. No cardiac-related deaths were reported in either group.
†Includes revascularization, myocardial infarction, acute coronary syndrome or cardiac death.

Table E34. Clinical management outcomes from retrospective observational studies including patients considered to be at low to intermediate risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Re-vascular-ization (any)	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Additional Noninvasive Testing (any)	Stress testing with imaging*	Stress testing without imaging†	Coronary computed tomography angiography	Outpatient cardiology visit
Cheezum 2011[3†‡]	CCTA (n = 244) Mean 30 ± 7 months	3.3% (8)	NR	NR	NR	9.8% (24)	6.9% (17)	2.5% (6)	0.4% (1)	11.9% (29)
	SPECT (n = 235) Mean 30 ± 7 months	8.1% (19)	NR	NR	NR	13.6% (32)	6.8% (16)	2.1% (5)	4.7% (11)	11.9% (28)
Nielsen 2011[33†]	CCTA (n = 251) 12 months	17.5% (44)	5.6% (14)	3.6% (9)	2.0% (5)	4.8% (12)	4.0% (10)	0.8% (2)	0% (0)	NR
	Exercise ECG (n = 247) 12 months	22.7% (56)	4.5% (11)	4.0% (10)	0.4% (1)	13.4% (33)	8.9% (22)	0% (0)	4.5% (11)	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography.
*For Cheezum 2011, additional stress testing with imaging consisted of single photon emission computed tomography and exercise echocardiography; rates in the CCTA group and SPECT group respectively were 5.7% (n=14) and 1.2% (n=3) versus 6.0% (n=14) and 0.9% (n=2). For Nielsen, patients received stress myocardial perfusion imaging (not specified further).
†Exercise electrocardiography for both studies.
‡Also reports total downstream clinical resource utilization, CCTA 24.6% (60), SPECT 27.7% (65); Includes post-test referral to specialist, ED visits, hospital admissions, and additional testing; per-patient composite rates

Table E35. Hospital or emergency department outcomes from retrospective observational studies including patients considered to be at low to intermediate risk for coronary artery disease*

Author, Year	Test, Sample Size, Final Followup	Hospitalization (any)	Hospitalization (cardiac)	Emergency department visit (cardiac)
Cheezum 2011[3]	CCTA (n = 244) Mean 30 ± 7 months	NR	6.6% (16)	13.1% (32)
	SPECT (n = 235) Mean 30 ± 7 months	NR	4.3% (10)	14.0% (33)
Nielsen 2011[33]	CCTA (n = 251) 12 months	NR	NR	NR
	Exercise ECG (n = 247) 12 months	NR	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography.
*Heart Failure and stroke were not reported in retrospective observational studies including patients considered to be at low-to-intermediate risk.

Table E36. Demographics for included RCTs in populations considered to be at low risk for coronary artery disease

Author (year)		**Chang (2008)**[2]		**Sabharwal (2007)**[35]	
Test **Sample size**		CCTA (n = 50)*	Usual Care (n = 49)*	SPECT (n = 27)*	Exercise ECG (n = 44)*
Patient demographics	Female, % (n)	39% (52)	38% (51)	44.4% (111)	42.5% (88)
	Age (years); mean ± SD	57 ± 14	58 ± 14	59.7 ± 12.2	58.9 ± 911.4
	Race, % (n)	NR	NR	White: 55.6% (139)	White: 46.9% (97)
	Pretest risk, % (n)†	Low: 37.6% (50) IM: 41.4% (55) High: 21.1% (28)	Low: 36.8% (49) IM: 42.1% (56) High: 21.1% (28)	Low: 10.8% (27) IM: 71.2% (178) High: 18.0% (45)	Low: 21.3% (44) IM: 49.3% (102) High: 29.5% (61)
	Subgroup	NR	NR	None	None
Cardiac risk factors, % (n)	Chest pain	100% (133)	100% (133)	100% (250)	100% (207)
	Typical angina	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR
	Unstable angina	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR
	Nonangina	NR	NR	NR	NR
	Noncardiac angina	NR	NR	NR	NR
	Silent ischemia	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR
	Prior MI	NR	NR	0% (0)	0% (0)
	Prior revascularization	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR
	Known CAD	12% (16)	17% (23)	0% (0)	0% (0)
	Chest pain frequency	NR	NR	NR	NR
	Hypertension	46% (61)	41% (55)	53.2% (133)	46.3% (96)
	Diabetes	16% (21)	19% (25)	19.2% (48)	14.5% (30)
	Hyperlipidemia	29% (39)	25% (33)	NR	NR
	Current smoker	17% (23)	23% (31)	12.8% (32)	16.4% (34)
Test details	CT images (slice)	64	NA	NA	NA
	CACS performed	NR	NR	NA	NA
	Type of stressor	NA	NA	Exercise (treadmill 62%) and/or pharmacologic stress (dipyradimole 38% (or dobutamine if contraindication))	Treadmill (Bruce protocol)
	Contrast (dose)	Lomeprol (80mL lomeron 400; Bracco, Milan, Italy)	NA	Radiotracer: Tc-99m sestamibi	NA
Study characteristics	Setting	ED	ED	Outpatient	Outpatient

Author (year)		**Chang (2008)**[2]		**Sabharwal (2007)**[35]	
	Followup period % completed followup (n)	30 days	30 days	Mean 19.6 months 96.9% (443/457)‡	Mean 19.6 months 96.9% (443/457)‡
	Study Design	RCT	RCT	RCT	RCT
	Study Quality	Fair	Fair	Fair	Fair

CABG = coronary artery bypass graft; CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; ECHO = echocardiogram; ED = emergency department; IM = intermediate risk; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography.
*Subgroup of patients at low pretest risk; demographics are reported for the entire population (demographics not reported separately for groups stratified by low risk).
†As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Tables E40-E41 for details.
‡Loss-to-followup not reported by group; 10 patients did not have followup data and there were 2 deaths in each group (SPECT: 2 malignancy; ECG: 1 malignancy and 1 cardiac).

Table E37. Clinical outcomes from randomized controlled trials including patients considered to be at low risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Mortality	Myocardial Infarction	Unstable Angina	Heart failure, stroke, MACE	Dysrhythmia	Quality of Life
Chang, 2008[2]*	CCTA (n = 50) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 4% (2) 30 days: NR	Index: 2% (1) 30 days: NR	NR	NR	NR
	Usual Care (n = 49) 30 days	Index: 0% (0) 30 days: 0% (0)	Index: 4% (2) 30 days: NR	Index: 2% (1) 30 days: NR	NR	NR	NR
Sabharwal 2007[35]*	SPECT (n = 27) Mean 21.7 ± 6.4 months	NR	NR	NR	NR	NR	NR
	Exercise ECG (n = 44) Mean 21.7 ± 6.4 months	NR	NR	NR	NR	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; MACE = major adverse cardiac events; NR = not reported; SPECT = single photon emission computed tomography.

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

Table E38. Clinical management outcomes from randomized controlled trials including patients considered to be at low risk for coronary artery disease

Author, Year	Test, Sample Size, Final Followup	Invasive Coronary Angiography	Re-vascularization (any)	Additional Noninvasive Testing (any)	Medical Therapy	Percutaneous Coronary Intervention	Coronary Artery Bypass Graft	Outpatient Cardio-vascular Visits
Chang, 2008[2*]	CCTA (n = 50) 30 days	Index: 6% (3) 30 days: NR	Index: 6% (3) 30 days: NR	Index: 0% (0) 30 days: NR	NR	NR	NR	NR
	Usual Care (n = 49) 30 days	Index: 10% (5) 30 days: NR	Index: 2% (1) 30 days: NR	Index: 80% (39) 30 days: NR	NR	NR	NR	NR
Sabharwal 2007[35*]	SPECT (n = 27) Mean 21.7 ± 6.4 months	7.4% (2)	NR	0% (0) (imaging)	92.5% (25)	NR	NR	NR
	Exercise ECG (n = 44) Mean 21.7 ± 6.4 months	0% (0)	NR	13.6% (6) (imaging)	75% (38)	NR	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography.
*Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the low risk group only are reported here.

Table E39. Hospital and emergency department outcomes from randomized controlled trials including patients considered to be at low risk for coronary artery disease*

Author, Year	Test, Sample Size, Final Followup	Hospitalization (any)	Hospitalization (cardiac)
Chang, 2008[2†]	CCTA (n = 50) 30 days	Index: 14% (7) 30 days: NR	Index: 6% (3)‡ 30 days: NR
	Usual Care (n = 49) 30 days	Index: 16% (8) 30 days: NR	Index: 6% (3)‡ 30 days: NR
Sabharwal 2007[35†]	SPECT (n = 27) FF: Mean 21.7 ± 6.4 months	NR	NR
	Exercise ECG (n = 44) FF: Mean 21.7 ± 6.4 months	NR	NR

CCTA = coronary computed tomography angiography; ECG = electrocardiography; NR = not reported; SPECT = single photon emission computed tomography.
* Emergency department revisits were not reported in studies with patients at low risk.
† Included low, intermediate, and high risk groups and stratified some results by pretest risk group. Results for the low risk group only are reported here.
‡Includes hospitalization for non-ST-segment elevation myocardial infarction or unstable angina, which are also reported separately under clinical outcomes.

Table E40. Pre-test risk assessment in included studies

Author (year)	Study Design	Method used to assess pre-test risk	Pretest risk (as reported by authors)	Risk scores or % of patients
CCTA vs. Usual Care				
Henzler 2013[17]	Retro cohort	TIMI risk score	• Intermediate (TIMI scores NR)	NR
Litt 2012[26]	RCT	TIMI risk score	• Low-to-intermediate (TIMI score 0 to 2)	CCTA (n = 908) • 0 (51%), 1 (36%), ≥2 (13%) Usual Care (n = 462) • 0 (51%), 1 (36%), ≥2 (13%)
Miller 2011[30]	RCT	"Established criteria" [see Table E41]	• Low-to-intermediate	NR
Hoffman 2012[20]	RCT	NR	NR	Number of cardiovascular risk factors: • CCTA (n=501): 0-1 (36%), 2-3 (54%), ≥4 (10%) • Usual Care (n=499): 0-1 (38%), 2-3 (52%), ≥4 (10%)
Stress Echo vs. Ex ECG				
Dodi 2001[7*]	Retro cohort	Diamond-Forrester risk algorithm	Mixed (results not stratified) • Low-to-intermediate (<70%) High (≥70%)	• Low-intermediate: 60% • High: 40% • Overall %: 56% ± 27%
Marwick 2003[27]	Retro cohort	predicted annualized probability of cardiac death or MI, derived from a Cox proportional hazards model that included age, gender, diabetes, angina class, cigarette smoking, hypertension, diabetes, hyperlipidaemia, prior revascularization and previous MI [see Table E41]	• Low (<0.6%) • Intermediate (0.6-2.0%) • High (>2.0%)	Ex Echo (n = 3860) • Low (11%), intermediate (58%), high (31%) Ex ECG (n = 3796) • Low (12%), intermediate (60%), high (28%)
Sanfilippo 2005[36]	RCT	NR	NR	NR
Ferrara 1991[46*]	Pro cohort	NR	NR	NR
Severi 1994[47*]	Pro cohort	CCS Angina Grading Scale, Classes I-III	NR	• Class I: 27% • Class II: 53% • Class III: 19%
Shreibati 2011[39]	Retro database	NR	NR	NR
SPECT vs. Ex ECG				
Sabharwal 2007[35]	RCT	determined from patient's symptoms and cardiac risk factors by use of the ACC/AHA guidelines (Diamond-Forrester) [see Table E41]	• Low • Intermediate • High	SPECT (n = 250) • Low (11%), intermediate (71%), high (18%) Ex ECG (n = 207) • Low (21%), intermediate (49%), high (29%)

Author (year)	Study Design	Method used to assess pre-test risk	Pretest risk (as reported by authors)	Risk scores or % of patients
Shaw 2011[38]	RCT	defined as women age ≥50 years with typical or atypical angina or age ≥60 years with nonanginal symptoms	• Intermediate	NR
Shreibati 2011[39]	Retro database	NR	NR	NR
PET vs. SPECT				
Hachamovitch 2012/Hlatky 2014[15, 19]	Pro cohort	method of Pryor et al [see Table E41]	• Intermediate-to-high	PET (n = 548): 0.45 ± 0.33 SPECT (n = 565): 0.38 ± 0.329
SPECT vs. Stress Echo				
Takeuchi 1996[40]	Retro cohort	Diamond-Forrester risk algorithm	Mixed (results not stratified): • Low (<20%) • Intermediate (20-80%) • High (>80%)	Overall %: 56.8% ± 4.0% Low: 33% Intermediate: 26% High: 41% (risk not reported by test)
Shreibati 2011[39]	Retro database	NR	NR	NR
CCTA vs. Ex ECG				
McKavanagh 2014[29]	RCT	Diamond-Forrester risk algorithm	Mixed (results not stratified): • Low (<30%) • Intermediate (30-60%) • High (>60%)	CCTA (n = 243) • Low (42%), intermediate (22%), high (37%) • Overall %: 47.8% ± 31.7% Ex ECG (n = 245) • Low (44%), intermediate (25%), high (31%) • Overall %: 44.9% ± 30.2%
Nielsen 2011[33]	Retro cohort	Diamond-Forrester risk algorithm	Mixed (results not stratified): • Low (<13.4%) • Intermediate (13.5-87.2%) • High (>87.2%)	CCTA (n = 251) • Low (27%), intermediate (69%), high (4%) • Overall %: 26% ± 23% Ex ECG (n = 247) • Low (28%), intermediate (69%), high (3%) • Overall %: 27% ± 23%
Hamilton-Craig 2014[16]	RCT	Cardiac Society of Australia and New Zealand guidelines [see Table E41]	• Low-intermediate	NR
Shreibati 2011[39]	Retro database	NR	NR	NR
CCTA vs. Stress Echo				
Shreibati 2011[39]	Retro database	NR	NR	NR
CCTA vs. SPECT				

Author (year)	Study Design	Method used to assess pre-test risk	Pretest risk (as reported by authors)	Risk scores or % of patients
Min 2012[31]	RCT	Diamond-Forrester risk algorithm	Mixed (results not stratified): • Low • Intermediate High	CCTA (n = 91) • Low (4%), intermediate (63%), high (33%) SPECT (n = 89) Low (9%), intermediate (67%), high (24%)
Goldstein 2011[12]	RCT	Unclear – see inclusion criteria; TIMI risk score reported	Low-intermediate	CCTA (n = 361) • TIMI score: 0.99 ± 0.84 SPECT (n = 338) • TIMI score: 1.04 ± 0.87 Median TIMI score for both groups = 1.0
Goldstein 2007[13]	RCT	Goldman Reilly criteria [see Table E41]; TIMI score reported	Very low to low • Very low (score 0) • Low (score 2) • Moderate (score 3)	CCTA (n = 99) • Very low (100%), low (0%) • TIMI score: 1.24 ± 0.8 SPECT (n = 98) • Very low (99%), low (1%) • TIMI score: 1.33 ± 0.8 Median TIMI score for both groups = 1.0
Cheezum 2011[3]	Retro cohort	Diamond-Forrester risk algorithm	Very low-intermediate • Very low (<5%) • Low (5-10%) • Intermediate (10-90%)	CCTA (n = 252) • Very low (1%), low (15%), intermediate (84%) SPECT (n = 241) • Very low (5%), low (14%), intermediate (81%)
Tandon 2012[41]	Pro cohort	Pretest probability calculated using age, gender and symptoms (scale NR) (Diamond-Forrester); Also report Morise score (based on pretest probability and cardiac risk factors)	NR	CCTA (n = 1221) • Pretest probability (median, IQR): 12.3 (7-22) • Morise score: 10.7 ± 3.0 SPECT (n = 1221) • Pretest probability (median, IQR): 12.3 (8-31) • Morise score: 10.7 ± 3.0
Yamauchi 2012[43]	Pro cohort	NYHA Class (I-IV) and CCS Angina Grading Scale (1-4)	NR	CCTA (n = 635) • NYHA class: I (81%), II (15%), III (2%), IV (3%) • CCS class: 1 (62%), 2 (32%), 3 (2%), 4 (4%) SPECT (n = 1221) • NYHA class: I (92%), II (8%), III (0%), IV (0%) • CCS class: 1 (78%), 2 (21%), 3 (1%), 4 (0%)
Min 2008[32]	Retro database	NR	NR	NR
Shreibati 2011[39]	Retro database	NR	NR	NR
CCTA vs. Functional testing				

Author (year)	Study Design	Method used to assess pre-test risk	Pretest risk (as reported by authors)	Risk scores or % of patients
Douglas 2015[8] (PROMISE trial)	RCT	Combined Diamond and Forrester / CASS risk score Also report risk burden (based on mean number of risk factors present)	CTA (n = 4996) • Combined Diamond & Forrester/CASS: Mean 53.4 ± 21.4 • Risk burden: 2.4 ± 1.1 Functional (n = 5007) • Combined Diamond & Forrester/CASS: Mean 53.2 ± 21.4 • Risk burden: 2.4 ± 1.1	NR

ACI-TIPI = Acute Cardiac Ischemia Time Insensitive Predictive Instrument; ACPS = acute chest pain syndromes; CCS = Canadian Cardiovascular Society; CCTA = coronary computer tomography angiography; CI = confidence interval; ECG = electrocardiogram; ECHO = echocardiogram; ICA = invasive coronary angiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; NYHA = New York Heart Association; RCT = randomized controlled trial; PET = positron emission tomography; pro = prospective; retro = retrospective; RR = risk ratio; SPECT = single photon-emission computed tomography; TIMI = Thrombolysis in Myocardial Infarction.
*Relevant clinical outcomes were not stratified by test; included for safety only.

Table E41. Definition of risk assessment in included studies

Risk criteria	Description
Cardiac Society of Australia and New Zealand guidelines[297]	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[298]	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[299]	"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[30]	"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[299]	"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[13, 300, 301]	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[302]	% risk at 14 days of: all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization. • Score of 0-1 = 4.7% risk • Score of 2 = 8.3% risk • Score of 3 = 13.2% risk • Score of 4 = 19.9% risk • Score of 5 = 26.2% risk • Score of 6-7 = at least 40.9% risk
Pryor et al.[303]	The probability of significant coronary artery disease was calculated as: $1/(1 + e^{-x})$ Where e = base of natural logarithm *Where* $x = a_1y_1 + a_2y_2 + . . . + a_ky_k + B$ Where $y_1, y_2, ..., y_k$ are the characteristics, $a_1, a_2, \ldots, a_k$ are the corresponding logistic regression coefficients, and B is the intercept term (in this case, -7.376).

Risk criteria	Description
Predicted annualized risk of death or MI[27]	Determining 10-year (short term) risk for developing CHD is carried out using Framingham risk scoring. The risk factors included in the Framingham calculation are age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking. Because of a larger database, Framingham estimates are more robust for total cholesterol than for LDL cholesterol. Note, however, that LDL cholesterol remains the primary target of therapy. Risk score is calculated using a downloadable excel file or risk assessment tool available here: http://cvdrisk.nhlbi.nih.gov/calculator.asp .

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

Table E42. Definitions for usual care in included studies

Author (year)	Definition of Usual Care
Hoffman (2012)[20*] RCT (ROMICAT II) Multicenter (9 sites)	Subjects will be evaluated according to each hospital's specific protocol to evaluate and manage patients with acute chest pain. Typically, the standard evaluation in the ED will include: • past and current medical history • physical examination • ECG • cardiac biomarker (troponin and CK-MB) as well as other routinely obtained blood testing Patients may undergo cardiac CT as part of Usual Care but only as a secondary diagnostic test. (Patients in the CT arm may undergo further diagnostic testing as well.) All admitted subjects will undergo each hospital's standard rule out myocardial ischemia protocol. This protocol typically consists of observation and monitoring including serial ECGs and repeated cardiac biomarker measurements as well as a noninvasive stress test (often imaging based) to evaluate for myocardial ischemia. The participating clinical sites perform routinely either: • nuclear perfusion imaging [SPECT] at rest and stress; • and/or stress echocardiography; • and/or exercise treadmill test [ETT] Depending on the results, subjects may undergo additional noninvasive or invasive testing (coronary angiography), and/or coronary revascularization during their hospital stay.

Litt (2012)[26*]
 	
RCT
Multicenter (5 sites)
	Patient's health care provider (ED physician) will make all disposition and management decisions:
	• Admit to hospital, admit to cardiac diagnostic unit, or discharge to home
	• ECG and serial markers (e.g., cardiac troponin) per Usual Care
	• Banked serum at up to 3 approximated time points: 0, 90 to 180 minutes, and 6 hours (blood sampling only up until the time of discharge) (performed only at HUP and PPMC sites)
	• Objective testing per attending during admission or as an outpatient:
	  o Stress testing with or without imaging [58% (267/462)]
	  o No objective assessment (i.e., stress test or cath) for ischemia or coronary artery disease [36% (167/462)]
	  o CCTA [6% (26/462)]
	  o Cardiac catheterization [4% (18/462)]

Miller (2011)[30] RCT Single center	Standard treatment included: • 12-lead ECG tracings • coronary biomarkers (troponin I) obtained at 0, 4, and 9 hours after ED arrival • continuous ECG monitoring All enrolled participants received: • aspirin (81 mg orally) and sublingual nitroglycerin (0.4 mg) for the chest pain until it was alleviated (up to three administrations, about 5 minutes apart) • cardiology consultation • and additional cardiac testing as required (types not specified) None of standard care group patients received a CCTA during the 90-days study period

Author (year)	Definition of Usual Care
Gruettner/ Henzler (2013)[17, 229] Retrospective cohort	The Usual Care diagnostic algorithm consisted of: • repetitive biomarker measurements • stress testing including exercise ECG, stress echocardiography, SPECT, and clinical observation • patients with positive/inconclusive or non-diagnostic stress test results as well as patients with mildly elevated Troponin values <0.5 µg/l were scheduled for ICC Usual Care group patients did not receive CCTA during the 90-days study period due to limited scanner availability (identified using clinical information and billing system) All Usual Care patients hospitalized at least one night. [ICC in 87% (87/100). The reminder (13/100) hospitalized for monitoring, including repeat ECG, cardiac biomarkers, and stress testing.]

CCTA = cardiac computed tomography angiogram; CK-MB = creatine kinase MB; ECG = electrocardiogram; ED = emergency department; ETT = exercise treadmill test; ICA = invasive coronary angiography; ICC = invasive coronary catheterization; RCT = randomized controlled trial; ROMICAT = rule out myocardial infarction using computer assisted tomography; SPECT = single-photon emission computerized tomography
*From published protocols.

Appendix F. Evidence Tables for Noncomparative Studies

Table F1. Demographics and study characteristics for noncomparative stress echocardiography studies with patients at low risk

		Exercise		Exercise or Pharmacologic
Author (year) Sample size		**Buchsbaum (2001)**[1] n = 149	**Elhendy (2001)**[9] n= 1618	**Innocenti (2014)**[21] n = 626
Patient demographics	Female, % (n)	44% (64)	65% (1047)	42% (265)
	Age (years); mean ± SD	47 ± 9	54.1	67 ± 12
	Race, % (n)	NR	NR	NR
	Pretest risk	Low-risk	Low pretest probability (≤25%)	Very low-to-low
	Subgroup	None	NR	None
Cardiac risk factors, % (n)	Chest pain	NR	NR	NR
	Typical angina	NR	0% (0)	NR
	Atypical angina	NR	38.0% (615)	NR
	Unstable angina	NR	NR	NR
	Noncardiac angina	NR	NR	NR
	Atypical chest pain or dyspnea	NR	67.3% (1090)	NR
	Prior MI	NR	0% (0)	NR
	Prior revascularization	NR	0% (0)	NR
	Prior CABG/PCI	NR	0% (0)	NR
	Known CAD	NR	NR	26% (162)*
	Hypertension	26% (38)	30.9% (501)	62% (389)
	Diabetes	3% (4)	5% (78)	17% (104)
	Hyperlipidemia/ hypercholesterolemia	20% (29)	46.3% (750)	NR
	Smoker	52% (75)	43.5% (704)	NR
Test details	Type of stressor	Exercise (treadmill)	Dobutamine (73%) or dipyridamole (171%z) ECHO	Exercise or Dobutamine
Study characteristics	Followup period % completed followup (n)	6 months, 99% (148/149)	36 ± 18 months, % NR	Mean 2.3 ± 1.1 years, % NR
	Setting	ED	NR	ED

CABG = coronary artery bypass graft; CAD = coronary artery disease; ECHO = echocardiography; ED = emergency department; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation.

* Results are for those without history of CAD; An additional 148 hand known CAD; Cardiac events included nonfatal ACS, fatal ACS and ventricular tachycardia over an average 4.5 years of followup. Authors excluded patients who died from noncardiac disease but do not report number for the group without a history of CAD

Table F2. Summary clinical outcomes from single arm studies of stress echocardiography in patients at low risk

Author (year) **Sample size**		**Buchsbaum (2001)[1*]** n = 149		**Elhendy (2001)[9]** N = 1618		**Innocenti (2014)[21]** N = 424	
Pretest risk		Low risk		Low pretest probability (≤25%)		Very low-to-low	
Followup		6 months		Median 3 yrs		Mean 4.5 years	
Test result **Sample size**		**Positive** (n = 7)	**Negative** (n = 138)	**Positive** (n = 344)	**Negative** (n = 1272)	**Positive** (n = 94)	**Negative** (n = 330)
Outcomes	Mortality % (n)	NR	NR	NR	NR	NR	NR
	MI % (n)	0% (0)	0.7% (1)*	NR	NR	NR	NR
	Any Cardiac Event	0% (0)	0.7% (1)*	2.6% (9)†	0.8% (10)†	5.3% (5)‡	0.8% (3)

CAD =coronary artery disease; CI = confidence interval; ECHO = echocardiography; MI = myocardial infarction; NR = not reported.

*non-Q-wave MI 6 months after discharge

†cardiac death, nonfatal MI over median of 3 years

‡ Results are for those without history of CAD; An additional 148 hand known CAD. Cardiac events included nonfatal ACS, fatal ACS and ventricular tachycardia over an average 4.5 years of followup. Authors excluded patients who died from noncardiac disease but do not report number for the group without a history of CAD

Table F3. Demographics and study characteristics for single arm coronary artery calcium scoring studies with patients at intermediate risk

Author (year) **Sample size**		**Petretta (2012)**[34] n=341	**Villines (2011)**[42] n=10,037	
Test Result		**Total population**	**Positive** (n=4909)	**Negative** (n=5128)
Patient demographics	Female, % (n)	33% (113)	57% (2798)	44% (2256)
	Age (years); mean ± SD	62 ± 12	61 ± 11	52 ± 12
	Race, % (n)	NR	NR	NR
	Pretest risk	Intermediate risk (15-85%)	Intermediate-risk (54%)	Intermediate risk (32%)
	Subgroup	NR	NR	NR
Cardiac risk factors, % (n)	Chest pain	100%	NR	NR
	Typical angina	32% (103)	16% (785)	13% (667)
	Atypical angina	63% (207)	NR	NR
	Unstable angina	0% (0)	NR	NR
	Noncardiac angina	5% (16)	NR	NR
	Atypical chest pain or dyspnea	NR	NR	NR
	Dyspnea	NR	37% (1816)	26% (1333)
	Prior MI	0% (0)	NR	NR
	Prior revascularization	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR
	Known CAD	0% (0)	0% (0)	0% (0)
	Hypertension	51% (167)	59% (2896)	44% (2256)
	Diabetes	12% (40)	18% (884)	9% (462)
	Hyperlipidemia/ Hypercholesterolemia	38% (124)	62% (3044)	51% (2615)
	Smoker	27% (89)	18% (884)	16% (820)
Test details	Type of stressor	NR	NR	NR
Study characteristics	Followup period % completed followup (n)	26 ± 12 months 95.6% (326/341)	Median 2.1 years 84.9% (4169/4909)	Median 2.1 years 92.3% (4738/5128)
	Setting	Outpatient	NR	NR

CABG = coronary artery bypass graft; CAD = coronary artery disease; ED = emergency department; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation.

Table F4. Summary outcomes for single arm coronary artery calcium scoring studies with patients at intermediate risk

Author (year) **Sample size**		**Petretta (2012)**[34] n=341		**Villines (2011)**[42] n=10,037	
Pretest risk		Intermediate (15-85%)		Diamond-Forrester pretest risk = 43%	
Followup		26 ± 12 months		Median 2.1 years	
Test result **Sample size**		**Positive** (n=220)	**Negative** (n=106)	**Positive** (n=4909)	**Negative** (n=5128)
Outcomes	Mortality % (n)	0% (0)	0% (0)	1.8% (74)	0.4% (21)
	MI % (n)	0% (0)	0% (0)	1.1% (46)	0.2% (9)
	Any Cardiac Event	8.2% (28)*	0% (0)	4.8% (191)†	0.9% (44)†

CAD =coronary artery disease; CI = confidence interval; ECHO = echocardiography; MI = myocardial infarction; NR = not reported.

* Includes nonfatal MI, cardiac death, and revascularization for unstable angina

† Major adverse events, includes all-cause mortality, nonfatal MI, or coronary revascularization occurring 90 days after testing.

Table F5. Demographics and study characteristics for single arm stress echocardiography studies with patients at low to intermediate risk

		Exercise		Exercise or pharmacologic
Author (year) **Sample size**		**Fine (2013)**[10] n = 7,236		**Colon (1998)**[5] n = 108
Test result		**Positive** (n = 1275)	**Negative** (n = 5961)	**Total population**
Patient demographics	Female, % (n)	21% (262)	32% (1899)	50% (54)
	Age (years); mean ± SD	60 ± 10	50 ± 10	54 ± 12
	Race, % (n)	NR	NR	NR
	Pretest risk	Low: 30% (386) Intermediate to High: 31% (396)	Low: 51% (3055) Intermediate to High: 42% (2488)	Low-moderate risk (mean 2.4 ± 1.3 risk factors)
	Subgroup	High exercise capacity	High exercise capacity	NR
Cardiac risk factors, % (n)	Chest pain	36% (465)	41% (2450)	100% (108)
	Typical angina	7% (85)	3% (204)	NR
	Atypical angina	27% (345)	33% (1993)	NR
	Unstable angina	NR	NR	NR
	Noncardiac angina	3% (35)	4% (253)	NR
	Dyspnea	18% (233)	19% (1109)	NR
	Prior MI	24% (306)	2% (148)	NR
	Prior revascularization	34% (432)	6% (371)	NR
	Prior CABG/PCI	NR	NR	NR
	Known CAD	39% (493)	7% (418)	NR
	Hypertension	52% (664)	34% (2053)	40% (43)
	Diabetes	9% (118)	6% (344)	11% (12)
	Hyperlipidemia	75% (960)	55% (3293)	31% (34)
	Smoker	50% (633)	39% (2332)	51% (55)
Test details	Type of stressor	Exercise (treadmill)	Exercise (treadmill)	Exercise (72%) or dobutamine (28%) echo
Study characteristics	Followup period % completed followup (n)	Mean 4.8 ± 1.7 years, %NR	Mean 4.8 ± 1.7 years, %NR	12.8 ± 7.2 months, %NR
	Setting	Clinic	Clinic	ED

CABG = coronary artery bypass graft; CAD = coronary artery disease; ED = emergency department; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation.

Table F6. Summary outcomes for single arm stress echocardiography studies with patients at low to intermediate risk

		Exercise		Exercise or pharmacologic	
Author (year) **Sample size**		**Fine (2013)**[10] n = 7,236		**Colon (1998)**[5] n = 108	
Pretest risk		Low: 30% (386) Intermediate to high: 31% (396)	Low: 51% (3055) Intermediate to high: 42% (2488)	Low-moderate risk (mean 2.4 ± 1.3 risk factors)	Low-moderate risk (mean 2.4 ± 1.3 risk factors)
Followup		Mean 4.8 ± 1.7 years		12 months	
Test result **Sample size**		**Positive** (n = 1275)	**Negative** (n = 5961)	**Positive** (n = 8)	**Negative** (n = 100)
Outcomes	Mortality % (n)	Ischemia* 0.53 (0.33 to 0.80) Fixed* 0.93 (0.56 to 1.31)	0.30 (0.24 to 0.37)*	0% (0)	0% (0)
	MI % (n)	NR	NR	NR	NR
	Any Cardiac Event	NR	NR	75% (6)†	0% (0)

MI = myocardial infarction; NR = not reported.
*Annualized mortality rates per person year of followup (95% CI)
†Calculated from author reported cardiac event-free rate

Table F7. Demographics and study characteristics for single arm stress electrocardiogram (ECG) studies with patients at low to intermediate risk

		Exercise		Exercise or pharmacologic	
Author (year) Sample size		**Cho (2012)[4]** n=2977	**Dedic (2011)[6*]** n =422	**Hachamovitch (1996)[14]** n=2268[†]	**Colon (1998)[5]** n = 108
Patient demographics	Female, % (n)	50% (1501)	49 (205)	40% (845/2113)	50% (54)
	Age (years); mean ± SD	50 ± 10	56 ± 9.9	61 ± 12	54 ± 12
	Race, % (n)	NR	NR	NR	NR
	Pretest risk	Very low (<5%): 8% (239) Low (6-9%): 28% (823) Intermediate (10-90%): 61% (1825) High (>90%): 3% (90)	Low-to-intermediate	Low: 8% Intermediate: 46% High: 3%	Low-moderate risk (mean 2.4 ± 1.3 risk factors)
	Subgroup	NR	None	NR	NR
Cardiac risk factors, % (n)	Chest pain	NR	100% (422)	30% (628/2113)	100% (108)
	Typical angina	NR	32% (136)	9.0% (191/2113)	NR
	Atypical angina	NR	52% (220)	20.6% (437/2113)	NR
	Unstable angina	NR	NR	NR	NR
	Noncardiac angina	NR	16% (66)	70% (1485/2113)	NR
	Dyspnea	NR	NR	2.5% (54/2113)	NR
	Prior MI	NR	NR	0%	NR
	Prior revascularization	0% (0)	NR	0%	NR
	Prior CABG/PCI	0% (0)	NR	0%	NR
	Known CAD	NR	0% (0)	NR	NR
	Hypertension	48% (1413)	50% (213)	39% (825/23113)	40% (43)
	Diabetes	16% (455)	14% (58)	9% (182/2113)	11% (12)
	Hyperlipidemia/ Hypercholesterolemia/ Dyslipidemia	44% (1300)	59% (249)	40% (849/2113)	31% (34)
	Smoker	13% (397)	27% (116)	17% (369/2113)	51% (55)
Test details	Type of stressor	Treadmill	Exercise (bicycle)	Treadmill	Exercise (72%) or dobutamine (28%) echo
Study characteristics	Followup period % completed followup (n)	Median 3.34 years (IQR 2.33 to 4.55), %NR	Mean 2.6 years, 90% (424)	Mean 566 ± 142 days 93.1% (2113/2268)[‡]	12.8 ± 7.2 months, %NR
	Setting	NR	Outpatient	NR	ED

CABG = coronary artery bypass graft; CAD = coronary artery disease; ED = emergency department; IQR = interquartile range; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation.

* Also includes groups who underwent calcium scoring or computed tomography angiography included for other comparisons; demographics based on overall population, calculated using weighted means; demographics only reported for patients with followup.

† Originally stated they enrolled 2268, have data on 2200 patients, but table 1 demos only report on 2113 patients, as they censored 89 patients for undergoing early revascularization (<60 days after testing).

‡ Patients lost to followup include 87 who were censored from demographics and results for receiving early revascularization/revascularization in the first 60 days after nuclear testing.

Table F8. Summary outcomes for single arm stress echocardiography studies with patients at low to intermediate risk

Author (year) Sample size		**Cho (2012)**[4] n=2977		**Dedic (2011)**[6*] n =422		**Hachamovitch (1996)**[14] n=2268[†]		**Colon (1998)**[5] n = 108	
Pretest risk		Very low (<5%): 8% (239) Low (6-9%): 28% (823) Intermediate (10-90%): 61% (1825) High (>90%): 3% (90)		Low-to-intermediate		Low: 8% Intermediate: 46% High: 3%		Low-moderate risk (mean 2.4 ± 1.3 risk factors)	
Followup		Median 3.34 years (IQR 2.33 to 4.55)		Mean 2.6 years		Mean 566 ± 142 days		12 months	
Test result **Sample size**		**Positive** (n=358)	**Negative** (n=2489)	**Positive** (n = 85)	**Negative** (n = 172)	**Positive** (n=587)	**Negative** (n=974)	**Positive** (n=10)	**Negative** (n=98)
Outcomes	Mortality % (n)	0.5% (2)	0.04% (1)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	MI % (n)	0.8% (3)	0.1% (3)	1% (1)	0.6% (1)	0% (0)	0% (0)	0% (0)	0% (0)
	Any Cardiac Event*	9.7% (35)§	2.0% (50)§	5% (4)	4% (7)	2.0% (12)**	0.9% (9)**	30% (3)[†]	3% (3)[†]

CAD =coronary artery disease; CI = confidence interval; IQR = interquartile range; MI = myocardial infarction; NR = not reported; SD = standard deviation.
* 12% (8/68) of patients with significant ST segment changes on exercise underwent primary revascularization or died of noncardiac causes and were excluded from analysis.† Originally stated they enrolled 2268, have data on 2200 patients, but table 1 demos only report on 2113 patients, as they censored 89 patients for undergoing early revascularization (<60 days after testing).
‡ Also includes equivocal/indeterminate outcome, see Table 3.
§ Also includes equivocal and nondiagnostic outcomes, see Table 4.
** Includes cardiac deaths (n=13) and nonfatal myocardial infarctions (n=26).

Table F9. Demographics and study characteristics for single arm coronary artery calcium scoring studies with patients at low to intermediate risk

Author (year) **Sample size**		**Kim (2012)**[23] n = 2088		**Dedic (2011)**[6] n =422*	**Laudon (2010)**[25] n=263
Test result		**Positive** (n = 974)	**Negative** (n = 1114)	**Total population**	**Total population**
Patient demographics	Female, % (n)	42.8 (417)	58 (643)	49 (205)	40% (104)
	Age (years); mean ± SD	NR	55.3 ± 10.1	56 ± 9.9	47.3 ± 7
	Race, % (n)	NR	NR	NR	NR
	Pretest risk	Very low: 2% Low: 12% Intermediate: 75% High: 11%	Very low: 4% Low: 18% Intermediate: 72% High: 7%	Low-to-intermediate	Low to moderate
	Subgroup	None	None	None	NR
Cardiac risk factors, % (n)	Chest pain	100% (974)	100% (1114)	100% (422)	100% (263)
	Typical angina	20% (195)	12% (130)	32% (136)	NR
	Atypical angina	44% (424)	45% (499)	52% (220)	NR
	Unstable angina	NR	NR	NR	100% (263)
	Noncardiac angina	36% (355)	44% (485)	16% (66)	NR
	Dyspnea	NR	NR	NR	NR
	Prior MI	0% (0)	0% (0)	NR	NR
	Prior revascularization	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR
	Known CAD	NR	NR	0% (0)	0% (0)
	Hypertension	64% (620)	41% (454)	50% (213)	32% (84)
	Diabetes	24% (238)	9% (102)	14% (58)	6% (16)
	Hyperlipidemia	52% (503)	44% (485)	59% (249)	NR
	Smoker	15% (145)	11% (126)	27% (116)	53% (140)
Test details	Type of stressor	Contrast (70 mL of iopamidol)	Contrast (70 mL of iopamidol)	Exercise (bicycle)	NR
Study characteristics	Followup period % completed followup (n)	Mean 2.8 years ± 4.5 months; 99.3% (2073)	Mean 2.8 years ± 4.5 months; 99.3% (2073)	Mean 2.6 years, 90% (424)	5 years, 81% (212/263)
	Setting	Hospital	Hospital	Outpatient	Emergency Department

CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation.

* Also includes groups who underwent calcium scoring or computed tomography angiography included for other comparisons; demographics based on overall population, calculated using weighted means; demographics only reported for patients with followup.

Table F10. Summary outcomes for single arm coronary artery calcium scoring studies with patients at low to intermediate risk

Author (year) Sample size		**Kim (2012)**[23] n = 2088		**Dedic (2011)**[6] n =422		**Laudon (2010)**[25] n=263	
Pretest risk		Very low: 2% Low: 12% Intermediate: 75% High: 11%	Very low: 4% Low: 18% Intermediate: 72% High: 7%	Low-to-intermediate	Low-to-intermediate	Low to moderate	Low to moderate
Followup		Mean 2.8 years ± 4.5 months		Mean 2.6 years		5 years	
Test result		**Positive** (n = 974)	**Negative** (n = 1114)	**Positive** (n = 266)	**Negative** (n = 151)	**Positive** (n=130)	**Negative** (n=133)
Outcomes	Mortality % (n)	1.6 (16)	0.7 (8)	2 (4)	0 (0)	NR	NR
	MI % (n)	0.4 (4)	0.1 (1)	2 (6)	0 (0)	11.5% (15)	0%
	Any Cardiac Event	4.7 (46)	1.3 (14)	11 (28)	1 (2)	0%*	0%*

CAD =coronary artery disease; CI = confidence interval; IQR = interquartile range; MI = myocardial infarction; NR = not reported; SD = standard deviation.
*Have cardiogenic chest pain as an outcome, not included.

Table F11. Demographics and study characteristics for single arm stress echocardiography studies with patients at intermediate to high risk

	Pharmacologic	
Author (year) **Sample size**		**Dodi (2001)**[7] n=244
Patient demographics	Female, % (n)	100% (244)
	Age (years); mean ± SD	60 ± 10
	Race, % (n)	NR
	Pretest risk	Pretest risk, mean: 56 ± 27 <70%: 60% (146) patients ≥70%: 40% (98) patients
	Subgroup	Women
Cardiac risk factors, % (n)	Chest pain	100%
	Typical angina	36% (89)
	Atypical angina	63% (155)
	Unstable angina	0%
	Noncardiac angina	NR
	Atypical chest pain or dyspnea	NR
	Dyspnea	NR
	Prior MI	0% (0)
	Prior revascularization	0% (0)
	Prior CABG/PCI)	0% (0)
	Known CAD	0% (0)
	Hypertension	39.7% (97)
	Diabetes	3.6% (9)
	Hyperlipidemia/ hypercholesterolemia	28.2% (69)
	Smoker	16.3% (40)
Test details	Type of stressor	Dobutamine (73) or dipyridamole (171) ECHO
Study characteristics	Followup period % completed followup (n)	36 ± 18 months, %NR
	Setting	NR

CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation.

Table F12. Summary outcomes for single arm stress echocardiography studies with patients at intermediate to high risk

Author (year) Sample size		**Dodi (2001)**[7] N = 244	
Pretest risk		Pretest risk, mean (SD): 56 ± 27 <70%: 60% (146) patients ≥70%: 40% (98) patients	
Followup		Mean 3yrs	
Test result **Sample size**		**Positive** (n = 33)	**Negative** (n = 211)
Outcomes	Mortality % (n)	NR	NR
	MI % (n)	NR	NR
	Any Cardiac Event	33% (11)	1.4% (3)

MI = myocardial infarction; NR = not reported; SD = standard deviation.

Table F13. Demographics and study characteristics for single arm stress echocardiography studies with patients at high risk

		Pharmacologic
Author (year) **Sample size**		Mazeika 1993[28] (n=51)
Patient demographics	Female, % (n)	11.7% (6)
	Age (years); mean ± SD	54 ± 9 (range 28 to 69)
	Race, % (n)	NR
	Pretest risk	Pretest risk, mean: 79.7 ± 5.6%
	Subgroup	NR
Cardiac risk factors, % (n)	Chest pain	NR
	Typical angina	78.4% (40)
	Atypical angina	17.6% (9)
	Unstable angina	NR
	Noncardiac angina	3.9% (2)
	Atypical chest pain or dyspnea	NR
	Dyspnea	NR
	Prior MI	27.4% (14)
	Prior revascularization	NR
	Prior CABG/PCI)	NR
	Known CAD	NR
	Hypertension	23.5% (12)
	Diabetes	NR
	Hyperlipidemia/ Hypercholesterolemia	NR
	Smoker	NR
Test details	Type of stressor	Dobutamine ECHO
Study characteristics	Followup period % completed followup (n)	24 ± 4 months 100% (51) completed followup
	Setting	NR

CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation.

Table F14. Summary outcomes for single arm Stress Echocardiography studies with patients at high risk

Author (year) Sample size		**Mazeika (1993)**[28] N = 51	
Pretest risk		79.7 ± 5.6%	
Followup		24 ± 4 months	
Test result **Sample size**		**Positive** (n = 25)	**Negative** (n = 26)
Outcomes	Mortality % (n)	0% (0)	0% (0)
	MI % (n)	NR*	NR*
	Any Cardiac Event*	33.3% (17)	11.7% (6)

MI = myocardial infarction; NR = not reported

* Events not stratified by test positive or test negative, but are reported as "Any Cardiac Event", which includes first (n=16) and second (n=7) cardiac events. First events include MI (n=1), unstable angina (n=9), CABG (n=10), and coronary angioplasty (n=3). Second events include unstable angina (n=1), CABG (n=4), and coronary angioplasty (n=2).

Table F15. Demographics and study characteristics for single arm stress echocardiography studies with patients not stratified by risk

	Exercise	
Author (year) **Sample size**		**Krivokapich (1993)**[24] n= 360
Patient demographics	Female, % (n)	34.1% (123)
	Age (years); mean ± SD	62 ±13
	Race, % (n)	NR
	Pretest risk	Known high pretest incidence of CAD
	Subgroup	NR
Cardiac risk factors, % (n)	Chest pain	NR
	Typical angina	NR
	Atypical angina	NR
	Unstable angina	NR
	Noncardiac angina	NR
	Atypical chest pain or dyspnea	NR
	Dyspnea	NR
	Prior MI	35.2% (127)
	Prior revascularization	NR (see below)
	Prior CABG/PCI)	17.7% (64)
	Known CAD	NR
	Hypertension	NR
	Diabetes	NR
	Hyperlipidemia/ hypercholesterolemia	46% (750)
	Smoker	44% (704)
Test details	Type of stressor	Treadmill exercise ECHO
Study characteristics	Followup period % completed followup (n)	12 months 100% (360/360) followup
	Setting	NR

CABG = coronary artery bypass graft; CAD = coronary artery disease; ECHO = echocardiography; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation.

Table F16. Summary results for single arm stress echocardiography studies with patients not stratified by risk

		Exercise	
Author (year) Sample size		**Krivokapich (1993)**[24] N = 211	
Pretest risk		Known high pretest incidence of CAD	Known high pretest incidence of CAD
Followup		1st year	
Test result **Sample size**		**Positive** (n = 22)	**Negative** (n = 189)
Outcomes	Mortality % (n)	0% (0)	0% (0)
	MI % (n)	9% (2)	1% (2)
	Any Cardiac Event	32% (7)*	7% (13)*

CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention.

*death, MI, CABG or PCI

Table F17. Demographics and study characteristics for single arm stress electrocardiography (ECG) studies with patients not stratified by risk

		Exercise or pharmacologic	Exercise
Author (year) Sample size		**Gentile (2001)*** n = 132	**Heupler (1997)†** n = 405
Patient demographics	Female, % (n)	31.2% (42)	100% (405)
	Age (years); mean ± SD	70.8	56 ± 11
	Race, % (n)	NR	NR
	Pretest risk	NR	8 ± 5% (range, 0% to 38%)‡
	Subgroup	Elderly (>65 years)	Women only
Cardiac risk factors, % (n)	Chest pain	63% (83)	NR
	Typical angina	27% (36)	NR
	Atypical angina	15% (20)	NR
	Unstable angina	14% (19)	NR
	Noncardiac angina	NR	NR
	Dyspnea	19% (25)	NR
	Prior MI	0% (0)	7% (36)
	Prior revascularization	0% (0)	0% (0)
	Prior CABG/PCI	NR	NR
	Known CAD	NR	18% (92)
	Hypertension	NR	39% (197)
	Diabetes	NR	10% (53)
	Hyperlipidemia	NR	NR
	Smoker	NR	16% (81)
Test details	Type of stressor	Exercise (bicycle, modified Balke protocol) or pharmacologic (dipyridamole)	Exercise (treadmill)
Study characteristics	Followup period % completed followup (n)	Mean 27.8 months (range 24-48), 94% (124)	Mean 41 ± 10 months, 94% (508)
	Setting	NR	Tertiary referral center

ED = emergency department; IM = intermediate risk; IQR = interquartile range; NA = not applicable; NR = not reported.
* Demographics based on overall population; results are only reported for patients with followup.
† Demographics based on patients with complete followup.
‡ 10 year cardiac risk based on Framingham in patients without known CAD

Table F18. Summary results for single arm stress electrocardiography (ECG) studies with patients not stratified by risk

		Exercise or pharmacologic		Exercise	
Author (year) Sample size		**Gentile (2001)**[11] n = 132		**Heupler (1997)**[18] n = 405	
Pretest risk		NR		8 ± 5% (range, 0% to 38%)*	
Followup		Mean 27.8 months		Mean 41 months	
Test result Sample size		**Positive** (n = 95)	**Negative** (n = 29)	**Positive** (n = 68)†	**Negative** (n = 337)
Outcomes	Mortality % (n)	7% (7)	7% (2)	NR	NR
	MI % (n)	3% (3)	10% (3)	NR	NR
	Any Cardiac Event	NR	NR	15% (9)	5% (8), OR 3.1, p=0.01

MI = myocardial infarction; NR = not reported; OR = odds ratio; SD = standard deviation.
* 10 year cardiac risk based on Framingham in patients without known CAD
†12% (8/68) of patients with significant ST segment changes on exercise underwent primary revascularization or died of noncardiac causes and were excluded from analysis

Table F19. Demographics and study characteristics for single arm coronary artery calcium scoring studies with patients not stratified by risk

Author (year) Sample size		**Schmermund (2004)**[37*] n=255
Test result		
Patient demographics	Female, % (n)	29% (74)
	Age (years); mean ± SD	58 ± 11 years
	Race, % (n)	NR
	Pretest risk	NR
	Subgroup	NR
Cardiac risk factors, % (n)	Chest pain	NR
	Typical angina	NR
	Atypical angina	NR
	Unstable angina	0% (0)
	Noncardiac angina	NR
	Dyspnea	NR
	Prior MI	0% (0)
	Prior revascularization	0% (0)
	Prior CABG/PCI	NR
	Known CAD	NR
	Hypertension	40.8% (104)
	Diabetes	7.1% (18)
	Hyperlipidemia/ hypercholesterolemia	NR
	Smoker	NR
Test details	Type of stressor	
Study characteristics	Followup period % completed followup (n)	3.5 years, 85% (255/300)
	Setting	Outpatient

CABG = coronary artery bypass graft; CAD = coronary artery disease; ECHO = echocardiography; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation.
*authors only report on patients with complete followup, though they do note that patients lost to followup were younger and had lower cholesterol than patients followed.

Table F20. Summary results for single arm coronary artery calcium scoring studies with patients not stratified by risk

Author (year) Sample size		**Schmermund (2004)**[37] n= 255	
Pretest risk		NR	
Followup		Mean 38 months	
Test result **Sample size**		**Positive*** (n = 193)	**Negative** (n = 62)
Outcomes	Mortality % (n)	1.6% (3)†	NR
	MI % (n)	1.0% (2)	NR
	Any Cardiac Event	20.2% (39)	1.6% (1)

MI = myocardial infarction; NR = not reported; SD = standard deviation.
*Patients with a positive result are reported as having a calcium score of 1.4 – 4041 (categorized in text into 4 quartiles, Q1 is 0-1.4 and Q2-4 are combined as positive)
†1 patient was excluded from analysis because of death for unknown cause (unclear which group this patient was in).

Appendix G. Safety Information in Included Comparative Studies and Studies Included for Safety Information Only

Table G1. Demographics for observational studies where patients received both tests and are included for safety information only[**]

Author, Year		**Ferrara (1991)[46]**		**Severi (1994)[47]**		**Takeuchi (1996)[*40]**	
Test Sample size		Stress Echo (n = 130)	Ex ECG (n = 130)	Stress Echo (n =429)	Ex ECG (n =429)	Stress Echo (n = 70)	SPECT (n = 61)
Patient demographics	Female, % (n)	38% (49)	38% (49)	28.4% (122)	28.4% (122)	100% (70)	100% (61)
	Age (years); mean ± SD	>65 years: 48% </= 65 years: 52%	>65 years: 48% </= 65 years: 52%	55 ± 4.1	55 ± 4.1	65 range (37 – 82)	NR
	Race, % (n)	NR	NR	NR	NR	NR	NR
	Pretest risk, % (n)[†]	NR	NR	NR	NR	High: 41% IM: 26% Low 33%	NR
	Subgroup	NR	NR	NR	NR	Women only	Women only
Cardiac risk factors, % (n)	Chest pain	100% (130)	100% (130)	100% (429)	100% (429)	NR	NR
	Typical angina	63.1% (82)	63.1% (82)	30.7% (132)	30.7% (132)	NR	NR
	Atypical angina	29.2% (38)	29.2% (38)	NR	NR	NR	NR
	Silent ischemia	13% (10)	13% (10)	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR
	Prior MI	5.4% (6)	5.4% (6)	NR	NR	NR	NR
	Prior revascularization	NR	NR	NR	NR	10% (7)	NR
	Prior CABG/PCI	NR	NR	NR	NR	NR	NR
	Known CAD	NR	NR	NR	NR	NR	NR
	Chest pain frequency	NR	NR	NR	NR	NR	NR
	Hypertension	NR	NR	28% (124)	28% (124)	NR	NR
	Diabetes	NR	NR	10% (44)	10% (44)	NR	NR
	Hyperlipidemia	NR	NR	15% (66)	15% (66)	NR	NR
	Current smoker	NR	NR	55% (238)	55% (238)	NR	NR
Test details	Type of stressor	Dobutamine	Bicycle	Dobutamine	Bicycle	Pharmacologic (dobutamine)	Exercise or pharmacologic (bicycle ergometer or dipyridamole)
	Contrast (dose)	NR	NA	NR	NA	NR	Thallium-201 tracer
Study characteristics	Setting	Outpatient	Outpatient[‡]	Outpatient	Outpatient	NR	NR
	Followup period	Median 9.7	Median 9.7	mean 37.8 ± 14 (range	mean 37.8 ± 14	NR	NR

Author, Year		Ferrara (1991)[46]		Severi (1994)[47]		Takeuchi (1996)[*40]	
	% completed followup (n)	months (range 5.4-15.4)[§] %NR	months (range 5.4-15.4)[§] %NR	1 to 73) months 100% (429)	(range 1 to 73) months 100% (429)	97.2% (70/72)	%NR
	Study Design	Prospective cohort	Prospective cohort	Prospective cohort	Prospective cohort	Retrospective	Retrospective
	Study Quality						

CAD = coronary artery disease; CABG = coronary artery bypass graft; ECG = electrocaardiogram; ECHP = echocardiogram; Ex = exercise; IM = intermediate risk; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation; SPECT = single photon emission computed tomography.

*Results reported only for patients with complete followup.

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

‡ Performed in a thermostatically controlled room.

§ Reported as days, converted to months by dividing by 30.

**Demographics for included comparative studies are included in Appendix E

Table G2. Demographics for observational studies where patients received both tests and are included for safety information only

		Masini (1988)[269]		**Nabi (2010)[44]**		**Nance (2012)[45]**	
Test **Sample size**		Stress ECHO (n = 83)	Ex ECG (n = 83)	SPECT (n = 1031)	CACS (n = 1031)	CCTA (n = 458)	CACS
Patient demographics	Female, % (n)	100% (83)	100% (83)	60% (623)	60% (623)	64% (293)	64% (293)
	Age (years); mean ± SD	55 ± 8 (range 38 – 69)	55 ± 8 (range 38 – 69)	54 ± 13.5	54 ± 13.5	55 ± 11	55 ± 11
	Race, % (n)	NR	NR	NR	NR	NR	NR
	Pretest risk, % (n)*	NR	NR	Low: 35.6% Moderate: 29.6% Moderately high: 15.1% High: 19.7%	Low: 35.6% Moderate: 29.6% Moderately high: 15.1% High: 19.7%	Low: 76% IN: 18% High: 6%	Low: 76% IN: 18% High: 6%
	Subgroup	Women only (100%)	Women only (100%)	None	None	None	None
Cardiac risk factors, % (n)	Chest pain	100% (83)	100% (83)	100% (1031)	100% (1031)	100% (458)	100% (458)
	Typical angina	NR	NR	NR	NR	NR	NR
	Atypical angina	NR	NR	NR	NR	NR	NR
	Unstabe angina	0% (0)	0% (0)	NR	NR	NR	NR
	Noncardiac angina	0% (0)	0% (0)	0% (0)	0% (0)	NR	NR
	Silent ischemia	NR	NR	NR	NR	NR	NR
	Nonspecific chest pain	NR	NR	NR	NR	NR	NR
	Dyspnea	NR	NR	NR	NR	NR	NR
	Prior MI	18.1% (15)	18.1% (15)	NR	NR	NR	NR
	Prior revascularization	NR	NR	NR	NR	NR	NR
	Prior CABG/PCI	NR	NR	NR	NR	NR	NR
	Known CAD	NR	NR	0% (0)	0% (0)	NR	NR
	Chest pain frequency	NR	NR	NR	NR	NR	NR
	Hypertension	NR	NR	57.2% (590)	57.2% (590)	69% (314)	69% (314)
	Diabetes	NR	NR	14.7% (152)	14.7% (152)	21% (96)	21% (96)
	Hyperlipidemia	NR	NR	34.1% (352)	34.1% (352)	45% (205)	45% (205)
	Current smoker	NR	NR	18.6% (192)	18.6% (192)	30% (138)	30% (138)
Test details	CT images (slice)	NA	NA	NA	16 multidetector	NR	NA
	CACS performed	NA	NA	Yes	Yes	Yes	Yes

		Masini (1988)[269]		Nabi (2010)[44]		Nance (2012)[45]	
	Type of stressor	Dipyridamole (0.84mg/kg over 10 min)	Exercise (bicycle)	Exercise (treadmill) or pharmacologic (adenosine or dobutamine) Technetium-99m	NR	NR	NR
	Contrast (dose)	NR	NR	None	None	Sublingual nitroglycerine (0.4mg)	NR
Study characteristics	Setting	Outpatient	Outpatient	ED	ED	ED	ED
	Followup period % completed followup (n)	NR %NR	NR %NR	Mean 7.4 ± 3.3 months 99% (1018)`	Mean 7.4 ± 3.3 months, 99% (1018)	Median 13 months	Median 13 months
	Study Design	Prospective cohort†	Prospective cohort†	Prospective cohort	Prospective cohort	Retrospective cohort	Retrospective cohort
	Study Quality						

CAD = coronary artery disease; CABG = coronary artery bypass graft; ECG = electrocaardiogram; ECHP = echocardiogram; Ex = exercise; IM = intermediate risk; MI = myocardial infarction; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; SD = standard deviation; SPECT = single photon emission computed tomography.

*As defined by the authors. Methods for assessing pretest risk of CAD varied across studies. See Table X for details.

†Patients were randomized as to the order in which tests were performed

Safety results for included comparative studies

Table G3. Safety outcomes reported in included comparative studies

Pretest CAD risk	Type of test comparison	Author Study design	Intervention	Comparator	Adverse events/side effects/harms (intervention vs. comparator)
Low	Functional vs. functional	Sabharwal 2007[35] RCT	SPECT	Exercise ECG	NR
Intermediate	Anatomic vs. usual care	Hoffman 2012[20] RCT	CCTA (+ Usual Care)	Usual Care	• Perioprocedural complications: 0.4% (2/501) vs. 0% (0/499)* • Undetected ACS: 0% (0/501) vs. 0% (0/499)
		Gruettner/Henzler 2013[17, 229] Pro cohort	CCTA	Usual Care	NR
	Functional vs. functional	Shaw 2011[38] RCT	SPECT	Exercise ECG	NR
		Sabharwal 2007[35] RCT	SPECT	Exercise ECG	NR
	Anatomic vs. functional	Douglas 2015[8] RCT	CCTA	"Functional testing" (primarily nuclear stress testing)	• Major procedural complication (includes stroke, major bleeding, anaphylaxis, and renal failure requiring dialysis): o 12 months followup: 0.1% (4/4996) vs. 0.1% (5/5007); RR 0.80† (95% CI 0.22 to 2.98); p=0.7413† o Mean 35 months followup: 0.1% (4/4996) vs. 0.1% (5/5007); RR 0.80† (95% CI 0.22 to 2.98); p=0.7413† • Stroke (procedural): 0.02% (1/4996) vs. 0.4% (2/5007); RR 0.50† (95% CI 0.05 to 5.52); p=0.5649† • Major bleeding (procedural): 0.1% (3/4996) vs. 0.1% (3/5007); RR 1.00† (95% CI 0.20 to 4.96); p=0.9978† • Anaphylaxis (procedural): 0% (0/4996) vs. 0% (0/5007) (RR, p-value NC) † • Renal failure requiring dialysis (from procedure): 0% (0/4996) vs. 0% (0/5007) (RR, p-value NC) † • Exercise-induced hypotension (BP fall >20 mmHg): 0% (0/4996) vs. 0.1% (6/5007) (RR 0† (95% CI NC); p=0.0144† • Stress-induced symptoms (not resolved <20 minutes): 0% (0/4996) vs. 0.1% (4/5007) (RR 0† 95% CI NC); p=0.0457† • Rapid atrial fibriallation that does not slow or convert: 0% (0/4996) vs. 0% (0/5007) (RR, p-value NC) †

Pretest CAD risk	Type of test comparison	Author Study design	Intervention	Comparator	Adverse events/side effects/harms (intervention vs. comparator)
					• Ventricular tachycardia: 0% (0/4996) vs. 0.1% (4/5007); RR 0[†] (95% CI NC); p=0.0457[†] • Hemodynamic instability (systolic BP < 80 mmHg): 0% (0/4996) vs. 0.04% (2/5007); RR 0[†] (95% CI NC); p=0.1577[†] • Any events potentially related to vasodilators: 0% (0/4996) vs. 0.1% (6/5007); RR 0[†] (95% CI NC); p=0.0255[†] • Mild contrast reaction (e.g., rash, hives): 0.4% (22/4996) vs. 0% (0/5007); RR 4.41[†] (95% 1.67 to 11.64), p=0.0010[†]
Low to intermediate	Anatomic vs. usual care	Litt 2012[26] RCT	CCTA	Usual Care [‡]	• Bradycardia (presumed to be related to the medication to control heart rate): 0.1% (1/908) vs. 0.2% (1/462)
		Miller 2011[30] RCT	CCTA+ Usual Care	Usual Care alone	NR
	Anatomic vs. functional	Goldstein 2011[12] RCT	CCTA	SPECT	NR
		Goldstein 2007[13] RCT	CCTA	SPECT	"no complication as a results of either test: 0% (0/99) vs. 0% (0/98)
		Cheezum 2011[3] Retro cohort	CCTA	SPECT	• Incidental findings requiring further investigation[§]: 7.1% (18/252) vs. 0% (0/241); p=0.0001
		Hamilton-Craig 2014[16] RCT	CCTA	Exercise ECG	NR
		Nielsen 2011[33] Retro cohort	CCTA	Exercise ECG	NR
Intermediate to high	Functional vs. functional	Hachamovitch 2012/Hlatky 2014[15, 19] Pro cohort	PET	SPECT	NR
	Anatomic vs. functional	Min 2012[31] RCT	CCTA	SPECT (exercise or pharm)	NR
	Functional vs. functional	Sabharwal 2007[35] RCT	SPECT	Exercise ECG	NR
Mixed population (risk NR or not stratified by risk)	Anatomic vs. usual care	Chang 2008[2] RCT	CCTA	Usual Care	• Clinical or laboratory evidence of contrast-induced nephropathy: 0% (0/133) vs. 0% (0/133) • Diffusing irritating skin rash after imaging, (resolved spontaneously): 1.5% (2/133) vs. NR
	Functional vs. functional	Sabharwal 2007[35] RCT	SPECT	Exercise ECG	NR

Pretest CAD risk	Type of test comparison	Author Study design	Intervention	Comparator	Adverse events/side effects/harms (intervention vs. comparator)
		Shreibati 2011[39] Retro Admin Database	SPECT	Exercise ECG	NR
		Sanfilippo 2005[36] RCT	Stress echo	Exercise ECG	NR
		Marwick 2003[27] Pro cohort	Stress echo	Exercise ECG	NR
		Shreibati 2011[39] Retro Admin Database	Stress Echo	Exercise ECG	NR
		Ferrera 1991[46**] Pro cohort	Stress echo (dipyridamole)	Exercise ECG	• Chest pain: 36.7% (40/109) vs. NR • Flushing: 22% (24/109) vs. NR • Headache: 30% (33/109) vs. NR • Dyspnea: 11% (13/109) vs. NR • Hypotension: 6.4% (7/109) vs. NR • Nausea: 5.5% (6/109) vs. NR • Dizziness: 4.5% (5/109) vs. NR • ST depression: 49.5% (54/109) vs. NR
		Severi 1994[47**] Pro cohort	Stress echo (dipyridamole)	Exercise ECG	• Major periprocedural side effects: 0% (0/429) vs. 0% (0/429) • Excessive tachycardia with palpitations: 0.2% (1/429) vs. NR • Hypotension and symptomatic bradycardia: 0.5% (2/429) vs. NR
		Dodi 2001[7**] Retro cohort	Stress echo (dipyradimole or dobutamine)	Exercise ECG	"No major complication as a result of either test" (details NR): 0% (0/244) vs. 0% (0/244)
		Takeuchi 1996[40] Retro cohort	Stress Echo (dobutamine)	SPECT	• No serious side effects vs. NR • Sustained arrhythmia: 0% (0/70) vs. NR • Severe hypotension: 0% (0/70) vs. NR • MI: 0% (0/70) vs. NR • Test terminated for severe chest pain: 11% (8/70) vs. NR • Extracardiac side effects (e.g., dyspnea and nausea): 5.7% (4/70) vs. NR • Increased BP: 2.9% (2/70) vs. NR • Multiple ventricular ectopy: 1.4% (1/70) vs. NR
		Shreibati 2011[39] Retro Admin Database	Stress Echo (exercise or pharmacologic)	SPECT	NR
	Anatomic vs. functional	McKavanagh 2014 RCT[29]	CCTA	Exercise ECG	"No complications after any investigation": 0% (0/243) vs. 0% (0/245)

Pretest CAD risk	Type of test comparison	Author Study design	Intervention	Comparator	Adverse events/side effects/harms (intervention vs. comparator)
		Shreibati 2011[39] Retro Admin Database	CCTA	Exercise ECG	NR
		Tandon 2012[41] Pro Registry	CCTA	SPECT	NR
		Min 2008[32] Retro Admin Database	CCTA	SPECT	NR
		Yamauchi 2012[43] Pro cohort	CCTA	MPI (Nuclear)	"adverse events during initial test" (details NR) ††: 0.5% (3/625) vs. 0.9% (11/1205)
		Shreibati 2011[39] Retro Admin Database	CCTA	MPI (Nuclear)	NR
		Shreibati 2011[39] Retro Admin Database	CCTA	Stress Echo	NR

CCTA = coronary computer tomography angiography; CI = confidence interval; ECG = electrocardiogram; ECHO = echocardiogram; ICA = invasive coronary angiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; NA = not applicable; NC = not calculable; NR = not reported; RCT = randomized controlled trial; PET = positron emission tomography; pro = prospective; retro = retrospective; RR = risk ratio; SPECT = single photon-emission computed tomography;

*One patient suffered from perioperative bleeding after cardiothoracic surgery for an identified anomalous coronary artery and the second had a transient increase in the creatinine level after CCTA w/o need for dialysis.

† RR and *p values calculated using Rothman Episheet.

‡total of 60% of patients received stress testing: 58% had stress test w/ imaging, 2% stress test w/o imaging.

§Incidental findings included (not reported by test group): pulmonary nodule ≥4 mm (n=5), hepatic cyst (n=3), liver hemangioma (n=2), fatty liver (n=2), mediastinal lymphadenopathy (n=2), pulmonary embolism (n=1), thoracic aortic aneurysm (n=1), esophageal thickening (n=1), and pleural thickening (n=1)

**All patients received both tests. Ferrera and Severi: tests performed-on different days and in random order-within 1 week of coronary angiography; Dodi: test performed in random order and on different days within 3 weeks of each other. All 3 studies included for safety only.

††Cases calculated from % given.

Table G4. Radiation exposure in included comparative studies

Tests	Author (year) Study design	Index Visit	Additional Testing
CCTA vs. Usual Care	Hoffman 2013[20] RCT	CCTA: 13.9 ± 10.4 Usual Care 4.7 ± 8.4 p<0.001	Cumulative radiation exposure, index visit plus followup (mSv) CCTA: 14.3 ± 10.9 Usual Care: 5.3 ± 9.6 p<0.001
	Litt 2012[26] RCT	Bradycardia (presumed to be related to the medication to control heart rate) CCTA: 0.1% (1/908) Usual Care: 0.2% (1/462)	NR
	Miller 2011[30] RCT	NR	NR
	Gruettner 2013/ Henzler 2013[17, 229] Cohort	Mean effective dose (mSv): CCTA: 8.7 Usual Care: NR	NR
CCTA vs. SPECT	Goldstein 2011[12] RCT (CT-STAT)	Median effective radiation dose at index visit (mSv) CCTA: 11.5 (6.8-16.8) SPECT: 12.8 (11.6-13.9 p=0.02	NR
	Goldstein 2007[13] RCT	Test complications CCTA: 0% (0/99) SPECT: 0% (0/99)	NR
	Min 2012[31] RCT	Estimated median (IQR) effective dose at index visit: CCTA: 6.5 mSv (5.1–13.3) SPECT: 13.3 mSv (13.1–38.0) p<0.0001	Cumulative radiation (estimated median (IQR) effective dose): CCTA: 7.3 mSv (5.1–13.7) SPECT: 13.3 mSv (13.1–38.0) p<0.0001
	Cheezum 2011[3]	Incidental findings requiring further investigation* CCTA: 7.1% (18/252) SPECT: 0% (0/241) P=0.0001 * included pulmonary nodule ≥4 mm (n=5), hepatic cyst (n=3), liver hemangioma (n=2), fatty liver (n=2), mediastinal lymphadenopathy (n=2), pulmonary embolism (n=1), thoracic aortic aneurysm (n=1), esophageal thickening (n=1), and pleural thickening (n=1)	NR
	Min 2008[32]	NR	NR

Tests	Author (year) Study design	Index Visit	Additional Testing
	Tandon 2012[41]	Radiation exposure (mSv, median (IQR)) CCTA: 14.9 (13.1, 17.1) SPECT: 10.5 (10.1, 11.4) p<0.001	Radiation exposure from ICA (mSv, median (IQR)) CCTA (n = 129): 15.2 (12.7, 17.1) SPECT (n = 125): 10.8 (10.2, 11.7) p<0.001
CCTA vs. MPI (nuclear)	Shreibati 2011[39]	NR	NR
	Yamauchi 2012[43]	"adverse events during initial test" (details NR) CCTA: 0.5% MPI: 0.9%	NR
CCTA vs. functional (various)	Douglas 2015[8]	A LOT	Cumulative radiation exposure
CCTA vs. Exercise ECG	Hamilton-Craig 2014[16] RCT	Mean radiation exposure CCTA: 3.8 mSv (95% CI: 3.5, 4.1) (range: 0.63–16.9) ECG: NA	NR
	McKavanagh 2014 RCT[29]	NR	NR
	Nielsen 2011[33] Retrospective cohort	NR	Cumulative radiation exposure by test results
	Shreibati 2011[39]	NR	NR
Stress Echocardiography vs. Exercise ECG	Sanfilippo 2005[36] RCT	NR	NR
	Ferrara 1991[46]	Dipyridamole stress echo: Chest pain 36.7% (40/109) Flushing 22% (24/109) Headache 30% (33/109) Dyspnea 11% (13/109) Hypotension 6.4% (7/109) Nausea 5.5% (6/109) Dizziness 4.5% (5/109) ST depression 49.5% (54/109) ECG: NR	NR
	Marwick 2003[27]	NR	NR
	Takeuchi 1996[40]	Dobutamine stress echo: No serious side effects defined as sustained arrhythmia, severe hypotension or MI Test terminated for severe chest pain: 11% (8/70) Extracardiac side effects: 5.7% (4/70) Increased BP: 2.9% (2/70) multiple ventricular ectopy: 1.4% (1/70) ECG: NR	NR

Tests	Author (year) Study design	Index Visit	Additional Testing
	Dodi 2001[7] Retrospective cohort	Dipyradimole or dobutamine stress echo NR "There was no major complication as a result of either test" (details NR)	NR
	Severi 1994[47] Prospective cohort	Dipyradimole stress echo "No major side effects from either test" Echo: excessive tachycardia with palpitations: 0.2% (1/429) hypotension and symptomatic bradycardia: 0.5% (2/429)	NR
	Shreibati 2011[39]	NR	NR
Stress Echocardiography vs. SPECT	Takeuchi 1996[40]	Dobutamine stress echo: No serious side effects defined as sustained arrhythmia, severe hypotension or MI Test terminated for severe chest pain: 11% (8/70) Extracardiac side effects: 5.7% (4/70) Increased BP: 2.9% (2/70) multiple ventricular ectopy: 1.4% (1/70) ECG: NR	NR
	Shreibati 2011[39]	NR	NR

BP = blood pressure; CCTA = coronary computer tomography angiography; CI = confidence interval; ECG = electrocardiogram; ECHO = echocardiogram; ICA = invasive coronary angiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; RCT = randomized controlled trial; SPECT = single photon-emission computed tomography;

Appendix H. Diagnostic Accuracy of Noninvasive Tests in Included Studies

Table H1. Diagnostic accuracy: Exercise ECG compared with coronary angiography as reference standard for diagnosis of CAD

Study (year)	Search dates	Number (type) of studies	Study Quality	Reference standard (threshold)	Population	History of CAD, MI, or revascularization	Diagnostic accuracy outcomes*	Risk of Bias
Dolor 2012[304]†	01/2000-09/2011	29†	Assessed with QUADAS; assigned summary score Good: 34% Fair: 52% Poor: 14%	Coronary angiography (≥ 50 - 75% stenosis)	• N = 3392 • % male: 0% • Age: NR • Condition: symptomatic for CAD • Subgroup: women	No known CAD	• Prevalence (mean): 41% (range, 18-67%) • Sensitivity: 62% (95% CI, 55-68%) • Specificity: 68% (95% CI, 63-73%) • PPV: 57% • NPV: 72% • LR+: 1.94 • LR-: 0.56 • DOR: NR	Low
		10†	Assessed with QUADAS; assigned summary score Good: 100%	Coronary angiography (≥ 50 - 75% stenosis)	• N = 1410 • % male: 0% • Age: NR • Condition: symptomatic for CAD • Subgroup: women	No known CAD	• Prevalence (mean): 38% (range, 18-67%) • Sensitivity: 70% (95% CI, 58-79%) • Specificity: 62% (95% CI, 53-69%) • PPV: 53% • NPV: 77% • LR+: 1.84 • LR-: 0.48 • DOR: NR	Low
Nielsen 2014[33]	01/2002-02/2013	7	Assessed with QUADAS-2 and Newcastle Ottawa Scale; assigned summary score. Fair to good (% NR)	Coronary angiography (≥ 50 stenosis)	• N = 911 • % male: 50-74% (range) • Age: 54-63 yrs. (range of means) • Condition: stable with suspected CAD	With or without known CAD (details NR)	• Prevalence: NR • Sensitivity: 67% (95% CI, 54-78%) • Specificity: 46% (95% CI, 30-64%) • PPV: 41% (95% CI, 30-55%) • NPV: 72% (95% CI, 54-84%) • LR+: NR • LR-: NR • DOR: 2 (95% CI, 1-4)	Low

CAD = coronary artery disease; CI = confidence interval; DOR = Diagnostic odds ratio; ECG = electrocardiogram; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; NR = not reported; PPV = positive predictive value; QUADAS = quality assessment of diagnostic accuracy studies.

*Results pooled unless otherwise indicated.

†For inclusion, data for women must have been presented separately from that of men. Results for men were reported but for mixed populations (i.e., with and without known CAD) only and thus were not included here.

Table H2. Diagnostic accuracy: Stress echocardiography compared with coronary angiography as reference standard for diagnosis of CAD

Study (year)	Search dates	Number of studies	Study Quality	Reference standard (threshold)	Population	History of CAD, MI, or revascularization	Diagnostic accuracy outcomes*	Risk of Bias
de Jong 2012[305]	01/2000-05/2011	10	Assessed with QUADAS. Number of items "yes": 13/16: 40% 12/16: 10% 11/16: 40% 10/16: 10%	Coronary angiography (≥ 50 - 75% stenosis)	• N = 795 • % male: 61-82% (range) • Age: 56-67 yrs. (range of means) • Condition: known or suspected CAD	Known (previously diagnosed) or suspected CAD	• Prevalence (mean): 66% • Sensitivity: 87% (95% CI, 81-91%) • Specificity: 72% (95% CI, 56-83%) • PPV: 85%§ • NPV: 73%§ • LR+: 3.08 (95% CI, 1.65-4.50) • LR-: 0.18 (95% CI, 0.13-0.24) • DOR: 16.94 (95% CI, 9.84-29.15)	Mod.
		1	Assessed with QUADAS. Number of items "yes": 11/16	Coronary angiography (≥ 50 stenosis)	• N = 50 • % male: 68% • Age: 67 yrs. (mean) • Condition: suspected CAD (and no history of MI, PCI or CABG)	Suspected CAD, without known CAD (no history of MI, PCI or CABG)	• Prevalence: 64% • Sensitivity: 88% (95% CI, 60-97%) • Specificity: 89% (95% CI, 58-98%) • PPV: 93%§ • NPV: 80%§ • LR+: 8.35 (95% CI, 6.67-21.76) • LR-: 0.13 (95% CI, -0.05-0.32) • DOR: 62.76 (95% CI, 7.37-534.54)	Mod.
Lapado 2013[306]	01/1990-11/2012	4	NR	Coronary angiography (≥ 50 - 75% stenosis)	• N = 5216 • % male: 46-100% (range) • Age: 53-62 yrs. (range of means) • Condition: stable with suspected CAD	With or without known CAD (Excluded studies with ≥ 15% history of MI or revascularization)	• Prevalence: 60-100%** • Prevalence, (estimated mean): 68%† • Sensitivity: 84% (95% CI, 80-89%) • Specificity: 77% (95% CI, 69-86%) • PPV: 89%§§ • NPV: 69%§§ • LR+: 3.65 (95% CI, 3.33-4.00§§ • LR-: 0.21 (95% CI, 0.19-0.23)§§	Mod.

CAD = coronary artery disease; CABG = coronary artery bypass graft; CI = confidence interval; DOR = Diagnostic odds ratio; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = quality assessment of diagnostic accuracy studies.
*Results pooled unless otherwise indicated.
§Calculated.
** A single study had 100%, but reported only on patients with abnormal exercise test result.
†Estimated from 2 studies (n = 4966); excluded one study with no reported prevalence (n = 50) and one study that only reported prevalence for patients with abnormal exercise test result (n = 200).
§§ Calculated based on estimated mean prevalence and reported sensitivity and specificity.

Table H3. Diagnostic accuracy: Single photon emission computed tomography compared with coronary angiography as reference standard for diagnosis of CAD

Study (year)	Search dates	Number of studies	Study Quality	Reference standard (threshold)	Population	History of CAD, MI, or revascularization	Diagnostic accuracy outcomes*	Risk of Bias
de Jong 2012[305]	01/2000-05/2011	13	Assessed with QUADAS. Number of items "yes": 13/16: 15.4% 12/16: 7.7% 11/16: 38.5% 10/16: 15.4% 9/16: 15.4% 8/16: 7.7%	Coronary angiography (> 50 to ≥ 75% stenosis)	• N = 1323 • % male: 0-95% (range) • Age: 51-67 yrs. (range of means) • Condition: known or suspected CAD	Known (previously diagnosed) or suspected CAD	• Prevalence (mean): 50% • Sensitivity: 83% (95% CI, 73-89%) • Specificity: 77% (95% CI, 64-86%) • PPV: 79%† • NPV: 79%† • LR+: 3.56 (95% CI, 2.07-5.04) • LR-: 0.22 (95% CI, 0.14-0.31) • DOR: 15.84 (95% CI, 9.74-25.77)	Mod.
		4	Assessed with QUADAS. Number of items "yes": 13/16: 25% 12/16: 25% 11/16: 50%	Coronary angiography (≥ 50 stenosis)	• N = 535 • % male: 54-68% (range) • Age: 57-67 yrs. (range of means) • Condition: suspected CAD (and no history of MI, PCI or CABG)	Suspected CAD, without known CAD (no history of MI, PCI or CABG)	• Prevalence: 41% • Sensitivity: 83% (95% CI, 70-91%) • Specificity: 79% (95% CI, 66-87%) • PPV: 72%† • NPV: 84%† • LR+: 3.88 (95% CI, 2.03-5.73) • LR-: 0.21 (95% CI, 0.09-0.34) • DOR: 18.15 (95% CI, 8.34-39.52)	Mod.
McArdle 2012[307]	01/2008-03/2012	8	Assessed with QUADAS. Unclear if ICA results blinded to SPECT results (75% of studies)	Coronary angiography (> 50 to > 70% stenosis)	• N = 1755 • % male: 55% • Age (mean): 61.1 yrs. (range: 59.1-63.2) • Condition: known or suspected CAD (previous MI: 3.4%; PCI/CABG: 3.2%)	Known or suspected CAD	• Prevalence: 50% • Sensitivity: 85% (95% CI, 82-87%) • Specificity: 85% (95% CI, 82-87%) • PPV: 85%† • NPV: 85%† • LR+: 5.13 (95% CI, 4.01-6.56) • LR-: 0.18 (95% CI, 0.15-0.21)§ • DOR: 28.29 (95% CI, 17.66-45.30)	Low

Study (year)	Search dates	Number of studies	Study Quality	Reference standard (threshold)	Population	History of CAD, MI, or revascularization	Diagnostic accuracy outcomes*	Risk of Bias
		NR	See above	NR	• N = 1320 • % male: NR • Age (mean): NR • Condition: No known CAD	Suspected CAD only (known CAD excluded)	• Prevalence: NR • Sensitivity: 84% (95% CI, 81-87%) • Specificity: 85% (95% CI, 82-88%) • PPV: 85%‡ • NPV: 84%‡ • LR+: 5.01 (95% CI, 3.36-7.47) • LR-: 0.19 (95% CI, 0.16-0.22)‡ • DOR: 23.83 (95% CI, 11.77-48.2)	Low

CAD = coronary artery disease; CABG = coronary artery bypass graft; CI = confidence interval; DOR = Diagnostic odds ratio; ECG = electrocardiogram; ICA = invasive coronary angiography; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = quality assessment of diagnostic accuracy studies; SPECT = single photon emission computerized tomography.
*Results pooled unless otherwise indicated.
†Calculated.
‡Calculated assuming prevalence of 50%.

Table H4. Diagnostic accuracy: Positron emission tomography compared with coronary angiography as reference standard for diagnosis of CAD

Study (year)	Search dates	Number of studies	Study Quality	Reference standard (threshold)	Population	History of CAD, MI, or revascularization	Diagnostic accuracy outcomes*	Risk of Bias
Jaarsma 2012[308]	01/1990-02/2010	8	Assessed for likelihood of verification bias. Yes: 12.5% Likely: 12.5% No: 75%	Coronary angiography (≥ 50 to ≥ 70% stenosis)	• N = 677 • % male: 49-86% (range) • Age: 56-67 yrs. (range of means) • Condition: known or suspected CAD	Known or suspected CAD	• Prevalence (mean): 80%† • Sensitivity: 82% (95% CI, 78-85%) • Specificity: 86% (95% CI, 78-92%) • PPV: 96%† • NPV: 53%† • LR+: 5.88 (95% CI, 3.72-9.28) † • LR-: 0.21 (95% CI, 0.17-0.26)† • DOR: 44.31 (95% CI, 23.93-82.06)	Mod.
		2	Assessed for likelihood of verification bias. No: 100%	Coronary angiography (≥ 50 stenosis)	• N = 290 • % male: 64% (reported for one study only) • Age: 57 yrs. (reported for one study only) • Condition: suspected CAD	Suspected CAD only	• Prevalence: 75%† • Sensitivity: 91% (95% CI, 86-95%)† • Specificity: 82% (95% CI, 71-90%)† • PPV: 94%† • NPV: 75%† • LR+: 4.97 (95% CI, 3.04-8.14)† • LR-: 0.11 (95% CI, 0.07-0.17)†	Mod.
McArdle 2012[307]	01/2008-03/2012	15	Assessed with QUADAS. Unclear if ICA results blinded to PET results in 27% of studies	Coronary angiography (> 50 to > 70% stenosis)	• N = 1344 • % male: 63.5% • Age (mean): 61.2 yrs. (range: 59.0-64.4) • Condition: known or suspected CAD (previous MI: 30%; PCI/CABG: 32%)	Known or suspected CAD	• Prevalence: 63% • Sensitivity: 90% (95% CI, 88-92%) • Specificity: 88% (95% CI, 85-91%) • PPV: 93%† • NPV: 84%† • LR+: 5.57 (95% CI, 4.02-7.72) • LR-: 0.11 (95% CI, 0.09-0.14)† • DOR: 56.73 (95% CI, 37.99-84.71)	Low

Study (year)	Search dates	Number of studies	Study Quality	Reference standard (threshold)	Population	History of CAD, MI, or revascularization	Diagnostic accuracy outcomes*	Risk of Bias
		NR	See above	NR	• N = 297 • % male: NR • Age (mean): NR • Condition: No known CAD	Suspected CAD only (known CAD excluded)	• Prevalence: NR • Sensitivity: 90% (95% CI, 84-94%) • Specificity: 91% (95% CI, 84-95%) • PPV: 94%‡ • NPV: 84%‡ • LR+: 8.89 (95% CI, 2.46-32.09) • LR-: 0.11 (95% CI, 0.07-0.17)‡ • DOR: 92.05 (95% CI, 18.54-456.98)	

CAD = coronary artery disease; CABG = coronary artery bypass graft; CI = confidence interval; DOR = Diagnostic odds ratio; ECG = electrocardiogram; ICA = invasive coronary angiography; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; PET = positron emission tomography; PPV = positive predictive value; QUADAS = quality assessment of diagnostic accuracy studies.
*Results pooled unless otherwise indicated.
†Calculated.
‡Calculated assuming prevalence of 63%.

Table H5. Diagnostic accuracy: Stress cardiac magnetic resonance imagining compared with coronary angiography as reference standard for diagnosis of CAD

Study (year)	Search dates	Number of studies	Study Quality	Reference standard (threshold)	Population	History of CAD, MI, or revascularization	Diagnostic accuracy outcomes*	Risk of Bias
Nandalur 2007[309]	01/1990-01/2007	13	Assessed with QUADAS. Number of items "yes": 10/10: 15.4% 9/10: 7.7% 8/10: 30.8% 7/10: 38.5% 6/10: 7.7%	Coronary angiography (≥ 50 - 75% stenosis)	• N = 735 • % male: 56-96% (range) • Age: 52-63 yrs. (range of means) • Condition: known or suspected CAD	Known or suspected CAD	• Prevalence (mean): 70.5% • Sensitivity: 83% (95% CI, 79-88%) • Specificity: 86% (95% CI, 81-91%) • PPV: 94%† • NPV: 68%† • LR+: 5.93 (95% CI, 4.25-8.26)† • LR-: 0.20 (95% CI, 0.16-0.24)†	Mod.
		8	Assessed with QUADAS. Number of items "yes": 10/10: 12.5% 9/10: 12.5% 8/10: 12.5% 7/10: 50% 6/10: 12.5%	Coronary angiography (≥ 50 - 75% stenosis)	• N = 520 • % male: 71-88% (range) • Age: 52-62 yrs. (range of means) • Condition: suspected CAD	Suspected CAD only	• Prevalence: 67%§ • Sensitivity: 81% (95% CI, 77-85%)† • Specificity: 87% (95% CI, 81-92%)† • PPV: 93%† • NPV: 70%† • LR+: 6.39 (95% CI, 4.31-9.47)† • LR-: 0.21 (95% CI, 0.17-0.27)†	Mod.

CAD = coronary artery disease; CI = confidence interval; DOR = Diagnostic odds ratio; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; MRI = magnetic resonance imaging; NR = not reported; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = quality assessment of diagnostic accuracy studies;
*Results pooled unless otherwise indicated.
†Calculated.

Table H6. Diagnostic accuracy: Coronary artery calcification (CAC score >0) compared with coronary angiography as reference standard for diagnosis of CAD

Study (year)	Search dates	Number of studies	Study Quality	Reference standard (threshold)	Population	History of CAD, MI, or revascularization	Diagnostic accuracy outcomes*	Risk of Bias
Skelly, 2009[310]	Through 07/2009	7	Good to Moderate (LoE I/II)†	NR	• N = 7354 • % male: 60-80% (range) • Age: 56-62 yrs. (range of means) • Condition: Symptomatic and suspected CAD	Symptomatic with suspected CAD and no history of revascularization (PCI or CABG)	• Prevalence (mean): 55.4% • Sensitivity: 99% (95% CI, 98-99%) • Specificity: 35% (95% CI, 33-36%) • PPV: 65%‡ • NPV: 95%‡ • LR+: 1.51 (95% CI, 1.47-1.54)‡ • LR-: 0.04 (95% CI, 0.03-0.06)‡	Mod.
Sarwar, 2009[311]	01/1990-03/2008	18	Formal quality assessment not reported; in all studies CT readers blinded to ICA results	Coronary angiography (> 50% stenosis)	• N = 10, 355 • % male: NR for diagnostic accuracy studies • Age: NR for diagnostic accuracy studies • Condition: Symptomatic and suspected CAD	Symptomatic with suspected CAD	• Prevalence (mean): 56% • Sensitivity: 98% • Specificity: 40% • PPV: 68% • NPV: 93%	Mod.

CABG = coronary artery bypass graft; CAC = coronary artery calcification; CAD = coronary artery disease; CI = confidence interval; DOR = Diagnostic odds ratio; ICA = invasive coronary angiography; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; MRI = magnetic resonance imaging; NR = not reported; PCI = percutaneous coronary intervention; PPV = positive predictive value.
*Results pooled unless otherwise indicated.
† LoE stands for level of evidence; studies rated as LoE I or II were at least risk of bias (broad spectrum of relevant patient populuation, blinded interpretation of test and referent, adequate description of test and referent).
‡Calculated.

Table H7. Diagnostic accuracy: Coronary computed tomography angiography compared with coronary angiography as reference standard for diagnosis of CAD

Study (year)	Search dates	Number of studies	Study Quality	Reference standard (threshold)	Population	History of CAD, MI, or revascularization	Diagnostic accuracy outcomes*	Risk of Bias
von Ballmoos, 2011[312]	Through 10/2010	13 (Review was of 16 studies, 13 of which assessed at patient level)	Assessed with QUADAS; not reported by study. Of 16 studies (including 3 additional that assessed at vessel level), 8 of 12 QUADAS criteria were met by 75% or more of the studies. In all studies, readers of CT were blinded to ICA results, and vice versa.	Coronary angiography (> 50% stenosis)	• N = 789 • % male: NR • Age: 63 yrs. (mean of 16 studies) • Condition: Symptomatic and suspected CAD	Symptomatic with suspected CAD	• Prevalence (mean): 58%† • Sensitivity: 100% (95% CI, 98-100%) • Specificity: 89% (95% CI, 85-92%) • PPV: 93%† • NPV: 99%† • LR+: 9.2 (95% CI, 6.7-12.5) • LR-: 0.00 (95% CI, 0.00-0.02)	Low

CABG = coronary artery bypass graft; CAD = coronary artery disease; CCTA = coronary computer tomography angiography; CI = confidence interval; DOR = Diagnostic odds ratio; ICA = invasive coronary angiography; LR (+) = positive likelihood ratio; LR (-) = negative likelihood ratio; NPV = negative predictive value; MI = myocardial infarction; MRI = magnetic resonance imaging; NR = not reported; PCI = percutaneous coronary intervention; PPV = positive predictive value; QUADAS = quality assessment of diagnostic accuracy studies.
*Results pooled unless otherwise indicated.
†Calculated.

Appendix I. Quality Ratings for Included Studies

Quality Ratings

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

Fair-quality studies may not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating will vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid. Fair-quality studies are susceptible to some bias, though not enough to invalidate the results.

Poor-quality studies have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies are at least as likely to reflect flaws in the study design as the true difference between the compared interventions. Poor quality studies have significant flaws that imply biases of various types that may invalidate the results.

Table I1. Individual study quality ratings in patients with mixed pretest risk for CAD

Methodological Principle		Chang 2008[2]*	Sabharwal 2007[35]*	Sanfilippo 2005[36]	Marwick 2003[27]	Shreibati 2011 (Stress Echo vs. Ex ECG)[39]	Shreibati 2011 (Stress Echo vs. Ex ECG)[39]	Shreibati 2011 (Stress Echo vs. MPI)[39]	Shreibati 2011 (MPI vs. Ex ECG)[39]
Study design	Randomized controlled trial		✓	✓					
	Prospective cohort study				✓				
	Retrospective cohort study								
	Administrative database study					✓	✓	✓	✓
	Registry study								
	Case-control								
	Case-series								
Random sequence generation†			Yes	Unclear	NA	NA	NA	NA	NA
Statement of Concealed allocation†			No	Unclear	NA	NA	NA	NA	NA
Analysis according to random assignment†			Yes	No	NA	NA	NA	NA	NA
Independent or blinded			Unclear	Yes	Unclear		Clinical outcomes:	Clinical outcomes:	Unclear

outcome assessment							Unclear Management: NA	Unclear Management: NA	
Patients comparable at baseline on key CAD risk factors			Yes	No	No		Yes	No	No
Prespecified threshold or definition for a positive test			Yes	Yes	Yes		No	No	No
Attrition (≤ 20% overall; ≤ 10% difference between groups)			Unclear	Yes	Unclear		Yes	Yes	Yes
Comparable followup time or accounting for time at risk			Yes	Yes	No		Yes	Yes	Yes
Controlling for possible confounding‡			Yes	No	Yes		Yes	Yes	Yes
Full reporting on pre-specified outcomes			Yes	Yes	Yes		Yes	Yes	Yes
Overall Quality Rating			Fair	Poor	Poor		Fair	Fair	Fair

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

Table I1. continued

Methodological Principle		McKavanaugh 2014[29]	Tandon 2012[41]	Min 2008[32]	Yamauchi 2012[43]	Shreibati 2011 (CCTA vs. Ex ECG)[39]	Shreibati 2011 (CCTA vs. MPI)[39]	Shreibati 2011 (CCTA vs. Stress echo)[39]
Study design	Randomized controlled trial	✓						
	Prospective cohort study				✓			
	Retrospective cohort study							
	Administrative database study			✓		✓	✓	✓
	Registry study		✓					
	Case-control							
	Case-series							
Random sequence generation*		Yes	NA	NA	NA	NA	NA	NA
Statement of Concealed allocation*		No	NA	NA	NA	NA	NA	NA
Analysis according to random assignment*		Yes	NA	NA	NA	NA	NA	NA
Independent or blinded outcome assessment		Unclear	Unclear	Unclear	Unclear		Clinical outcomes: Unclear Management: NA	
Patients comparable at baseline on key CAD risk factors		Yes	No	Yes	No		No	
Prespecified threshold or definition for a positive test		Yes	Yes	No	No		No	
Attrition (≤ 20% overall; ≤ 10% difference between groups)		Yes	Unclear	Unclear	Yes		Yes	
Comparable followup time or accounting for time at risk		Yes	Yes	Yes	Yes		Yes	
Controlling for possible confounding†		Yes	No	Yes	Yes		Yes	
Full reporting on pre-specified outcomes		Yes	Yes	Yes	Yes		Yes	
Overall Quality Rating		Fair	Poor	Fair	Fair		Fair	

CAD = coronary artery disease; NA = not applicable.
*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods)
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Table I2. Individual study quality ratings in patients considered to have intermediate-to-high pretest risk for CAD.

Methodological Principle		Hachamovitch 2012/ Hlatky 2014[15, 19]	Min 2012[31]
Study design	Randomized controlled trial		✓
	Prospective cohort study		
	Retrospective cohort study		
	Administrative database study		
	Registry study	✓ (prospective)	
	Case-control		
	Case-series		
Random sequence generation*		NA	Unclear
Statement of Concealed allocation*		NA	Unclear
Analysis according to random assignment*		NA	Yes
Independent or blinded outcome assessment		Unclear	No
Patients comparable at baseline on key CAD risk factors		No	No
Prespecified threshold or definition for a positive test		Yes	Yes
Attrition (≤ 20% overall; ≤ 10% difference between groups)		Yes	Yes
Comparable followup time or accounting for time at risk		Yes	Unclear
Controlling for possible confounding†		Yes	Yes
Full reporting on pre-specified outcomes		Yes	Yes
Overall Quality Rating		Fair	Poor

CAD = coronary artery disease; NA = not applicable.
*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods)
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Table I3. Individual study quality ratings in patients considered to have low-to-intermediate pretest risk for CAD.

Methodological Principle		Litt 2012[26]	Miller 2011[30]	Goldstein 2011[12]	Goldstein 2007[13]	Cheezum 2011[3]	Hamilton-Craig 2014[16]	Neilsen 2011[33]
Study design	Randomized controlled trial			✓	✓		✓	
	Prospective cohort study							✓
	Retrospective cohort study					✓		
	Administrative database study							
	Registry study							
	Case-control							
	Case-series							
Random sequence generation*				Yes	Yes	NA	Unclear	NA
Statement of Concealed allocation*				Yes	Unclear	NA	No	NA
Analysis according to random assignment*				Yes	Unclear	NA	Yes	NA
Independent or blinded outcome assessment				Yes	No	Unclear	Unclear	Unclear
Patients comparable at baseline on key CAD risk factors				Yes	No	Yes	Yes	Yes
Prespecified threshold or definition for a positive test				Yes	Yes	Yes	Yes	Yes
Attrition (≤ 20% overall; ≤ 10% difference between groups)				Yes	Yes	Yes	Overall, Yes Differential, Unclear	Yes
Comparable followup time or accounting for time at risk				Yes	Yes	Yes	Yes	Unclear
Controlling for possible confounding†				Yes	No	Yes	Yes	No
Full reporting on pre-specified outcomes				Yes	Yes	Yes	Yes	Unclear
Overall Quality Rating				Good	Fair	Fair	Fair	Fair

CAD = coronary artery disease; NA = not applicable.
*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods)
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Table I4. Individual study quality ratings in patients considered to have intermediate pretest risk for CAD

	Methodological Principle	Hoffman 2012[20]	Gruettner/Henzler 2013[17, 229]	Shaw 2011[38]	Douglas 2015[8]
Study design	Randomized controlled trial			✓	✓
	Prospective cohort study				
	Retrospective cohort study				
	Administrative database study				
	Registry study				
	Case-control				
	Case-series				
Random sequence generation*				Yes	Yes
Statement of concealed allocation*				No	Yes
Analysis according to random assignment*				Yes	Yes
Independent or blinded outcome assessment				Yes	Yes
Patients comparable at baseline on key CAD risk factors				Yes	Yes
Prespecified threshold or definition for a positive test				Yes	Yes
Attrition (≤ 20% overall; ≤ 10% difference between groups)				Yes	Yes
Comparable followup time or accounting for time at risk				Yes	Yes
Controlling for possible confounding†				Yes	Yes
Full reporting on pre-specified outcomes				Yes	Yes
				Fair	Good

CAD = coronary artery disease; NA = not applicable.
*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods)
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Appendix J. Strength of Evidence Tables

Strength of Evidence Grades:

"High" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect;

"Moderate" grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate;

"Low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate;

"Insufficient" grade indicates evidence either is unavailable or is too limited to permit any conclusion, due to the availability of only poor-quality studies, extreme inconsistency, or extreme imprecision.

Table J1. Strength of evidence for included studies with patients considered to be at low risk for coronary artery disease

Outcomes	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause)	CCTA vs. Usual Care (ED setting)	1 RCT (n=99 in low-risk subgroup)	medium	direct	unknown	Imprecise (downgraded by 2; subanalysis)	undetected	Insufficient
Invasive Coronary Angiography Referral	CCTA vs. Usual Care (ED setting)	1 RCT (n=99 in low-risk subgroup)	medium	direct	unknown	Imprecise (downgraded by 2; subanalysis)	undetected	Insufficient
	SPECT vs. Exercise ECG	1 RCT (n=68 in low risk subgroup)	medium	direct	unknown	Imprecise (downgraded by 2; subanalysis)	undetected	Insufficient
Revascularization	CCTA vs. Usual Care (ED setting)	1 RCT (n=99 in low-risk subgroup)	medium	direct	unknown	Imprecise (downgraded by 2; subanalysis)	undetected	Insufficient
Additional Testing	SPECT vs. Exercise ECG	1 RCT (n=68 in low risk subgroup)	medium	direct	unknown	Imprecise (downgraded by 2; subanalysis)	undetected	Insufficient
Hospitalization (Cardiac related)	CCTA vs. Usual Care (ED Index visit)	1 RCT (n=99 in low-risk subgroup)	medium	direct	unknown	Imprecise (downgraded by 2; subanalysis)	undetected	Insufficient

CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; ED = emergency department; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography.

Table J2. Strength of evidence for included studies with patients considered to be at low-to-intermediate risk for coronary artery disease

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause)	CCTA vs. Usual Care (ED setting)	1 RCT (N=1392)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. SPECT (ED setting for RCTs	2 RCTS (N=952)	low	direct	consistent	imprecise	undetected	Moderate
	CCTA vs. SPECT (inpatient or outpatient for observational study)	1 Observational (N=252)	low	direct	consistent	imprecise	undetected	Insufficient
	CCTA vs. Exercise ECG (ED)	1 RCT (N=562)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Exercise ECG	1 Observational (N=468)	medium	direct	unknown	imprecise	undetected	Insufficient
Myocardial Infarction	CCTA vs. Usual Care (ED setting)	1 RCT (N=1392)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. SPECT (ED setting)	2 RCTS (N=952)	low	direct	consistent	imprecise	undetected	Low
	CCTA vs. Exercise ECG (ED)	1 RCT (N=562)	medium	direct	consistent	imprecise	undetected	Low
	CCTA vs. Exercise ECG	1 Observational (N=468)	medium	direct	consistent	imprecise	undetected	Insufficient
Invasive Coronary Angiography Referral	CCTA vs. Usual Care (ED setting)	1 RCT (N=1392)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Usual Care (ED setting)	2 RCTs (N=1452)	medium	direct	consistent	imprecise	undetected	Low
	CCTA vs. SPECT (ED setting for RCTs)	2 RCTS (N=952)	low	direct	inconsistent	imprecise	undetected	Low
	CCTA vs. SPECT inpatient or outpatient for observational study	1 Observational (N=252)	medium	direct	unknown	imprecise	undetected	Insufficient
	CCTA vs. Exercise ECG	1 RCT (N=562)	medium	direct	unknown	imprecise	undetected	Low

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	CCTA vs. Exercise ECG	1 Observational (n=468)	medium	direct	unknown	imprecise	undetected	Insufficient
Revascularization	CCTA vs. Usual Care (ED setting)	1 RCT (N=1392)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Usual Care (ED setting)	2 RCTs (N=1452)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. SPECT (ED setting)	2 RCTS (N=952)	low	direct	consistent	imprecise	undetected	Moderate
	CCTA vs. Exercise ECG	1 RCT (N=562)	medium	direct	consistent	precise	undetected	Low
	CCTA vs. Exercise ECG	1 Observational (n=96 subset of test-positive patients)	medium	direct	consistent	precise	undetected	Insufficient
Percutaneous Coronary Intervention	CCTA vs. Usual Care (ED setting)	1 RCT (N=60)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. SPECT (ED setting)	2 RCTS (N=952)	low	direct	consistent	imprecise	undetected	Moderate
	CCTA vs. Exercise ECG	1 Observational (n=96 subset of test-positive patients)	medium	direct	unknown	precise	undetected	Insufficient
Coronary Artery Bypass Graft	CCTA vs. Usual Care (ED setting)	1 RCT (N=60)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. SPECT (ED setting)	2 RCTS (N=952)	low	direct	consistent	imprecise	undetected	Moderate
	CCTA vs. Exercise ECG	1 Observational (n=96 subset of test-positive patients)	medium	direct	unknown	imprecise	undetected	Insufficient
Additional Testing	CCTA vs. Usual Care (ED setting)	1 RCT (N=1392)	medium	direct	unknown	precise	undetected	Moderate
	CCTA vs. Usual Care (ED setting)	1 RCT (N=1392)	medium	direct	unknown	precise	undetected	Moderate
	CCTA vs. Usual Care (ED setting)	1 RCT (N=60)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. SPECT (ED setting for RCTs	2 RCTS (N=952)	low	direct	consistent	precise	undetected	High

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	CCTA vs. SPECT (ED setting for RCTs	1 RCT (N=197)	medium	direct	consistent	imprecise	undetected	Low
	CCTA vs. SPECT (inpatient or outpatient for observational study)	1 Observational (N=252)	medium	direct	consistent	imprecise	undetected	Insufficient
	CCTA vs. Exercise ECG	1 Observational (n=468)	medium	direct	unknown	precise	undetected	Insufficient
Hospitalization (Cardiac related)	CCTA vs. Usual Care (ED setting)	1 RCT (N=1392)	medium	direct	unknown	precise	undetected	Moderate
	CCTA vs. Usual Care (ED setting)	1 RCT (N=1392)	medium	direct	unknown	precise	undetected	Moderate
	CCTA vs. SPECT (ED setting for RCT)	1 RCT (N=749)	low	direct	unknown	imprecise	undetected	Moderate
	CCTA vs. SPECT (inpatient or outpatient for observational study)	1 Observational (N=252)	medium	direct	unknown	imprecise	undetected	Insufficient
Harms	CCTA vs. Usual Care (ED setting)	1 RCT (N=1392)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. SPECT (inpatient or outpatient for observational study)	1 Observational (N=252)	medium	direct	unknown	imprecise	undetected	Insufficient

CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; ED = emergency department; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography.

Table J3. Strength of evidence for included studies with patients considered to be at intermediate risk for coronary artery disease.

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause)	CCTA vs. Usual Care (ED setting)	2 RCTs (N=1098*)	medium	direct	consistent	imprecise	undetected	Low
	CCTA vs. Usual Care (ED setting)	1 Observational (N=200)	low	direct	unknown	imprecise	undetected	Insufficient
	SPECT vs. Exercise ECG	1 RCT (N=824 women)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Functional	1 RCT (N=10,003)	low	direct	unknown	imprecise	undetected	Moderate
Myocardial Infarction	CCTA vs. Usual Care (ED setting)	2 RCTs (N=1098*)	medium	direct	consistent	imprecise	undetected	Low
	CCTA vs. Usual Care (ED setting)	1 Observational (N=200)	low	direct	consistent	imprecise	undetected	Insufficient
	CCTA vs. Functional	1 RCT (N=10,003)	low	direct	unknown	imprecise	undetected	Moderate
Heart Failure	CCTA vs. Usual Care (ED setting)	1 Observational (N=200)	low	direct	consistent	imprecise	undetected	Insufficient
Invasive Coronary Angiography Referral	CCTA vs. Usual Care (ED setting)	2 RCTs (N=1098*)	medium	direct	consistent	imprecise	undetected	Low
	CCTA vs. Usual Care (ED setting)	1 RCT (N=987)	medium	direct	consistent	imprecise	undetected	Low
	SPECT vs. Exercise ECG (women)	1 RCT (N=824 women)	medium	direct	unknown	imprecise	undetected	Low
	SPECT vs. Exercise ECG	1 RCT (n=280 in intermediate risk subgroup)	medium	direct	unknown	Imprecise	undetected	Low
	CCTA vs. Functional	1 RCT (N=10,003)	low	direct	unknown	precise	undetected	High
Revascularization	CCTA vs. Usual Care (ED setting)	2 RCTs (N=1098*)	medium	direct	consistent	imprecise	undetected	Low
	SPECT vs. Exercise ECG	1 RCT (N=824 women)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Functional	1 RCT (N=10,003)	low	direct	unknown	precise	undetected	High
Percutaneous Coronary Intervention	CCTA vs. Usual Care (ED setting)	1 RCT (N=987)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Usual Care (ED setting)	1 Observational (N=200)	low	direct	unknown	imprecise	undetected	Insufficient
	CCTA vs. Functional	1 RCT (N=10,003)	low	direct	unknown	precise	undetected	High

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Coronary Artery Bypass Graft	CCTA vs. Usual Care (ED setting)	1 RCT (N=987)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Usual Care (ED setting)	1 Observational (N=200)	low	direct	unknown	imprecise	undetected	Insufficient
	CCTA vs. Functional	1 RCT (N=10,003)	low	direct	unknown	precise	undetected	High
Additional Testing	CCTA vs. Usual Care (ED setting)	1 RCT (N=987)	medium	direct	unknown	imprecise	undetected	Low
	SPECT vs. Exercise ECG	1 RCT (N=824 women)	medium	direct	unknown	precise	undetected	Moderate
	SPECT vs. Exercise ECG	1 RCT (n=280 in intermediate risk subgroup)	medium	direct	unknown	Imprecise (subgroup)	undetected	Low
Hospitalization (Cardiac related)	CCTA vs. Usual Care (ED setting)	2 RCTs (N=1098*)	medium	direct	inconsistent	precise	undetected	Low
	CCTA vs. Usual Care (ED setting)	1 Observational (N=200)	low	direct	unknown	imprecise	undetected	insufficient
	SPECT vs. Exercise ECG	1 RCTs (N=824 women)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Functional	1 RCT (N=10,003)	low	direct	unknown	imprecise	undetected	Moderate
Harms	CCTA vs. Functional	1 RCT (N=10,003)	low	direct	unknown	imprecise	undetected	Moderate

CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; ECHO = echocardiogram; ED = emergency department; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography.

*Number of patients includes the 987 patients in the Hoffman trial and the subset of 111 patients who were at intermediate pre-test risk in the Chang trial.

Table J4. Strength of evidence for included studies with patients considered to be at intermediate-to-high risk for coronary artery disease

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause)	PET vs. SPECT	1 Observational (N=1113)	medium	direct	unknown	imprecise	undetected	Insufficient
	CCTA vs. SPECT	1 RCT (N=180)	medium	direct	unknown	Imprecise (downgrade 2)	undetected	Insufficient
Myocardial Infarction	PET vs. SPECT	1 Observational (N=1113)	medium	indirect	unknown	imprecise	undetected	Insufficient
	CCTA vs. SPECT	1 RCT (N=180)	medium	direct	unknown	Imprecise (downgrade 2)	undetected	Insufficient
Invasive Coronary Angiography Referral	PET vs. SPECT	1 Observational (N=1113)	medium	direct	unknown	precise	undetected	Insufficient
	CCTA vs. SPECT	1 RCT (N=180)	medium	direct	unknown	imprecise	undetected	Low
Revascularization	PET vs. SPECT	1 Observational (N=1113)	medium	direct	unknown	precise	undetected	Insufficient
	CCTA vs. SPECT	1 RCT (N=180)	medium	direct	unknown	imprecise	undetected	Low
Percutaneous Coronary Intervention	PET vs. SPECT	1 Observational (N=1113)	medium	direct	unknown	precise	undetected	Insufficient
Coronary Artery Bypass Graft	PET vs. SPECT	1 Observational (N=1113)	medium	direct	unknown	imprecise	undetected	Insufficient
Additional Testing	CCTA vs. SPECT	1 RCT (N=180)	medium	direct	unknown	imprecise	undetected	Low
Hospitalization (Cardiac related)	CCTA vs. SPECT	1 RCT (N=180)	medium	direct	unknown	imprecise	undetected	Low

CCTA = coronary computed tomography angiogram; PET = positron emission tomography; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography.

Table J5. Strength of evidence for included studies with patients considered to be at high risk for coronary artery disease

Outcomes	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause)	CCTA vs. Usual Care (ED setting)	1 RCT (n=56 in high-risk subgroup)	medium	direct	unknown	imprecise (downgraded by 2; subanalysis)	undetected	Low
Invasive Coronary Angiography Referral	CCTA vs. Usual Care (ED setting)	1 RCT (n=56 in high-risk subgroup)	medium	direct	unknown	imprecise (downgraded by 2; subanalysis)	undetected	Low
	SPECT vs. Exercise ECG	1 RCT (n=106 in high-risk subgroup)	medium	direct	unknown	imprecise (downgraded by 2; subanalysis)	undetected	Low
Revascularization	CCTA vs. Usual Care (ED setting)	1 RCT (n=56 in high-risk subgroup)	medium	direct	unknown	imprecise (downgraded by 2; subanalysis)	undetected	Low
Additional Testing	SPECT vs. Exercise ECG	1 RCT (n=106 in high-risk subgroup)	medium	direct	unknown	imprecise (downgraded by 2; subanalysis)	undetected	Low
Hospitalization (Cardiac related)	CCTA vs. Usual Care (ED Index visit)	1 RCT (n=56 in high-risk subgroup)	medium	direct	unknown	imprecise (downgraded by 2; subanalysis)	undetected	Low

CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; ED = emergency department; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography.

Table J6. Strength of evidence for comparative studies with patients of mixed risk

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause)	SPECT vs. Exercise ECG	1 RCT (N=457)	medium	direct	unknown	imprecise	undetected	Low
	Nuclear MPI vs. Exercise ECG (Medicare Population)	1 Observational (N=193,406)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. Stress ECG	1 Observational (n=5894 with no known CAD)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. Exercise ECG (Medicare Population)	1 Observational (N=141,667)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. MPI (Medicare Population)	1 Observational (N=212,947)	low	direct	unknown	precise	undetected	Low
	Excerice ECG vs. MPI (Medicare Population)	1 Observational (N=193,406)	low	direct	unknown	precise	undetected	Low
	CCTA vs. Exercise ECG	1 RCT (N=500)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Exercise ECG (Medicare Population)	1 Observational (N=69,883)	medium	direct	unknown	precise	undetected	Insufficient
	CCTA vs. MPI (nuclear) (Medicare Population)	1 Observational (N=141,163)	low	direct	unknown	precise	undetected	Low
	CCTA vs. Stress Echo (Medicare Population)	1 Observational (N=89,424)	medium	direct	unknown	precise	undetected	Insufficient
Myocardial Infarction	CCTA vs. Usual Care	1 RCT (N=266)	medium	direct	unknown	imprecise	undetected	Low
	SPECT vs. Exercise ECG	1 RCT (N=457)	medium	direct	unknown	imprecise	undetected	Low
	Nuclear MPI vs. Exercise ECG (Medicare Population)	1 Observational (N=141,163)	low	direct	unknown	precise	undetected	Low
	Stress Echo vs. Exercise ECG	1 Observational (N=141,163)	low	direct	unknown	precise	undetected	Low
	Stress Echo vs. MPI	1 Observational (N=141,163)	low	direct	unknown	precise	undetected	Low
	CCTA vs. Exercise ECG	1 RCT (N=500)	medium	direct	inconsistent	imprecise	undetected	Low
	CCTA vs. Exercise ECG	1 Observational (N=141,163)	low	direct	unknown	precise	undetected	Low
	CCTA vs. SPECT	1 Observational (N=9690)	medium	direct	unknown	imprecise	undetected	Insufficient
	CCTA vs. MPI (nuclear)	1 Observational	low	direct	unknown	precise	undetected	Low

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
		(N=141,163)						
	CCTA vs. Stress Echo	1 Observational (N=141,163)	low	direct	unknown	precise	undetected	Low
Composite measures	Stress Echo vs. Stress ECG (WOMEN)	1 RCT (N=158)	high	direct	unknown	imprecise	undetected	Low
	Stress Echo vs. Stress ECG	1 Observational (n=5894 with no known CAD)	medium	direct	unknown	precise	undetected	Low
Invasive Coronary Angioplasty Referral	Nuclear MPI vs. Exercise ECG	1 Observational (N=193,406)	low	direct	unknown	precise	undetected	Low
	Stress Echo vs. Exercise ECG	1 Observational (N=5894)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. Exercise ECG (Medicare Population)	1 Observational (N=141,667)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. MPI (Medicare Population)	1 Observational (N=212,947)	low	direct	unknown	precise	undetected	Low
	CCTA vs. Exercise ECG	1 RCT (N=500)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Exercise ECG (Medicare Population)	1 Observational (N=69,883)	medium	direct	unknown	precise	undetected	Insufficient
	CCTA vs. SPECT	2 observational (N=12,132)	medium	direct	inconsistent	precise	undetected	Insufficient
	CCTA vs. MPI (nuclear)	1 Observational (N=1856)	low	direct	unknown	precise	undetected	Insufficient
	CCTA vs. MPI (nuclear) (Medicare Population)	1 Observational (N=141,163)	low	direct	unknown	precise	undetected	Low
	CCTA vs. Stress Echo	1 Observational (N=89,424)	medium	direct	unknown	precise	undetected	Insufficient
Revascularization	SPECT vs. Exercise ECG	1 RCT (N=457)	medium	direct	unknown	imprecise	undetected	Low
	Nuclear MPI vs. Exercise ECG	1 Observational (N=193,406)	low	direct	unknown	precise	suspected	Low
	Stress Echo vs. Exercise ECG	1 Observational (N=5894)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. Exercise ECG (Medicare Population)	1 Observational (N=141,667)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. MPI (Medicare Population)	1 Observational (N=212,947)	low	direct	unknown	precise	suspected	Low

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	CCTA vs. Exercise ECG	1 RCT (N=500)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Exercise ECG (Medicare Population)	1 Observational (N=69,883)	medium	direct	unknown	precise	undetected	Insufficient
	CCTA vs. SPECT	2 observational (N=12,132)	medium	direct	consistent	precise	undetected	Insufficient
	CCTA vs. MPI (nuclear)	1 observational (N=1856)	low	direct	consistent	precise	undetected	Low
	CCTA vs. MPI (nuclear) (Medicare Population)	1 observational (N=141,163)	low	direct	consistent	precise	undetected	Low
	CCTA vs. Stress Echo	1 Observational (N=89,424))	medium	direct	unknown	precise	undetected	Insufficient
Percutaneous Coronary Intervention	Nuclear MPI vs. Exercise ECG	1 Observational (N=193,406)	low	direct	unknown	precise	undetected	Low
	Stress Echo vs. Exercise ECG	1 Observational (N=5894)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. Exercise ECG	1 Observational (N=141,667)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. MPI	1 Observational (N=212,947)	low	direct	unknown	precise	undetected	Low
	CCTA vs. Exercise ECG	1 RCT (N=500)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Exercise ECG (Medicare Population)	1 Observational (N=69,883)	medium	direct	unknown	precise	undetected	Insufficient
	CCTA vs. SPECT	2 Observational (N=12,132)	medium	direct	consistent	precise	undetected	Insufficient
	CCTA vs. MPI (nuclear) (Medicare Population)	1 Observational (N=141,163)	low	direct	unknown	precise	undetected	Low
	CCTA vs. Stress Echo (Medicare Population)	1 Observational (N=89,424)	low	direct	unknown	precise	undetected	Insufficient
Coronary Artery Bypass Graft	Nuclear MPI vs. Exercise ECG	1 Observational (N=193,406)	low	direct	unknown	precise	undetected	Low
	Stress Echo vs. Exercise ECG	1 Observational (N=5894)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. Exercise ECG (Medicare Population)	1 Observational (N=141,667)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. MPI (Medicare Population)	1 Observational (N=212,947)	low	direct	unknown	precise	undetected	Low
	CCTA vs. Exercise ECG	1 RCT (N=500)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Exercise ECG	1 Observational	medium	direct	unknown	imprecise	undetected	Insufficient

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
		(N=69,883)						
	CCTA vs. SPECT	2 observational (N=12,132)	medium	direct	consistent	precise	undetected	Insufficient
	CCTA vs. MPI (nuclear) (Medicare Population)	1 Observational (N=141,163)	low	direct	unknown	precise	undetected	Low
	CCTA vs. Stress Echo (Medicare Population)	1 Observational (N=89,424)	medium	direct	unknown	precise	undetected	Insufficient
Additional Testing	CCTA vs. Usual Care	1 RCT (N=266)	medium	indirect	unknown	imprecise	undetected	Insufficient
	SPECT vs. Exercise ECG	1 RCT (N=457)	medium	direct	unknown	imprecise	undetected	Low
	Exercise Echo vs. Exercise ECG	1 RCT (N=111)	high	direct	unknown	imprecise	undetected	Insufficient
	Stress Echo vs. Exercise ECG	1 Observational (N=141,667)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. MPI	1 Observational (N=212, 947)	low	direct	unknown	precise	undetected	Low
	CCTA vs. Exercise ECG	1 RCT (N=500)	medium	direct	unknown	precise	undetected	Moderate
	CCTA vs. Exercise ECG (Medicare Population)	1 Observational (N=69,883)	medium	direct	unknown	precise	undetected	Insufficient
	CCTA vs. SPECT	1 Observational (N=9960)	medium	direct	inconsistent	imprecise	undetected	Insufficient
	CCTA vs. MPI (nuclear) (Medicare Population)	1 Observational (N=141,163)	low	direct	unknown	precise	undetected	Low
	CCTA vs. Stress Echo (Medicare Population)	1 Observational (N=89, 424)	medium	direct	unknown	imprecise	undetected	Insufficient
Hospitalization (cardiac related)	Nuclear MPI vs. Exercise ECG	1 Observational (N=193,406)	medium	direct	unknown	imprecise	undetected	Insufficient
	Stress Echo vs. Exercise ECG	1 Observational (N=141,667)	medium	direct	unknown	precise	undetected	Insufficient
	Stress Echo vs. MPI	1 Observational (N=212,947)	medium	direct	unknown	precise	undetected	Insufficient
	CCTA vs. Exercise ECG	1 RCT (N=500)	medium	direct	unknown	precise	undetected	Moderate
	CCTA vs. Exercise ECG	1 Observational (N=69,883)	medium	direct	unknown	precise	undetected	Insufficient
	CCTA vs. SPECT	1 observational (N=9690)	medium	direct	unknown	precise	undetected	Insufficient
	CCTA vs. MPI (nuclear)	1 Observational (N=141,163)	medium	direct	unknown	precise	undetected	Insufficient

Outcome	Comparison	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	CCTA vs. Stress Echo (Medicare Population)	1 Observational (N=89,424)	medium	direct	unknown	precise	undetected	Insufficient
Harms	CCTA vs. Usual Care	1 RCT (N=266)	medium	direct	unknown	imprecise	undetected	Low
	CCTA vs. Exercise ECG	1 RCT (N=500)	medium	direct	unknown	imprecise	undetected	Insufficient
	CCTA vs. MPI (nuclear)	1 Observational (N=1856)	medium	direct	unknown	precise	undetected	Insufficient

CAD = coronary artery disease; CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; Echo = echocardiogram; ED = emergency department; MPI = myocardial perfusion imaging; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography.

Appendix K. Clinical Trials in Patients with Suspected Coronary Artery Disease

Table K1. Clinical trials in patients with suspected coronary artery disease listed on the Clinical Trials Website (clinicaltrials.gov)

Trial Name (Number)	Intervention	Condition (Estimated N)	Outcomes	Status (Estimated Completion) Related Publications
Stress Testing Compared to Coronary Computed Tomographic Angiography in Patients With Suspected Coronary Artery Disease (NCT01368770)	Stress MPI, SPECT, CCTA	Patients with chest pain or suspected CAD N = 303	• Angiography • Revascularization • MACE	Completed, June 2014 Publications: not provided
Computed Tomography Versus Exercise Testing in Suspected Coronary Artery Disease (NCT01393028)	CCTA, CCS, Usual Care	Patients with chest pain N = 350	• Chest pain • Revascularization • Overall medical expenses • Cost-effectiveness • Radiation dose • MACE • QOL	Terminated, Estimated completion July 2011 Publications: not provided
Coronary CT Angiography as the Primary Initial Method of Evaluating Patients With Subacute Chest Pain (CT PRIME) (NCT00584337)	CCTA, Usual Care	Patients with chest pain N = 300	• Diagnostic accuracy	Withdrawn prior to enrollment, estimated completion June 2009 Publications: not provided
PROspective Multicenter Imaging Study for Evaluation of Chest Pain - The PROMISE Trial (NCT01174550)	Coronary angiography, stress echocardiography, nuclear stress test, exercise ECG	Patients with chest pain N = 10,003	• Death • MI • Unstable angina hospitalization • Major complications from CV procedures • Cumulative radiation exposure • Medical costs • QOL	Completed, October 2014 Publications: Douglas (2015)[8]; Douglas (2014)[313] *included in present report*
Usefulness of Coronary CTA for the Diagnosis of Acute Coronary Syndrome in the Emergency Room. (NCT01682096)	CCTA, Exercise echocardiography	Patients with chest pain N = 150	• Diagnosis of acute coronary syndrome • MACE • Costs during admission	Completed, October 2013 Publications: not provided
Utility of 2D Strain Echocardiography in Triage of Patients With Chest Pain in the Emergency Department (NCT01163019)	Echocardiography, ECG, nuclear imaging	Patients with chest pain N = 700	• Diagnosis of acute coronary syndrome • Significant CAD • MACE	Completed, February 2014 Publications: not provided

Trial Name (Number)	Intervention	Condition (Estimated N)	Outcomes	Status (Estimated Completion) Related Publications
Myocardial Perfusion Assessment With Multidetector Computed Tomography (NCT00846079)	Multi-detector CT	Patients with suspected CAD N = 100	• Diagnostic accuracy • Radiation dosimetry	Unknown, Estimated completion September 2009 Publications: not provided
Association of Endothelial Function and Clinical Outcomes in Subjects Admitted to Chest Pain Unit (NCT01618123)	ECG, EndoPAT, stress nuclear imaging, stress echo	Patients with chest pain N = 300	• Long-term outcomes • Short-term outcomes (no further details provided)	Recruiting, July 2015 Publications: not provided
A Study of Stress Heart Imaging in Patients With Diabetes at Risk for Coronary Disease. (NCT00162344)	MPI, Exercise ECG	Diabetic patients with atypical chest pain N = 205	• Diagnosis of ischemic heart disease • Diagnostic accuracy • Relative value for identifying risk	Completed, December 2005 Publications: not provided
Role of Cardiac CT in Rapid Access Chest Pain Clinics (RADICAL) (NCT01464203)	CCTA, Usual Care	Patients with chest pain N = 600	• Diagnostic accuracy • QOL • Number of invasive angiograms • Revascularization • Prognostic value	Unknown, Estimated completion December 2011 Publications: Yerramasu (2010)*; Yerramasu (2014)†
Combined Use of Coronary MDCTA, Coronary Doppler Ultrasonography and PET Perfusion in Diagnosing Coronary Artery Disease (PECTUS) (NCT00627172)	CCTA, PET, ICA, FFR	Patients with chest pain N = 107	• Diagnosis of coronary artery lesions • QOL	Completed, January 2007 Publications: Kajander (2011)*; Bucci (2011)*; Kajander (2010)*
Stress Testing Versus Non-Stress Testing Based Strategy in Patients Hospitalized With Low-Risk Acute Coronary Syndromes: A Randomized, Single-Center Pilot Study (NCT01703156)	Stress test, no stress test	Patients with chest pain N = 70	• All-cause mortality • Hospitalization for STEMI • Revascularization • Angiography • Further testing • Medication adjustments • Medication side effects	Completed, July 2012 Publications: not provided

CAD = coronary artery disease; CACS = coronary artery calcium scan; CCTA = coronary computed tomography angiogram; ECG = electrocardiogram; FFR = fractional flow reserve; ICA = invasive coronary angiography; MACE = major adverse cardiovascular events; MPI = myocardial perfusion imaging; QOL = quality of life; SPECT = single photon-emission computed tomography.
*Excluded from present report at title/abstract.
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