National Institute for Health and Care Excellence

Draft for consultation

Addendum to Clinical Guideline (CG95), Chest pain of recent onset: Assessment and diagnosis

Clinical Guideline Addendum: CG95.1

Methods, evidence and recommendations

April 2016

Draft for consultation

Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

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Clinical guidelines update

The NICE clinical guidelines update team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the NICE surveillance programme.

These guidelines are updated using a standing committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the committee are joined by up to 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the committee' is referred to, this means the entire committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the committee.

Details of the committee membership and the NICE team can be found in appendix A. A link to the committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The NICE guideline on chest pain (NICE clinical guideline CG95) was reviewed in December 2014 as part of NICE's routine surveillance programme to decide whether it required updating. The surveillance report identified new evidence relating to the use of non-invasive tests for the diagnosis of coronary artery disease (CAD) in people with stable chest pain of suspected cardiac origin. It also identified new evidence on clinical prediction models which may impact on the assessment of the pre-test likelihood of CAD in this population.

The full surveillance report can be found here.

Some recommendations can be made with more certainty than others. The committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

Information for consultation

You are invited to comment on the new recommendations in this update. These are marked as:

- **[new 2016]** if the evidence has been reviewed and the recommendation has been added or updated, or

- **[2016]** if the evidence has been reviewed but no change has been made to the recommended action.

Where recommendations are shaded in grey and end **[2010]**, or **[2010, amended 2016]**, the evidence has not been reviewed since the original guideline. We will not be able to accept comments on these recommendations.

1.2 Recommendations

People presenting with stable chest pain

1. Diagnose or exclude stable angina based on:

- clinical assessment alone **or**
- clinical assessment plus diagnostic testing (that is, anatomical testing for obstructive CAD or functional testing for myocardial ischaemia or both). **[2016]**

Clinical assessment

2. Take a detailed clinical history documenting:

- the age and sex of the person
- the characteristics of the pain, including its location, radiation, severity, duration and frequency, and factors that provoke and relieve the pain
- any associated symptoms, such as breathlessness
- any history of angina, MI, coronary revascularisation, or other cardiovascular disease and
- any cardiovascular risk factors. **[2010]**

3. Carry out a physical examination to:

- identify risk factors for cardiovascular disease
- identify signs of other cardiovascular disease
- identify non-coronary causes of angina (for example, severe aortic stenosis, cardiomyopathy) and
- exclude other causes of chest pain. **[2010]**

Making a diagnosis based on clinical assessment

4. Assess the typicality of chest pain as follows:

- Presence of three of the features below is defined as typical angina.
- Presence of two of the three features below is defined as atypical angina.
- Presence of one or none of the features below is defined as non-anginal chest pain.

Anginal pain is:

- constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms
- precipitated by physical exertion

- relieved by rest or GTN within about 5 minutes. **[2010, amended 2016]**

5. **Do not define typical and atypical features of anginal chest pain and non-anginal chest pain differently in men and women. [2010]**

6. **Do not define typical and atypical features of anginal chest pain and non-anginal chest pain differently in ethnic groups. [2010]**

7. **Take the following factors, which make a diagnosis of stable angina more likely, into account when estimating people's likelihood of angina:**
   - age
   - whether the person is male
   - cardiovascular risk factors including:
     - a history of smoking
     - diabetes
     - hypertension
     - dyslipidaemia
     - family history of premature CAD
     - other cardiovascular disease
   - history of established CAD, for example, previous MI, coronary revascularisation. **[2010]**

8. **Unless clinical suspicion is raised based on other aspects of the history and risk factors, exclude a diagnosis of stable angina if the pain is non-anginal (see recommendation 4). Features which make a diagnosis of stable angina unlikely are when the chest pain is:**
   - continuous or very prolonged and/or
   - unrelated to activity and/or
   - brought on by breathing in and/or
   - associated with symptoms such as dizziness, palpitations, tingling or difficulty swallowing.

   Consider causes of chest pain other than angina (such as gastrointestinal or musculoskeletal pain). **[2010]**

9. **Consider investigating other causes of angina, such as hypertrophic cardiomyopathy, in people with typical angina-like chest pain and a low likelihood of CAD. [2010, amended 2016]**

10. **Arrange blood tests to identify conditions which exacerbate angina, such as anaemia, for all people being investigated for stable angina. [2010]**

11. **Only consider chest X-ray if other diagnoses, such as a lung tumour, are suspected. [2010]**

12. **If a diagnosis of stable angina has been excluded at any point in the care pathway, but people have risk factors for cardiovascular disease, follow the appropriate guidance, for example the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification and the**

NICE guideline on hypertension in adults: diagnosis and management [2010]

13. **For people in whom stable angina cannot be diagnosed or excluded on the basis of the clinical assessment alone, take a resting 12-lead ECG as soon as possible after presentation. [2010]**

14. **Do not rule out a diagnosis of stable angina on the basis of a normal resting 12-lead ECG. [2010]**

15. **Do not offer diagnostic testing to people with non-anginal chest pain on clinical assessment (see recommendation 4) unless there are resting ECG ST-T changes or Q waves. [new 2016]**

16. **A number of changes on a resting 12-lead ECG are consistent with CAD and may indicate ischaemia or previous infarction. These include:**
    - pathological Q waves in particular
    - LBBB
    - ST-segment and T wave abnormalities (for example, flattening or inversion).

    Note that the results may not be conclusive.

    Consider any resting 12-lead ECG changes together with people's clinical history and risk factors. **[2010]**

17. **For people with confirmed CAD (for example, previous MI, revascularisation, previous angiography) in whom stable angina cannot be diagnosed or excluded based on clinical assessment alone, see recommendation 23 about functional testing. [2010]**

18. **Consider aspirin only if the person's chest pain is likely to be stable angina, until a diagnosis is made. Do not offer additional aspirin if there is clear evidence that people are already taking aspirin regularly or are allergic to it. [2010]**

19. **Follow local protocols for stable angina while waiting for the results of investigations if symptoms are typical of stable angina. [2010]**

Diagnostic testing for people in whom stable angina cannot be diagnosed or excluded by clinical assessment alone

20. **Include the typicality of anginal pain features (see recommendation 4) in all requests for diagnostic investigations and in the person's notes. [2010, amended 2016]**

21. **Use clinical judgement and take into account people's preferences and comorbidities when considering diagnostic testing. [2010]**

22. **Offer 64-slice (or above) CT coronary angiography if:**
    - clinical assessment (see recommendation 4) indicates typical or

atypical anginal chest pain, or

- clinical assessment indicates non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves. **[new 2016]**

23. **For people with confirmed CAD (for example, previous MI, revascularisation, previous angiography), offer non-invasive functional testing when there is uncertainty about whether chest pain is caused by myocardial ischaemia. See the section on non-invasive functional imaging for myocardial ischaemia for further guidance on non-invasive functional testing. An exercise ECG may be used instead of functional imaging [2010]**

Additional diagnostic investigation

24. **Offer non-invasive functional imaging (see the section on non-invasive functional imaging for myocardial ischaemia) for myocardial ischeamia if 64-slice (or above) CT coronary angiography has shown CAD of uncertain functional significance or is nondiagnostic. [2016]**

25. **Offer invasive coronary angiography as a second-line investigation when the results of non-invasive functional imaging are inconclusive. [2016]**

Use of non-invasive functional testing for myocardial ischaemia

26. **When offering non-invasive functional imaging for myocardial ischaemia use:**

    - myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT) or
    - stress echocardiography or
    - first-pass contrast-enhanced magnetic resonance (MR) perfusion or
    - MR imaging for stress-induced wall motion abnormalities.

    Take account of locally available technology and expertise, the person and their preferences, and any contraindications (for example, disabilities, frailty, limited ability to exercise) when deciding on the imaging method. [This recommendation updates and replaces recommendation 1.1 of Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction (NICE technology appraisal guidance 73)]. **[2016]**

27. **Use adenosine, dipyridamole or dobutamine as stress agents for MPS with SPECT and adenosine or dipyridamole for first-pass contrast-enhanced MR perfusion. [2010]**

28. **Use exercise or dobutamine for stress echocardiography or MR imaging for stress-induced wall motion abnormalities. [2010]**

29. **Do not use MR coronary angiography for diagnosing stable angina. [2010]**

30. Do not use exercise ECG to diagnose or exclude stable angina for people without known CAD. [2010]

Making a diagnosis following investigations

Box 1 Definition of significant coronary artery disease

Significant coronary artery disease (CAD) found during CT coronary angiography is ≥ 70% diameter stenosis of at least one major epicardial artery segment or ≥ 50% diameter stenosis in the left main coronary artery:

Factors intensifying ischaemia

Such factors allow less severe lesions (for example ≥ 50%) to produce angina:

- Reduced oxygen delivery: anaemia, coronary spasm.
- Increased oxygen demand: tachycardia, left ventricular hypertrophy.
- Large mass of ischaemic myocardium: proximally located lesions.
- Longer lesion length.

Factors reducing ischaemia which may render severe lesions (≥ 70%) asymptomatic

- Well-developed collateral supply
- Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply. **[2016]**

31. Confirm a diagnosis of stable angina and follow local guidelines for angina[a] when:

- significant CAD (see box 1) is found during invasive or 64-slice (or above) CT coronary angiography, or
- reversible myocardial ischaemia is found during non-invasive functional imaging. **[2016]**

32. Investigate other causes of chest pain when:

- significant CAD (see box 1) is not found during invasive coronary angiography or 64-slice (or above) CT coronary angiography, **or**
- reversible myocardial ischaemia is not found during non-invasive functional imaging **[2016]**

33. Consider investigating other causes of angina, such as hypertrophic cardiomyopathy or syndrome X, in people with typical angina-like chest pain if investigation excludes flow-limiting disease in the epicardial coronary arteries. [2010]

[a] Stable angina. NICE guideline CG126 (2011).

1.3 Patient-centred care

This addendum to CG95 offers best practice advice on the evaluation and diagnostic testing of people with stable chest pain of suspected cardiac origin.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have the capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

1.4 Methods

This update was developed based on the process and methods described in the guidelines manual 2014. For details specific to the evidence review, see Section 2.

2 Evidence review and recommendations

2.1 Introduction

Chest pain is one of the symptoms of coronary artery disease (CAD). It occurs when blood supply to heart muscles is restricted as a result of atherosclerosis in surrounding vessels. This type of chest pain, known as angina, can affect quality of life, functional and physical ability. If left untreated, it can lead to myocardial infarction which is life threatening. Mortality from CAD in the UK accounts for 12.9% of all-cause mortality and prevalence of angina in England is 2.9% (British Heart Foundation, 2014)

The NICE guideline on Chest pain of recent onset was reviewed in 2014 and new evidence was identified on the use of non-invasive tests to diagnose CAD in people with stable (non-acute) chest pain. New evidence was also identified on clinical prediction models that may lead to an improved performance in estimating the pre-test likelihood of CAD.

2.2 Review question 1

In people with stable chest pain of suspected cardiac origin, what is the accuracy, clinical utility and cost effectiveness of:

- non-invasive diagnostic tests
- invasive diagnostic tests
- calcium scoring

2.2.1 Clinical evidence review

2.2.1.1 Methods and results

A systematic review of the literature search was conducted as specified in the review protocol (Appendix C). The protocol was developed in consultation with the topic experts and then reviewed by the core committee members before the review was carried out. The following outcomes were considered important for decision making: true positive, false positive, false negative, true negative, sensitivity, specificity. A number of protocol refinements were made during the evidence review phase. These were informed by the advice of topic experts due to the complexity and variation in the technology of the included diagnostic tests and because of the large body of evidence. Refinements were subsequently agreed by the standing committee and can be viewed in Appendix C.

A systematic search (see Appendix D) identified 10,637 articles. The titles and abstracts were screened and 749 articles were identified as potentially relevant. An additional 3 articles were identified from the existing guideline which were not retrieved in the searches. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (Appendix C). Of these 693 were excluded as they did not meet the criteria and 60 met the criteria and were included.

A review flowchart is provided in Appendix E and the excluded studies (with reasons for exclusion) are shown in Appendix F.

Ten different diagnostic tests were identified as of current diagnostic importance. Invasive coronary angiography (ICA) is the gold standard for establishing the presence, location, and severity of coronary artery disease, but the technique is invasive, costly and associated with a small but definite risk of morbidity and mortality. Using ICA as the reference standard,

evidence for each of the nine alternative identified testing strategies was evaluated separately. These nine index tests are listed in Table 2.

Sixty cross-sectional, diagnostic studies were included, with a total of 9,780 participants. Data from each included study were extracted into evidence tables (Appendix G). A summary of key characteristics of each study are shown in Table 1. Population was classified as one of the following 4 categories:

- A: Population had suspected coronary artery disease (CAD), but there was no breakdown of numbers with chest pain, or the numbers with chest pain was less than 50%.
- B: Population had suspected CAD and 50% or more had chest pain.
- C: All participants had suspected CAD and chest pain (combination of types e.g. typical angina, atypical angina, non cardiac)
- D: All participants had suspected CAD and typical chest pain of suspected cardiac origin

Table 1: Summary of included studies

Study (author/year)	Total sample size	Age Mean (SD)	Study population category	Index test (a)	Location
Arnold et al 2010	65	64 (9)	A: Suspected CAD	4a, 4b, 4a+4b	Unclear (?UK, Australia, Poland)
Bettencourt et al 2011	90	62 (8)	B: Suspected CAD, 92% with chest pain	2,9, 2+9	Portugal
Budoff et al 1998	33	55 (9)	C: 100% with chest pain (combination of types)	7	USA
Budoff et al 2007	30	54 (9)	A: Suspected CAD	7	USA
Budoff et al 2008	230	57 (10)	C: 100% with chest pain (combination of types)	2	USA
Budoff et al 2013	230	57 (10)	C: 100% with chest pain (combination of types)	3	USA
Cademartiri et al 2007	72	54 (8)	C: 100% with chest pain (combination of types)	2	Italy
Cademartiri et al 2008	145	63 (10)	B: Suspected CAD, 81% with chest pain	2	Italy
Carrascosa et al 2010	50	62 (13)	B: Suspected CAD, 82% with chest pain	2	Argentina
Chen et al 2011	113	62 (SD not reported)	C: 100% with chest pain (combination of types)	2	Taiwan
Cramer et al 1997	78	58 (SD not reported)	D: 100% stable chest pain of suspected cardiac origin	7	The Netherlands
Di Bello et al 1996a	45	53 (7)	C: 100% with chest pain (combination of types)	4b,7	Italy
Di Bello et al 1996b	45	53 (7)	C: 100% with chest pain (combination of types)	4b,7	Italy
Donati et al 2010	52	64 (10)	C: 100% with chest pain (combination of types)	2	Switzerland/USA (unclear)
Fleming et al 1992	44	57 (11)	A: Suspected CAD	7	USA
Fujitaka et al	125	70 (11)	C: 100% with chest pain	2, 2+7	Japan

Study (author/year)	Total sample size	Age Mean (SD)	Study population category	Index test (a)	Location
2009			(combination of types)		
Hennessy et al 1998	157	59 (11)	C: 100% with chest pain (combination of types)	4b	UK
Herzog et al 2007	40	61 (8)	A: Suspected CAD	2	USA
Herzog et al 2008	30	59 (10)	B: Suspected CAD, 63% with chest pain	2	Switzerland
Herzog et al 2009	42	62 (8)	B: Suspected CAD, 62% with chest pain	2	Switzerland
Hoffmann et al 1993	66	57 (10)	A: Suspected CAD	4b	Germany
Javadrashid et al 2009	158	58 (10)	A: Suspected CAD	3	Iran
Kaminek et al 2015	164	61 (12)	A: Suspected CAD	7	Czech Rep.
Kawase et al 2004	50	67 (12)	A: Suspected CAD	6	Japan
Klein et at 2008	54	60 (10)	B: Suspected CAD, 83% with chest pain	6	Germany
Klem et al 2006	92	58 (12)	A: Suspected CAD	6	USA
Krittayaphong et al 2009	66	61 (12)	B: Suspected CAD, 52% with chest pain	6	Thailand
Marangelli et al 1994	82	68 (8)	C: 100% with chest pain (combination of types)	4b	Italy
Marwick et al 1993	217	58 (10)	B: Suspected CAD, >=65% with chest pain	4b,7	Belgium
Mazeika et al 1992	55	55 (9)	A: Suspected CAD	4b	UK
Meng et al 2009	109	63 (9)	A: Suspected CAD	2	China
Miszalaski-Jamka et al 2012	61	57 (12)	A: Suspected CAD	4a	Poland
Muhlenbruch et al 2007	51	59 (8)	A: Suspected CAD	2	Germany
Nagel et al 1999	208	60 (9)	A: Suspected CAD	4b, 5	Germany
Nazeri et al 2009	168	58 (11)	A: Suspected CAD	2	Iran
Nieman et al 2009	98	56 (10)	C: 100% with chest pain (combination of types)	2	Holland
Nixdorff et al 2008	71	62 (SD not reported)	A: Suspected CAD	4b	Unclear (Europe)
Onishi et al 2010	59	64 (11)	A: Suspected CAD	4a	Japan
Overhus et al 2010	100	61 (9)	B: Suspected CAD, 80% with chest pain	2	Denmark
Parodi et al 1999	101	55 (9)	D: 100% stable chest pain of suspected cardiac origin	4b	Italy
Piers et al 2008	60	64 (SD not reported)	A: Suspected CAD	2	The Netherlands

Study (author/year)	Total sample size	Age Mean (SD)	Study population category	Index test (a)	Location
Pontone et al 2014	91	Not reported	A: Suspected CAD	2	Italy
Pugliese et al 2008	204	59 (11)	A: Suspected CAD	2	The Netherlands
Raff et al 2005	70	59 (11)	A: Suspected CAD	2	USA
Rixe et al 2009	76	68 (9)	B: Suspected CAD, 80% with chest pain	2	Germany
Ropers et al 2006	84	58 (10)	A: Suspected CAD	2	Germany
San Roman et al 1996	102	64 (11)	D: 100% stable chest pain of suspected cardiac origin	4b	Spain
San Roman et al 1998	102	64 (10)	D: 100% stable chest pain of suspected cardiac origin	4b,7	Spain
Santoro et al 1998	60	Not reported	C: 100% with chest pain (combination of types)	4b, 7	Italy
Schepis et al 2007	77	66 (9)	B: Suspected CAD, 57% with chest pain	7, 3+7	Switzerland
Senior et al 2004	55	median 61 (range 47-61)	C: 100% with chest pain (combination of types)	4b, 7	UK/Germany
Severi et al 1993	429	55 (4)	C: 100% with chest pain (combination of types)	4b	Italy
Shaikh et al 2014	45	61 (7)	A: Suspected CAD	4b	USA
Sheikh et al 2009	73	60 (9)	C: 100% with chest pain (combination of types)	2	Kuwait
Stolzmann et al 2011	60	64 (10)	B: Suspected CAD, 65% with chest pain	6, 3+6	Switzerland
Swailam et al 2010	30	53 (6)	C: 100% with chest pain (combination of types)	2	Egypt
Thomassen et al 2013	44	66 (9)	C: 100% with chest pain (combination of types)	2,7,2+7	Denmark
Van Werkhoven et al 2010	61	57 (9)	C: 100% with chest pain (combination of types)	2	The Netherlands
Von Ziegler	4,137	61 (12)	C: 100% with chest pain (combination of types)	3	Germany
Yao et al 2004	73	53 (11)	A: Suspected CAD	7	China

All studies were cross-sectional diagnostic studies.
Mean/SD are rounded to whole numbers.
Index tests 2=CTCA, 3=Calcium Scoring, 4a=Stress Echo (perfusion), 4b=Stress Echo (wall motion), 5=CMR (wall motion), 6=CMR (Perfusion), 7=MPS SPECT/PET, 8=CT FFR, 9=CT Perfusion, 10=PET
All studies had invasive coronary angiography as the reference standard. Studies reporting combined analyses are indicated by (+)

Forest plots are shown in Appendix J and illustrate the sensitivity and specificity reported for each study arranged by index test. The forest plots include individual (rather than pooled) study data and no overall point estimates are shown. In addition they illustrate covariates of interest, including stenosis level for diagnosis according to invasive coronary angiography (ICA; 50% or 70% stenosis level) and population categories for each study (A, B, C or D).

Covariates relating to specifics of a test are also shown where appropriate (e.g. method of inducing stress for stress echocardiography, calcium threshold for calcium scoring).

In addition to diagnostic data, side-effects or minor or major adverse events associated with either test were extracted and reported in the evidence tables. No studies reported stroke or death in relation to ICA or any index test. One study reported coronary artery dissection in relation to ICA (Budoff et al 2008). Three studies reported a total of 4 cardiac events in relation to administration of index tests. These are:

- Cardiac arrest (n=1) Mazeika et al 1992 (stress echo for wall motion).
- Left heart failure (n=1) San Roman et al 1998 (after administration of dobutamine)
- Left heart failure (n=1) San Roman et al 1998 (after administration of dipyridamole)
- Left heart failure (n=1) San Roman et al 1996 (after dobutamine-atropine infusion).

2.2.1.21 Evidence synthesis

In instances where more than one study evaluated the same index text, a meta-analysis was considered. Decisions on whether to undertake meta-analysis, and for which subsets of studies were taken in conjunction with committee members, based on the clinical heterogeneity of the included studies and following preliminary examination of the data. The strategy for evidence synthesis is shown for each test in Table 2 and compared with the reference test (invasive coronary angiography) listed in row 1. The committee agreed that data for 50% and 70% stenosis should be analysed and considered separately for each test.

Table 2: Evidence synthesis strategy

Index test	Subgroups for analysis		Number of studies	Synthesis method	Notes
1. Invasive coronary angiography (ICA)					Reference standard
2. Computed tomography coronary angiography (CTCA)	50% sten.		25	Meta-analysis	
	70% sten.		3	Meta-analysis	
3. Calcium score	50% sten.	Threshold: 0	2	Meta-analysis	
		Threshold: 400	2	Meta-analysis	
	70% sten.	Threshold: 0	1	Single study	
		Threshold: 400	1	Single study	
4a. Stress echocardiography (echo) - perfusion	50% sten.		3	Meta-analysis	Despite variation in stress inducing methods, all serve to achieve coronary vasodilatation, and so pooling is justified.
	70% sten.		1	Single study	
4b. Stress echo - wall motion	50% sten.	Stress method: vasodilatation	5	Meta-analysis	Studies induced stress by modifying vasodilation or heart rate: analysis is based on these categories.
		Stress method: heart rate modification	8	Meta-analysis	

Index test	Subgroups for analysis		Number of studies	Synthesis method	Notes
	70% sten.	Stress method: vasodilatation	7	Meta-analysis	
		Stress method: heart rate modification	4	Meta-analysis	
5. Cardiac magnetic resonance (CMR) - wall motion	50% sten.		1	Single study	
	70% sten.		0	N/A	
6. CMR - perfusion	50% sten.		5	Meta-analysis	The topic experts advised that delayed enhancement is not usually used in isolation, so data using this method in isolation were excluded. When data was reported for perfusion imaging alone and perfusion + delayed enhancement, the later was used in the meta-analysis.
	70% sten.		3	Meta-analysis	
7a. Myocardial perfusion scintigraphy - single-photon emission computed tomography (MPS - SPECT)	50% sten.		11	Meta-analysis	Despite variation in stress inducing methods, all serve to achieve coronary vasodilatation, and so pooling is justified.
	70% sten.		3	Meta-analysis	
7b. MPS – positron emission tomography (MPS - PET)	50% sten.		0	N/A	
	70% sten.		1	Single study	
8. Computed tomography fractional flow reserve (CT FFR)			0	N/A	
9. Computed tomography (CT) - perfusion	50% sten.		1	Single study	
	70% sten.		1	Single study	

Meta-analysis

Meta-analysis was performed using the statistical software package 'R'. The 'reitsma' function from the 'mada' R library (https://cran.r-project.org/web/packages/mada/index.html) was used to produce pooled estimates for sensitivity and specificity, together with 95% confidence intervals. This function implements the bivariate model of Reitsma et al. (2005), which takes into account the paired nature of sensitivity and specificity values. Chi^2 and I^2 values were calculated in order to assess heterogeneity. The results of the analyses are shown in Table 3 and plotted in Appendix J. A sensitivity analysis was also performed, in order to assess the impact of low quality studies on the overall effect estimates. Studies with

very serious concerns over risk of bias or applicabilityaccording to the QUADAS-2 checklist (see Section 2.2.1.3) were excluded from the sensitivity analysis. The results of the sensitivity analysis are shown in Table 3 ('-' indicates that no studies had very serious risk of bias or applicability concerns, so a sensitivity analysis was not performed).

Table 3: Diagnostic test accuracy meta-analysis results

	Main analysis				Sensitivity analysis			
Index test	**Sensitivity (95% CI)**	**I^2**	**Specificity (95% CI)**	**I^2**	**Sensitivity (95% CI)**	**I^2**	**Specificity (95% CI)**	**I^2**
CTCA – 50% stenosis	0.96 (0.94 to 0.97)	0%	0.79 (0.72 to 0.84)	80%	0.96 (0.94 to 0.97)	0%	0.79 (0.73 to 0.85)	79%
CTCA – 70% stenosis	0.96 (0.88 to 0.99)	0%	0.72 (0.55 to 0.85)	79%	-	-	-	-
Calcium score – 50% stenosis, threshold:0	0.99 (0.97 to 0.99)	0%	0.49 (0.36 to 0.63)	92%	-	-	-	-
Calcium score – 50% stenosis, threshold:400	0.54 (0.52 to 0.57)	0%	0.88 (0.87 to 0.88)	0%	-	-	-	-
Stress echocardiography, Perfusion – 50% stenosis	0.84 (0.76 to 0.90)	28%	0.79 (0.69 to 0.86)	0%	-	-	-	-
Stress echocardiography, Wall motion – 50% stenosis, vasodilators	0.77 (0.69 to 0.83)	50%	0.86 (0.68 to 0.95)	77%	-	-	-	-
Stress echocardiography, Wall motion – 50% stenosis, heart rate modifiers	0.76 (0.72 to 0.79)	0%	0.80 (0.71 to 0.88	65%	-	-	-	-
Stress echocardiography, Wall motion – 70% stenosis, vasodilators	0.64 (0.49 to 0.76)	85%	0.90 (0.86 to 0.93)	0%	-	-	-	-
Stress echocardiography, Wall motion – 70% stenosis, heart rate modifiers	0.75 (0.62 to 0.85	64%	0.88 (0.79 to 0.93)	0%	-	-	-	-
CMR, Perfusion – 50% stenosis	0.84 (0.76 to 0.90)	18%	0.85 (0.77 to 0.90)	0%	-	-	-	-
CMR Perfusion – 70% stenosis	0.93 (0.84 to 0.97)	0%	0.81 (0.56 to 0.93)	83%	-	-	-	-
MPS-SPECT – 50% stenosis	0.81 (0.74 to 0.86)	75%	0.78 (0.70 to 0.85)	45%	0.78 (0.68 to 0.85)	74%	0.81 (0.70 to 0.89)	60%
MPS-SPECT – 70% stenosis	0.76 (0.44 to 0.93)	88%	0.76 (0.58 to 0.88)	0%	-	-	-	-

2.2.1.36 Quality assessment

QUADAS-2 checklist

The QUADAS-2 quality assessment checklist for diagnostic studies was used to evaluate each included study, as recommended in the NICE guideline manual (2014). The rating strategy used to derive a rating for each quality parameter is shown in Table 4.

Table 4: QUADAS-2 Quality rating strategy by quality parameter

Quality Parameter	Rating strategy

Quality Parameter	Rating strategy
Domain 1 Patient Selection A. Risk of bias 1) Consecutive/random sample. 2) Case-control study design 3) Avoid inappropriate exclusions *(3 signalling questions, rate Yes/No/Unclear)*	Could the selection of patients have introduced bias? Rating: LOW/HIGH/UNCLEAR (3/3 Yes) rate as LOW risk, (1/3 unclear) rate as UNCLEAR risk, (≥1 unclear or No) rate as HIGH risk.
B. Concerns regarding applicability *(1 signalling question rate concern as low/high/unclear)*	Considerations relating to population were: 1) The population in the review protocol is defined as people with suspected CAD with or without chest pain. The desired population for informing guideline recommendations is one of chest pain but agreement was made in conjunction with topic experts that if suspected CAD formed the entire population (no breakdown provided) we would rate as UNCLEAR applicability. If suspected CAD with a breakdown of sub categories (including chest pain at a rate of at least 50%), we rated as LOW. 2) Pre-test probability stated as LOW, MODERATE/INTERMEDIATE OR HIGH defining the entire study population was rated as HIGH risk of bias. If a study provided analysis by each risk level this is would not be rated down as this would reflect a real-world population and would have been desired. 3) Whether recruitment into the study was based on referral for coronary angiography. If so we rated as HIGH concern re applicability since the study population was likely to reflect a higher prevalence population.
Domain 2 Index Tests A Risk of Bias *(2 signalling questions rate as Yes/No/Unclear)*	Overall rating if both Yes, rated as LOW risk, if ≥1 are no or unclear, rated as HIGH risk.
B Concern regarding applicability *(1 signalling question)*	Concern rated as LOW/HIGH/UNCLEAR.
Domain 3 Reference Standard A Risk of Bias *(2 signalling questions, rate concern as Yes/No/Unclear)*	Overall rating if both yes rated as LOW, if ≥1 unclear/no rate as High.
B Concern regarding applicability *(1 signalling question)*	Concern rated as LOW/HIGH/UNCLEAR
Domain 4 Flow and Timing A Risk of Bias *(4 signalling questions, rate concern as Yes/No/Unclear)*	Overall rating if ≥2 of the 4 with UNCLEAR or NO rate as HIGH risk of bias. If 1 of 4 is NO/UNCLEAR rate as low. 1) Time limit up to 3 months rated as YES (per protocol inclusion). If no time limit specified rate as UNCLEAR. 2) Drop outs/exclusions – If exceeded 20% (arbitrary figure) then rate as NO.

An overall summary rating for each study of 'no serious', 'serious' or 'very serious' for 'risk of bias' and 'applicability' was derived from the QUADAS-2 ratings for each domain as follows:

- **No serious:** 0 or 1 domain rated as 'unclear', no domains rated as 'high'.
- **Serious:** 2 domains rated as 'unclear' or 1 domain rated as 'high'.
- **Very serious:** 3 or more domains rated as unclear or 2 or more domains rated as 'high'.

The rationale for ratings for each study can be found in the comments section of individual evidence tables (Appendix G). A summary individual study quality ratings for each domain, and summary ratings for 'risk of bias' and 'applicability' are shown in Appendix H.

GRADE quality assessment

GRADE quality assessment was carried out for each index test according to the methods for assessing a body of evidence on diagnostic test accuracy described by the GRADE working group (see: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3364356/). In the modified version of the GRADE quality assessment for diagnostic test accuracy evidence, evidence from cross sectional studies begins with a quality rating of high and is 'downgraded' to moderate, low or very-low quality according to serious or very serious sources of uncertainty in four domains: risk of bias, indirectness, inconsistency and imprecision. 'No serious', 'serious' or 'very serious' judgements were made in each domain as follows:

Risk of bias: Risk of bias was rated according to the most common summary rating (see Table 79 in Appendix H) derived from the QUADAS 'risk of bias' elements for the studies contributing to the effect estimate.

Indirectness: Indirectness was rated according to the most common summary rating (see Table 79 in Appendix H) derived from the QUADAS 'applicability' elements for the studies contributing to the effect estimate.

Inconsistency: This criterion applied only when meta-analysis had been performed. I^2 and Chi^2 statistics were calculated to assess the heterogeneity of contributing studies. Inconsistency was rated as 'serious' if there was substantial unexplained heterogeneity (I^2>50%) in either the sensitivity or specificity analysis, and very serious if there was very substantial heterogeneity (I^2>75%) in either analysis.

Imprecision:

The GRADE working group recommend downgrading if confidence intervals are wide, but what constitutes 'wide' depends on the specific review. The topic experts were consulted on maximum width of 95% CIs deemed acceptable when considering imprecision around the sensitivity and specificity. A range of >20% in either the sensitivity or specificity estimate was considered serious imprecision and a range of >40% was considered very serious.

2.2.1.4 Test and treat randomised controlled trials

In the course of development, the NICE team became aware of a number of 'test and treat' randomised controlled trials relevant to the update that had not been identified in the main review because they did not report diagnostic test accuracy outcomes. A supplementary narrative review was therefore conducted to identify test and treat randomised controlled trials that included one of more of the index tests identified in the main diagnostic test accuracy review. The search strategy, review flowchart, list of excluded studies, and evidence tables for this supplementary review can be found in Appendices D.2, E.2, F.2 and G.2, respectively.

The search identified 9200 records. Of these 995 were articles that were also identified in the main diagnostic test accuracy review, and so were not examined further, and 8194 were excluded on the basis of title and abstract. Eleven full text articles were examined and 8 were excluded (for a list of excluded studies and reasons for exclusion, see Appendix F.2), leaving 3 included studies. Details of the included studies were extracted into evidence tables (see Appendix G.2), and narrative summaries are provided below.

SCOT-HEART (The SCOT-HEART team, 2015)

9,849 participants with stable chest pain of suspected cardiac origin were recruited from multiple chest pain clinics in Scottish hospitals between 2010 and 2014 (mean age 57.1 years, 56% male). Participants were randomised to standard diagnostic care (which included clinical assessment, calculation of cardiovascular risk, exercise electrocardiography and further testing at the discretion of the clinician) or standard care with additional CT coronary angiography (CTCA). At 6 weeks, CTCA reclassified the diagnosis of coronary heart disease in 558 (27%) patients and the diagnosis of angina due to coronary heart disease in 481 (23%) patients. This changed planned investigations (15% vs 1%; p<0·0001) and treatments (23% vs 5%; p<0·0001) but did not affect 6-week symptom severity or subsequent admittances to hospital for chest pain. After 1·7 years, CTCA was associated with a 38% reduction in fatal and non-fatal myocardial infarction (26 vs 42, HR 0·62, 95% CI 0·38–1·01; p=0·053), but this was not statistically significant.

PROMISE (Douglas et al. 2015)

10,003 participants with suspected coronary artery disease from several centres in the USA were recruited between 2010 and 2014 (mean age 60.8 years, 53% male). Participants were randomised to CTCA or functional testing (which could include exercise electrocardiography, nuclear stress testing or stress echocardiography). Over a median follow-up period of 25 months, a primary end-point event (death, myocardial infarction, hospitalisation for unstable angina, major complication of cardiovascular or diagnostic testing procedure) occurred in 164 of 4996 patients in the CTCA group (3.3%) and in 151 of 5007 (3.0%) in the functional-testing group (adjusted hazard ratio, 1.04; 95% confidence interval, 0.83 to 1.29; p=0.75). CTCA was associated with fewer catheterizations showing no obstructive CAD than was functional testing (3.4% vs. 4.3%, p=0.02).

CAPP trial (McKavanagh et al. 2015)

500 participants with stable chest pain but without known coronary artery disease were recruited from several chest pain clinics in Northern Ireland (mean age 58.4 years, 55% male). Participants were randomised to CTCA or exercise electrocardiography as the initial diagnostic investigation and followed up for 12 months. More participants in the CTCA group were diagnosed with significant CAD (128 vs 72), and more were treated both medically and surgically (136 vs 54). Fewer hospital admissions were recorded for the CTCA group than the exercise electrocardiography group. There was a significantly greater improvement in quality of life, measured by the Seattle angina questionnaire at 12 months in the CTCA group than the exercise electrocardiography group (mean difference, 24.9, 95% confidence interval 29.6 to 20.2, p=0.04).

2.2.2 Health economic evidence review

2.2.2.1 Methods

Evidence of cost effectiveness

The committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected

costs of the different options in relation to their expected health benefits rather than the total implementation cost.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought. For review question 1, the health economist:

- undertook a systematic review of the published economic literature; and
- undertook a new cost-effectiveness analysis.

Economic literature search

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to diagnostic strategies stable chest pain of suspected cardiac origin in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 2 June 2015. The health economic search strategies are detailed in appendix K.

The health economist also sought out relevant studies identified by the surveillance review or Committee members.

Economic literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies.
- Critically appraised relevant studies using the economic evaluations checklist as specified in *Developing NICE Guidelines: the manual 2014*.
- Extracted key information about the studies' methods and results into full economic evidence tables (appendix N).
- Generated summaries of the evidence in economic evidence profiles.

Inclusion and Exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the excluded economic studies table (appendix M).

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual 2014*.

Economic evidence profile

The economic evidence profile summarises cost-effectiveness estimates. It shows an assessment of the applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from *Appendix H* of *Developing NICE Guidelines: the manual 2014*. It also shows the incremental cost, incremental effect and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty.

The table below explains the information contained in the economic evidence profile.

Table 5: Explanation of fields used in the economic evidence profile

Item	Description
Study	This field is used to reference the study and provide basic details on the included interventions and country of origin.
Applicability	Applicability refers to the relevance of the study to specific review questions and the NICE reference case. Attributes considered include population, interventions, healthcare system, perspective, health effects and discounting. The applicability of the study is rated as: • Directly applicable – the study meets all applicability criteria or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	This field provides an assessment of the methodological quality of the study. Attributes assessed include the relevance of the model's structure to the review question, timeframe, outcomes, costs, parameter sources, incremental analysis, uncertainty analysis and conflicts of interest. The methodological quality of the evaluation is rated as having: • Minor limitations – the study meets all quality criteria or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	This field contains particular issues that should be considered when interpreting the study, such as model structure and timeframe.
Incremental cost	The difference between the mean cost associated with one strategy and the mean cost of a comparator strategy.
Incremental effect	The difference between the mean health effect associated with the intervention and the mean health effect associated with the comparator. This is usually represented by quality-adjusted life years (QALYs) in accordance with the NICE reference case.

Item	Description
Incremental cost effectiveness ratio (ICER)	The incremental cost divided by the incremental effect which results in the cost per quality-adjusted life year gained (or lost). Negative ICERs are not reported as they could represent very different conclusions: either a decrease in cost with an increase in health effects; or an increase in cost with a decrease in health effects. For this reason, the word 'dominates' is used to represent an intervention that is associated with decreased costs and increased health effects compared to the comparator, and the word 'dominated' is used to represent an intervention that is associated with an increase in costs and decreased health effects.

Item	Description
Uncertainty	A summary of the extent of uncertainty about the ICER. This can include the results of deterministic or probabilistic sensitivity analysis or stochastic analyses or trial data.

Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, new economic analysis was undertaken by the health economist.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.
- The committee was involved in the design of the model, selection of inputs and interpretation of results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available, Committee expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was quality assured by another health economist within NICE's Centre for Clinical Practice.

Full methods for the cost-effectiveness analysis conducted for this guideline are described in appendix O.

Cost-effectiveness criteria

NICE's report *Social value judgements: principles for the development of NICE guidance* sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'evidence to recommendations' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance*.

4.1.1.1 Results of the economic literature review

2438 articles were identified in the search. 2360 of these were excluded based on title and abstract alone. 78 full text articles were obtained. 76 full text articles were excluded. Because there was a cost-utility analysis using UK costs included, studies were selectively excluded if they used non-UK costs. Studies were included if they used UK costs and any type of health benefit such as QALYs or correct diagnoses. Two studies from the published literature were

included as well as the 2 cost-effectiveness analyses from the original guideline for a total of 4 included models. Table 6 contains the economic evidence profile for this review question summarising the results of the studies included in the systematic review, modelling conducted for the previous guideline and the economic model developed for the present update. Full economic evidence tables are contained in appendix N.

The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in appendix L. Appendix M contains a list of excluded studies and the reason for their exclusion.

A 2015 cost-utility analysis (Genders et al.) investigated the cost effectiveness of CTCA, CMR, ECHO, SPECT; and CTCA followed by CMR, ECHO or SPECT after positive CTCA results. With additional options for conservative or invasive diagnostic workups, there were a total of 16 diagnostic strategies compared in the model. A lifetime time horizon was adopted and a markov state-transition model was used for lifetime prognoses. The populations were 60 year old males and females with no history of coronary artery disease. The perspective was the NHS for costs and the person with stable chest pain for health benefits. The cost year was 2011 and a discount rate of 3.5% was used. Sensitivity and specificity of tests were taken from meta-analyses available in the published literature. The authors found that health benefits in terms of QALYs were very similar for all strategies, CTCA prior to ICA increased effectiveness, and ECHO was consistently more effective and less expensive than other imaging tests. For the men with a 30% pre-test likelihood CTCA+ECHO was the optimal strategy with an ICER of £7,000 per QALY. For women with a 30% pre-test likelihood, the invasive version of ECHO was the optimal strategy with an ICER of £8,000 per QALY. For both men and women with pre-test likelihoods of 50%, 70% and 90%, either the conservative or invasive versions of ECHO were the optimal strategies. These results were robust to one way sensitivity analysis. Probabilistic sensitivity analysis was carried out but not well reported. This study was directly applicable with minor limitations.

The 2010 economic model developed for the original guideline was a short term model comparing 10 strategies of various combinations of exercise ECG, SPECT, CT calcium scoring, CTCA and ICA. ECHO and CMR were not included in the model. Incremental analysis of results was repeated for this update excluding strategies containing exercise ECG as one of the tests because this was excluded as an index test in the clinical review. The structure of the model was a decision tree that reported results in terms of cost per correct diagnosis and also identified total true positives, false negatives, true negatives and false positives for each strategy. The perspective was the NHS for costs. The model was rerun for 5 levels of pre-test likelihood: 5%, 20%, 40%, 60% and 80%. CT calcium scoring followed by CTCA was the least cost per correct diagnosis for all pre-test likelihoods. Both CTCA and ICA were potentially cost effective for pre-test likelihoods greater than 40% although there was no threshold for cost per correct diagnosis. For the 5% and 20% pre-test likelihoods, two strategies, CT calcium scoring followed by CTCA followed by ICA, and CTCA followed by ICA, were potentially cost effective with relatively low costs per correct diagnosis and ICA was unlikely to be cost effective. This study was directly applicable with potentially serious limitations due to the lack of long term modelling. Probabilistic sensitivity analysis was not programmed into the model.

A second 2010 model was conducted for the original guideline comparing SPECT with ICA for people with a pre-test likelihood of 20-60%. This analysis had potentially serious limitations due to the lack of including all relevant comparators.

A 2007 cost-utility analysis by Hernandez et al. compared 4 strategies: ECG, SPECT then ICA; ECG then ICA; SPECT then ICA; and ICA. The first two strategies including ECG were excluded and results incrementally reanalysed for this update. The reanalysis found that CA was not cost effective with an ICER of £44,444 per QALY compared with SPECT+ICA for the 10.5% pre-test likelihood. ICA was cost effective for 30%, 50% and 85% pre-test likelihoods with ICERs well below £20,000 per QALY compared with SPECT+ICA. This analysis was

only partially applicable because costs and evidence on diagnostic accuracy are now different compared with when this analysis was carried out and there were many relevant comparators not in the analysis.

4.1.1.24 Economic modelling

De novo economic modelling was carried out for this review question. Please refer to appendix O for full details of this analysis. Economic modelling conducted for this update found that CTCA had the lowest cost per correct diagnosis for all levels of pre-test likelihood due to the low cost of the test, high sensitivity, and low probability of fatal and non-fatal complications. The addition of ECHO or CMR after positive CTCA results had the potential to be considered cost effective for lower levels of pre-test likelihood but the optimal strategy was unknown without a cost-effectiveness threshold for cost per correct diagnosis. The average costs per correct diagnosis for strategies of functional testing following CTCA (4, 5 and 6) were very close together for lower pre-test likelihoods, so one functional test could not be chosen above others with certainty. When a 70% stenosis threshold was used for sensitivity and specificity in a sensitivity analysis, the results were similar to the base case. The cost of CTCA had to triple before it ceased to be the least cost per correct diagnosis. When the cost of CMR was reduced, CTCA remained the lowest cost per correct diagnosis, but CTCA+ECHO was dominated. This analysis was directly applicable with potentially serious limitations because it was a short term model.

Table 6: Economic evidence profile, review question 1

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	Effect	ICER	
NICE 2016 1. ICA 2. CTCA 3. CTCA+ICA 4. CTCA+SPECT 5. CTCA+ECHO 6. CTCA+CMR 7. SPECT+ICA 8. ECHO+ICA 9. CMR+ICA 10. SPECT+CTCA 11. ECHO+CTCA 12. CMR+CTCA 13. CTCA-SPECT 14. CTCA-ECHO 15. CTCA-CMR 16. no testing (where '+' indicates 2nd test occurs after positive 1st test and '–' indicates 2nd test occurs after negative 1st test) United Kingdom	Directly applicable	Potentially serious limitations 1	Short term diagnostic decision tree 45% pre-test likelihood (see appendix O for full results): 16. no testing 2. CTCA 5. CTCA+ECHO 6. CTCA+CMR 1. ICA	- £122.49 £99.59 £88.00 £1,384.84	- 81.95% 9.09% 2.37% 5.77% (correct diagnoses)	- £149 £1,096 £3,707 £23,983 (per correctly diagnosis)	SA1: sensitivity and specificity based on 70% stenosis level: similar results SA2: Cost of CTCA: had to triple before it ceased to be the least cost per correct diagnosis SA3: Cost of CMR: strategy CTCA+CMR became more cost effective PSA: 100% likelihood that CTCA was the least cost per correct diagnosis at all pre-test likelihoods; cost-effectiveness acceptability curves and scatterplots provided
Genders et al.	Directly	Minor	Decision tree for short				The following parameters

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	Effect	ICER	
2015 No imaging ECHO CTCA +ECHO ECHO-i CTCA+SPECT-i CTCA +ECHO-i CTCA CTCA +CMR CTCA +SPECT-i CTCA +CMR-i CTCA -i SPECT SPECT-i CMR CMR-i CAG United Kingdom, The Netherlands, United States	applicable	limitations	term diagnostic outcomes and markov model for long term prognoses Results for men, 30% pre-test likelihood (see appendix N for full evidence tables): No imaging ECHO CTCA +ECHO CTCA +ECHO-i Results for women, 30% pre-test likelihood (see appendix N for full evidence tables): No imaging ECHO CTCA +ECHO ECHO-i CTCA +ECHO-i	- £1,140 £46 £90 - £1,157 £37 £19 £64	- 0.22 QALYs 001 QALYs 0.00 QALYs (rounding) - 0.23 QALYs 0.00 QALYs 0.00 QALYs 0.01 QALYs (rounding)	- £5,000/QALY £7,000/QALY £32,000/QALY - £5,000/QALY £7,000/QALY £8,000/QALY £53,000/QALY	were tested in one way sensitivity analysis: Pre-test likelihood of CAD (reported in full evidence tables) False negative results returned to physician in 3 years rather than 1: increased the cost effectiveness of CTCA No QALY reduction for false positives taking unnecessary medication: CTCA+ECHO became more favourable Probabilistic sensitivity analysis: credible intervals for all ICERs cross; otherwise pooly reported.
NCGC 2010a ECG, SPECT, ICA ECG, CTCA, ICA ECG, ICA SPECT, ICA CTCA, ICA ICA ECG, CTCA	Directly applicable	Potentially serious limitations 2	Decision tree for short term diagnostic outcomes Results for 20% pre-test likelihood: Ca+CTCA Ca+CTCA+ICA CTCA+ICA ICA	- £1,722.26 £882.99 £4,204.19	- 4.98% 1.73% 3.91% (correct diagnoses)	- £3,458 £5,104 £10,752 (per correct diagnosis)	No PSA The original Guideline Committee made the following determinations about what consistuted cost effective in the absence of a threshold for the following one way sensitivity analyses. Reducing the specificity of CTCA to 67% from 89%: At 5% CAD prevalence,

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	Effect	ICER	
CTCA CaScore, CTCA CaScore, CTCA, ICA United Kingdom							Ca+CTCA+ICA is still likely to be cost-effective although with a higher ICER than base case At 20% CAD prevalence, the ICER for Ca+CTCA+ICA compared with Ca+CT is lower than the base case because the number of correct diagnoses is higher At 40% CAD prevalence and above, the most cost-effective strategy is still sending all patients directly for invasive coronary angiography Increasing the calcium score threshold from >0 to >100, the sensitivity of calcium scoring decreases to 72% but the specificity increases to 81% Ca+CTCA remains the least cost option at all levels of CAD prevalence but Ca+CTCA+ICA is less cost effective compared to the base case. At 5% CAD prevalence, Ca+CTCA+ICA is still likely to be cost effective with an increased ICER of £2183 At 20% CAD prevalence, Ca+CTCA+ICA is ruled out due to extended dominance so CTCA+ICA is likely to be

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	Effect	ICER	
							the cost effective option with an ICER of $4764 compared with Ca+CTCA. At 40% CAD prevalence and greater, the strategy of sending all patients directly to ICA is still likely to be cost effective.
NCGC 2010b SPECT ICA United Kingdom	Partially applicable	Potentially serious limitations 3, 4	Decision tree for short term diagnostic outcomes	Not reported	Not reported	£21,549 per correct diagnosis (ICA vs. SPECT)	Not conducted
Hernandez et al. 2007 ECG, SPECT, ICA ECG, ICA SPECT, ICA ICA United Kingdom	Partially applicable 5	Potentially serious limitations 6	Decision tree for short term diagnostic outcomes followed by Markov model for long term consequences All results ICA vs. SPECT for 30% pre-test likelihood (full results in appendix N)	£329	0.042 QALYs	£7,833/QALY	Probabilistic sensitivity analysis was conducted. Interpretation of CEACs: At a CAD prevalence of 10.5%, SPECT-CA has a 90% likelihood of being the optimal strategy. At 30% CAD prevalence, SPECT-CA is most optimal up to a threshold of £20,000 per QALY when CA takes over. For higher levels of CAD prevalence and thresholds over £10,000 per QALY, coronary angiography is the optimal strategy.

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PSA: probabilistic sensitivity analysis
[1] *No long term modelling*
[2] *No long term modelling*
[3] *No long term modelling*

[4] *Only 2 comparators, excludes many relevant alternatives*
[5] *Costs and diagnostic accuracy now different to when the analysis was conducted*

4.1.21 Evidence statements

4.1.2.12 Clinical evidence statements

Evidence for the accuracy of different diagnostic tests (compared with the gold standard of invasive coronary angiography, ICA) was evaluated for two different diagnostic thresholds. No evidence meeting the review protocol inclusion criteria was found for CT FFR

Diagnosis of coronary artery disease - 50% stenosis threshold

High quality evidence was found for the following tests:

- CMR (wall motion analysis): a single study (172 patients) reported a sensitivity of 0.86 (95%CI 0.78 to 0.92) and a specificity of 0.86 (95%CI 0.75 to 0.93).

Moderate quality evidence was found for the following tests:

- Calcium scoring at a threshold level of 400 Hounsfield units: a meta-analysis of 2 studies (8,504 patients) had a pooled sensitivity of 0.54 (95%CI 0.52 to 0.57) and specificity of 0.88 (95%CI 0.87 to 0.88);
- Stress echocardiography (perfusion analysis): a meta-analysis of 3 studies (182 patients) had a pooled sensitivity of 0.84 (95%CI 0.76 to 0.90) and specificity of 0.79 (95%CI 0.69 to 0.86);
- Stress echocardiography (wall motion analysis) - using heart rate modification to induce stress: a meta-analysis of 8 studies (899 patients) had a pooled sensitivity of 0.76 (95%CI 0.72 to 0.79) and specificity of 0.80 (95%CI 0.71 to 0.88);
- CMR (perfusion analysis): a meta-analysis of 5 studies (331 patients) had a pooled sensitivity of 0.84 (95%CI 0.76 to 0.90) and specificity of 0.85 (95%CI 0.77 to 0.90).
- Combined CTCA and Myocardial perfusion scintigraphy: a single study (125 patients) reported a sensitivity of 0.94 (95%CI 0.84 to 0.99) and a specificity of 0.95 (95%CI 0.87 to 0.99)

Low quality evidence was found for the following tests:

- CT perfusion: a single study (90 patients) reported a sensitivity of 0.54 (95%CI 0.39 to 0.69) and specificity of 1.00 (95%CI 0.92 to 1.00).
- Combined CTCA and Myocardial perfusion scintigraphy: a single study (44 patients) reported a sensitivity of 0.91 (95%CI 0.71 to 0.99) and a specificity of 1.00 (95%CI 0.85 to 1.00)
- Combined CTCA and CT Perfusion: a single study (90 patients) reported a sensitivity of 0.83 (95% CI 0.70 to 0.93) and a specificity of 0.98 (95%CI 0.87 to 1.00)
- Combined Calcium scoring and Stress CMR: a single study (60 patients) reported a sensitivity of 0.89 (95%CI 0.74 to 0.97) and a specificity of 0.83 (95%CI 0.63 to 0.95)
- Combined Calcium Scoring and Myocardial Perfusion Scintigraphy (SPECT): a single study (77 patients) reported a sensitivity of 0.86 (95%CI 0.71 to 0.95) and a specificity of 0.86 (95%CI 0.70 to 0.95)
- Combined Stress Echo Perfusion and Wall motion: a single study (62 patients) reported a sensitivity of 0.85 (95%CI 0.71 to 0.94) and a specificity of 0.76 (95%CI 0.53 to 0.92)

Very low quality evidence was found for the following tests:

- CTCA: A meta-analysis of 25 studies (2,058 patients) had a pooled sensitivity of 0.96 (95%CI 0.94 to 0.97) and specificity of 0.79 (95%CI 0.72 to 0.84);
- Calcium scoring at a threshold level of 0 Hounsfield units: a meta-analysis of 2 studies (8,504 patients) had a pooled sensitivity of 0.99 (95%CI 0.97 to 0.99) and specificity of 0.49 (95%CI 0.36 to 0.63);
- Stress echocardiography (wall motion analysis) - using vasodilators to induce stress: a meta-analysis of 5 studies (422 patients) had a pooled sensitivity of 0.77 (95%CI 0.69 to 0.83) and specificity of 0.86 (95%CI 0.68 to 0.95);
- Myocardial perfusion scintigraphy (MPS - SPECT): a meta-analysis of 11 studies (923 patients) had a pooled sensitivity of 0.81 (95%CI 0.74 to 0.86) and specificity of 0.78 (95%CI 0.70 to 0.85).

Diagnosis of coronary artery disease - 70% stenosis threshold

Moderate quality evidence was found for the following tests:

- Calcium scoring at a threshold level of 0 Hounsfield units: a single study (8,274 patients) reported a sensitivity of 0.99 (95%CI 0.98 to 0.99) and specificity of 0.42 (95%CI 0.41 to 0.43);
- Calcium scoring at a threshold level of 400 Hounsfield units: a single study (8,274 patients) reported a sensitivity of 0.84 (95%CI 0.82 to 0.87) and specificity of 0.84 (95%CI 0.83 to 0.85).
- Combined CTCA and CT Perfusion: a single study (90 patients) reported a sensitivity of 0.95 (95%CI 0.82 to 0.99) and a specificity of 0.94 (95%CI 0.84 to 0.99)

Low quality evidence was found for the following tests:

- Sress echocardiography (perfusion analysis): a single study (62 patients) reported a sensitivity of 0.90 (95%CI 0.73 to 0.98) and specificity of 0.73 (95%CI 0.54 to 0.87);
- Myocardial perfusion scintigraphy (MPS - PET): a single study (44 patients) reported a sensitivity of 0.91 (95%CI 0.71 to 0.99) and a specificity of 0.86 (95%CI 0.65 to 0.97);
- CT perfusion: a single study of (90 patients) reported a sensitivity of 0.66 (95%CI 0.49 to 0.80) and specificity of 0.98 (95%CI 0.90 to 1.00).
- Combined Stress Echo Perfusion and Wall motion: a single study (62 patients) reported a sensitivity of 0.97 (95% CI 0.82 to 1.00) and a specificity of 0.64 (95%CI 0.45 to 0.80)

Very low quality evidence was found for the following tests:

- CTCA: a meta-analysis of 3 studies (371 patients) had a pooled sensitivity of 0.96 (95%CI 0.88 to 0.99) and specificity of 0.72 (95%CI 0.55 to 0.85);
- Stress echocardiography (wall motion analysis) - using vasodilators to induce stress: a meta-analysis of 7 studies (767 patients) had a pooled sensitivity of 0.64 (95%CI 0.49 to 0.76) and specificity of 0.90 (95%CI 0.86 to 0.93);
- Stress echocardiography (wall motion analysis) - using heart rate modification to induce stress: a meta-analysis of 4 studies (257 patients) had a pooled sensitivity of 0.75 (95%CI 0.62 to 0.85) and specificity of 0.88 (95%CI 0.79 to 0.93);
- CMR (perfusion analysis): a meta-analysis of 3 studies (204 patients) had a pooled sensitivity of 0.93 (95%CI 0.84 to 0.97) and specificity of 0.81 (95%CI 0.56 to 0.93);
- Myocardial perfusion scintigraphy (MPS – SPECT): a meta-analysis of 3 studies (145 patients) had a pooled sensitivity of 0.76 (95%CI 0.44 to 0.93) and specificity of 0.76 (95%CI 0.58 to 0.88).

4.1.2.21 Health economic evidence statements

Economic modelling conducted for this update found that CTCA had the lowest cost per correct diagnosis for all levels of pre-test likelihood due to the low cost of the test, high sensitivity, and low probability of fatal and non-fatal complications. This analysis was directly applicable with potentially serious limitations because it was a short term model.

A 2015 cost-utility analysis found that CTCA+ECHO was the optimal strategy for low pre-test likelihoods and ECHO was the optimal strategy for pre-test likelihoods greater than 50%. This analysis was directly applicable with minor limitations.

Cost-effectiveness analysis conducted for the original guideline found that strategies starting with CT calcium scoring and CTCA were likely to be cost effective for lower pre-test likelihoods and ICA was likely to be cost effective for higher pre-test likelihoods. This analysis was partially applicable with potentially serious limitations due to the lack of long term modelling.

A 2007 cost-utility analysis found that SPECT prior to ICA was likely to be cost effective for the lowest pre-test likelihood and ICA was likely to be cost effective for pre-test likelihoods greater than 30%. This analysis was partially applicable with potentially serious limitations due to the lack of relevant comparators.

4.1.3 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The committee agreed to use sensitivity and specificity (with 95% CIs) as primary measures of diagnostic accuracy. Further conditional measures such as positive predictive value (PPV) and negative predictive value (NPV) were not calculated since these are strongly affected by prevalence, and the body of evidence came from multiple countries worldwide with varying prevalence rates. Thus it was felt they would be of limited interpretability. The committee did not define a minimum acceptability threshold for either sensitivity or specificity for any test (see below comments under 'Benefits and Harms'). Prior to the committee meetings, the topic experts were asked to provide their thoughts on the desirable and undesirable consequences of diagnosis using tests with varying degrees of sensitivity and specificity. These are summarised below: • True positive (desirable) – a speedy and accurate diagnosis is achieved and early detection means treatment can be instigated and deterioration can be prevented. • True negative (desirable) – reassurance on the absence of disease, unnecessary treatment and testing is avoided. • False positive (undesirable) – creates unnecessary patient anxiety and exposes them to unnecessary treatments and testing and their associated risks. Can lead to patients making unnecessary lifestyle changes such as giving up work which could negatively impact quality of life. Wasted healthcare costs. • False negative (undesirable) – high risks to patients who receive no/insufficient treatment or further testing. May go on to have preventable cardiac events and/or die. Likely to have a higher reliance on NHS at a later date and additional costs associated with misdiagnosis.

	Committee discussions
	In terms of incorrect diagnoses, the committee were agreed that the consequences of a false negative result (possible cardiac event or death) were likely to be more serious for the patient and the healthcare system than a false positive result.
Quality of evidence	The committee noted that only three of the included studies were conducted in the UK; however the age range of patients across the included studies was that which would be expected of people presenting in the UK with stable chest pain of recent onset. In the majority of studies, the population as reported by the investigators did not directly match that specified in the review protocol (that is, people with chest pain of suspected cardiac origin). Study populations fell into four categories: • A: Population had suspected CAD, but there was no breakdown of numbers with chest pain, or the numbers with chest pain was less than 50%. • B: Population had suspected CAD and 50% or more had chest pain • C: All participants had suspected CAD and chest pain (combination of types e.g. typical angina, atypical angina, non cardiac) • D: All participants had suspected CAD and typical chest pain of suspected cardiac origin. The committee noted that concerns about population applicability were accounted for in the quality appraisal of individual studies. Examination of forest plots generated for each test showed no clear systematic differences in sensitivity or specificity estimates attributable to differences in population category. The topic experts noted that the study populations may be the same as that specified in the review protocol even if this is not specifically stated in the article. The committee were presented with a comparative plot of the meta-analyses of all four of the index tests that were prioritised for economic modelling (namely CTCA, Stress Echo, MPS-SPECT and CMR perfusion). The slides (included in Appendix J1.15, figs. 21 and 22) incorporated a visual breakdown of the relative distribution of the population categories contributing to each dataset. On reviewing this, the committee were satisfied that population differences were unlikely to account for differences in the comparative accuracy of diagnostic testing strategies. The topic experts had advised that it was important to consider evidence for both 50% and 70% stenosis diagnostic thresholds, as the former threshold may favour anatomical testing, while the latter is more likely to favour functional tests. The comparative plot of four meta-analyses showed that CTCA outperformed the other three tests when sensitivity was considered relative to 1 minus specificity at both the 50% and 70% stenosis thresholds. However, it was noted that there was significant imprecision in the results for all tests at the 70% threshold, due to small numbers of studies and sample sizes. At the 50% stenosis level, the committee noted that the evidence for CTCA and MPS-SPECT was very low quality, while that for Stress Echo and CMR

<table>
<tr><th></th><th>Committee discussions</th></tr>
<tr><td></td><td>perfusion was rated moderate overall. The committee noted that differences in evidence quality may relate as much to variation in study methods and reporting over time as to the value of the different tests, favouring newer techniques evaluated using more rigorous statistical standards.

The committee noted that the majority of studies MPS-SPECT and CTCA studies had recruited patients on the basis of referral for coronary angiography. The concern is that such patients are a higher prevalence population than if recruited as part of a wider inclusion strategy. This may lead to higher estimates of diagnostic accuracy than would be expected in clinical practice with an unselected population. The quality ratings for population applicability assigned to each dataset reflected these concerns.

There was also very significant inconsistency in the sensitivity data for MPS-SPECT and the specificity data for CTCA. The committee discussed why a small number of studies reported very low specificities in the CTCA dataset. Topic experts noted that there have been dramatic improvements over the past 10-15 years in the technology of CTCA and radiologists' skill in interpreting the images. However, no obvious relationship with publication date was observed that might account for the observed heterogeneity.

A sensitivity analysis was undertaken for the CTCA and MPS-SPECT meta-analyses to evaluate the impact of excluding studies with very serious risk of bias or applicability issues, but this made little difference to the estimated sensitivity or specificity for either index test (table 3).

Topic experts noted that the results for some diagnostic tests are more subjective than others, particularly CTCA and stress echocardiography, which require considerable expertise for interpretation. Furthermore, although invasive coronary angiography (ICA) is the agreed gold standard for diagnosis of coronary artery disease (CAD), it too involves a degree of subjectivity, and variations in expertise and methods of interpretation of the reference standard may be a source of heterogeneity in the meta-analyses.

Additional evidence from three test and treat RCTs was considered by the committee. While recognising the importance of searching for these study designs to ensure consistency with the review protocol, the committee felt that evidence from these trials could not be used to inform the development of the recommendations.. This is because none of the studies reported the diagnostic accuracy outcomes specified in the review protocol, and not all patients underwent the reference standard (invasive coronary angiography). The prognostic value of diagnostic tests is outside the remit of this guideline.</td></tr>
<tr><td>Trade-off between benefits and harms</td><td>The Topic Experts summarised the benefits and harms of each diagnostic test as follows:

<table>
<tr><td>Invasive Coronary Angiography</td><td>• Most expensive
• Highest risks (stroke, MI, death)
• Radiation exposure 4-6mSv
• Lengthy – takes 1.5hours
• Patients dislike due to side effects
• Renal failure and contrast allergy are complications</td></tr>
<tr><td>CTCA</td><td>• Widely available</td></tr>
</table>
</td></tr>
</table>

	Committee discussions
	<table><tr><td></td><td>• Involves insertion of a needle • Quick to perform (20 mins) • Radiation exposure of 2-5mSv • Renal failure and contrast allergy are complications</td></tr><tr><td>Calcium Scoring</td><td>• Radiation exposure of around 1-3mSv</td></tr><tr><td>Stress Echo</td><td>• No radiation exposure but risk associated with inducing stress (death: 1 in 10,000, ventricular arrhythmia or MI: 1 in 5000, asthma) • Widely available • Patients may not be suitable (e.g. people who are obese or who have chronic lung disease) • Results dependent on operator expertise</td></tr><tr><td>CMR</td><td>• Lengthy procedure (1hr) • Claustrophobia, metal implants, foreign bodies and renal failure are contraindications • Stress CMR not commonly available in UK hospitals • Risks associated with inducing stress (death, MI, asthma, bronchoconstriction, heart block)</td></tr><tr><td>SPECT</td><td>• Prone to artefacts but reporting reproducible. • Involves radiation exposure (2-10mSv. • Time consuming (3-4 hrs) • Widely available. • Almost no contraindications. • Risks associated with stress: death (1 in 10000), other risks dependent on type of stress induction.</td></tr><tr><td>PET</td><td>• Very few centres use this • Involves radiation exposure of around 3mSv.</td></tr></table> In the case of all tests involving radiation exposure, this should be considered in the context of patient age. Radiation exposure is reduced with with more modern machines and testing techniques. The method of inducing stress (as is the case for echocardiography, CMR and MPS SPECT) is important. Dobutamine is unpopular with patients as it has unpleasant side effects including a flushed feeling.
Trade-off between net health benefits and resource use	Four cost-effectiveness analyses were included in the economic systematic review. A 2015 cost-utility analysis found that CTCA+ECHO was the optimal strategy for low pre-test likelihoods and ECHO was the optimal

	Committee discussions
	strategy for pre-test likelihoods and ECHO was the optimal strategy for pre-test likelihoods greater than 50%. This analysis was directly applicable with minor limitations. Cost-effectiveness analysis conducted for the original guideline in 2008 found that strategies starting with CT calcium scoring and CTCA were likely to be cost effective for lower pre-test likelihoods and ICA was likely to be cost effective for higher pre-test likelihoods. This analysis was partially applicable with potentially serious limitations. A 2007 cost-utility analysis found that SPECT prior to ICA was likely to be cost effective for the lowest pre-test likelihood and ICA was likely to be cost effective for pre-test likelihoods greater than 30%. This analysis was partially applicable with potentially serious limitations. Economic modelling was conducted for review question 1 so that all relevant diagnostic strategies could be compared using the sensitivity and specificity calculated from the meta-analysis for each test in the clinical review. The economic modelling conducted for this update found that the testing strategy of CTCA only had the lowest cost per correct diagnosis for all population subgroups in both the base case and the sensitivity analysis based on a 70% stenosis threshold. The addition of functional testing following a positive CTCA result may be cost effective for lower pre-test likelihoods, but which specific functional test would be the most cost-effective could not be determined without a cost-effectiveness threshold. After noting that CTCA+SPECT was dominated in the 20% pre-test likelihood subpopulation and CTCA+SPECT and CTCA+ECHO were dominated in the 45% pre-test likelihood subpopulation, the committee discussed that it was difficult to clearly prefer one functional test over another after positive CTCA results because their average costs per correct diagnosis were so close together for lower pre-test likelihoods and slight changes in cost or diagnostic accuracy were likely to change whether these strategies dominate each other or not. Some committee members were concerned that the cost of CTCA may be too low and not reflect its true cost. Two comparisons were provided as to why the NHS reference cost was chosen as the base case. The 2015-16 tariffs for computerised tomography scan RA12Z, RA13Z, RA14Z and RA50Z range from £103 to £128 and therefore similar to the reference cost of £122.11. Secondly, a bottom-up microcosting was conducted for NICE diagnostics guidance 3 to establish the cost of 64-slice CT scanners and new generation CT scanners. Westwood et al. (2013) calculated a total cost per scan of £132.62, not substantially different to the NHS reference cost 2014-15 used in the base case. The second sensitivity analysis found that the cost of CTCA had to triple before it would not be considered the least cost per correct diagnosis. The committee noted that there is local variation in the cost of tests which will depend, amongst other factors, on the daily volume of the centre. The purpose of the analysis was to establish the average cost effectiveness on a national basis so nationally representative costs from the NHS reference costs or national tariff were the most appropriate to use in the model. The topic experts advised that in clinical practice the diagnosis of coronary artery disease is often not a binary outcome like it is in the economic model. For example, there will be varying degrees of atherosclerosis that may or may not be flow limiting.

	Committee discussions
	The committee discussed that the results reported in terms of cost per correct diagnosis assume the avoidance of false positives and false negatives are of equal value. Topic experts advised that false negatives are more important to avoid because, generally speaking, it is important to identify disease where it exists so that it can be appropriately treated. This was recognised as a limitation of the short term model and reporting results in terms of cost per correct diagnosis. Although it is difficult to quantify (and therefore not explicitly included in the form of long term modelling), these results should be interpreted within the context of the implications for false negatives and false positives. The potential implications for false negatives include remaining symptomatic with stable chest pain, returning for additional appointments with their GP or cardiologist, further testing with the same or alternative tests which may include ICA, and the costs involved for each of these elements. Due to the ongoing chest pain symptoms, most people with false negative results would be expected to be correctly diagnosed within 12 months although this may take 2 to 3 years. The potential implications and costs for people with false positive test results are varied. Some people will be treated with medication and, because their symptoms were due to a non-cardiac, transient cause, their chest pain alleviates and the medication is assumed to have worked. Therefore, even though they don't have disease, they continue on taking this medication for many years. It is unclear whether this would have negative or positive health effects because most people of this age group have some level of atheroma. In other words, although a person may not have clinically significant CAD, the medicine may have a protective effect, benefit to both health and costs. Alternatively, the medicines may cause side effects, and a cost to the NHS, that otherwise did not need to occur because they don't have disease. Some people treated with medication would continue to experience chest pain because it is caused by something other than CAD. This could be gastrointestinal reflux or a musculoskeletal problem, for example. Because their symptoms continue, they would usually be correctly diagnosed within the space of a year. This may be via an ICA, but not necessarily. In addition to the ICA or other test, people would incur the cost of additional GP and cardiologist visits. There would be a small proportion of people that would experience complications during the ICA or other test. There could also be further complications of whatever it is they do have but this canot be defined. Some people with false positive results would be sent for treatment with PCI or CABG. However, because ICA is always conducted prior to revascularisation, the only cost incurred would be the cost of an ICA, not the incorrect treatment with PCI or CABG. There would be a small proportion of people who experience complications during the ICA. The assumption of conditional independence may be a particular limitation of this model because the diagnosis based on functional testing after a positive CTCA result may be treated differently than after a negative CTCA result. For example, when functional testing is conducted following a positive CTCA result, the committee encountered difficulty in interpreting the importance of false negatives because they will not all strictly be false negatives: some people will have stenosis as identified by the CTCA but it may not be not flow limiting or ischaemic as identified by functional testing. The economic model for this update was compared with the studies included in the economic systematic review. The results were broadly in line with the modelling conducted for the original guideline in 2008 in terms of finding that CTCA has a low cost per correct diagnosis. This is despite some substantial differences in the models such as the 2008 model having

	Committee discussions
	a far lower sensitivity for CTCA, higher specificity for CTCA, and higher cost for CTCA. The 2008 model included SPECT but not ECHO or CMR. When compared with the 2015 model by Genders et al., the results were similar for men with a low (30%) pre-test likelihood of disease with CTCA+ECHO as the optimal strategy, but remainder of the subpopulations favoured ECHO. The modelling conducted for this update contained different inputs for ECHO which go some way to explaining the difference in results: lower sensitivity and specificity based on the most recent meta-analysis conducted for this update; and a higher cost of testing. Overall, the committee determined that the results of the economic model conducted for this update were consistent with the findings of the clinical review in terms of favouring CTCA as a first line test.
Other considerations	The committee noted that neither functional testing nor calcium scoring were used as singular testing strategies in the economic modelling on the advice of the topic experts. Functional testing provides an assessment of the haemodynamic consequences of obstructive CAD. However, the review protocol specifies that accuracy should be measured with reference to invasive coronary angiography (ICA), which is an anatomical imaging technique for identifying the location and degree of atherosclerosis. Clinically these are different pieces of the overall diagnostic 'jigsaw'. Anatomical tests can adequately diagnose presence of CAD, but do not give any information on the haemodynamic consequences of observed coronary artery stenosis. On the other hand, stress testing will give an accurate indication of the presence of flow-limiting CAD, but not all atherosclerosis will be flow-limiting. Furthermore, decisions about whether to treat observed coronary lesions medically or more aggressively with invasive techniques will usually require prior visualisation of the coronary anatomy. Topic experts also noted that calcium scoring would not be undertaken as a stand-alone diagnostic test, but may be performed at the same time as a CT coronary angiography to provide supplementary prognostic information to guide treatment decision-making. This is because the patient would already be in hospital with access to the CT scanner, and the additional time and cost to do a full CTCA is minimal. While there may be a very small risk of adverse reaction to contrast dye and a potential cancer risk associated with radiation exposure, these risks are regarded as minimal considering the wealth of additional diagnostic information yielded. This advice was the basis for updating one of the recommendations from the original guideline. In clinical practice, topic experts noted that diagnostic management and treatment decisions are not made in isolation of one another. However, they acknowledged that the remit of the review is restricted to the accurate and cost-effective diagnosis of the presence (or absence) of CAD and cannot consider the prognostic value of different testing strategies. After reviewing the clinical and economic evidence, the committee were agreed that the evidence strongly favoured recommending CTCA as the first line diagnostic strategy for all patients presenting with stable chest pain who have features characteristic of typical or atypical angina. This is because CTCA has greater overall accuracy compared with Stress echo, MPS-SPECT and CMR, is appropriate and well-tolerated by the majority of patients with relatively few potential risks, and has the lowest cost per correct diagnosis at all pre-test probability thresholds. The committee were confident that these advantages outweighed possible concerns associated

	Committee discussions
	with CTCA having lower quality evidence than was the case for some other tests included in the review. The committee discussed in what circumstances secondary testing might be indicated. Topic experts advised that where a CTCA scan shows 50-70% stenosis, or if parts of the cardiac arterial tree cannot be clearly evaluated and a definitive diagnosis made, additional functional testing should be considered. The committee noted that the evidence was unclear as to which type of functional test is most cost-effective following CTCA. Decisions regarding second-line functional testing should take account of availability, and patients' preferences and clinical suitability. The topic experts emphasised that Stress echo perfusion analysis is not commonly available in the UK. **Equalities considerations:** **Age** • During protocol development it was agreed that no sub-group reporting of diagnostic test accuracy would be carried out. As such, potential differences in DTA by age are not reported. • Age variation within included studies was discussed. The committee were satisfied that the ages of the study participants accurately represented the age of adults who might be presenting with first episodes of stable chest pain. • The topic experts advised that age was an important factor in the interpretation of calcium scoring (index test 3). However, as the committee decided that calcium scoring should not be recommended as a standalone testing strategy, this issue is not a concern. • There was no detail on age (or any other characteristics) of people who experienced serious adverse events (n=4) therefore it is not possible to evaluate the effect of age on the risk of serious adverse events. **Gender** • No studies that solely evaluated men or women were included. Some studies included a much higher proportion of men than women. As this reflects the demographic that disease is more prevalent in men than women, it was decided that there was no inequality in the evidence base in relation to gender. • One topic expert noted that women tend to describe symptoms differently to men which should be considered when assessing and classifying type of chest pain. **Ethnicity** • As stated above, no sub-group analyses were carried out according to ethnicity. This body of evidence includes studies from all over the world and only 3 studies from the UK. It represents a diverse range of ethnicities and nationalities. This body of evidence may thus not be representative of a UK population. . • In addition it was noted that many people seeking medical advice in the UK do not have English as a first language. In this group of patients, it can be harder to accurately establish clinical characteristics and symptom history. No population groups were excluded that would impact on equality.

	Committee discussions
	The committee also identified the following as important considerations: People with learning difficulties, conditions such as dementia and with communication impairments may also be misclassified due to the difficulties associated with determining medical history and symptoms. People who are over-weight or have a disability may be unable to access the MRI scanning machines and echocardiography may also be difficult to perform. CT often obtains poor quality images from people who are overweight. Recommendations in DG3 include reference to newer generation CT scanners for people who do not fit into standard scanners. People with disabilities, frailty or limited exercise ability that limit range of movement or manoeuvrability may not be able to undergo some diagnostic tests that involve inducing stress such as stress echocardiography or CMR. They may also require adaptions such as pharmaceutical stress instead of exercise stress tests. People with renal impairment or allergies to contrast material would be contraindicated for certain tests. People with claustrophobia or difficulty holding breath may be unable to undergo CMR. Pregnant women seldom present with stable chest pain but this would usually be managed medically and investigated after delivery. The exception would be if this became acute/unstable pain. There is known geographical variation in access to services and in turn, to diagnostic tests.

4.1.4 Recommendations

1. **Offer 64-slice (or above) CT coronary angiography if:**
   - clinical assessment (see recommendation 4) indicates typical or atypical angina chest pain, or
   - clinical assessment indicates non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves. **[new 2016]**

2. **Offer non-invasive functional imaging (see the section on non-invasive functional imaging for myocardial ischaemia) for myocardial ischaemia if 64-slice (or above) CT coronary angiography has shown CAD of uncertain functional significance or is nondiagnostic. [2016]**

4.1.5 Research recommendations

The committee did not make any research recommendations for this review question.

4.2 Review question 2

What is the accuracy, clinical utility and cost effectiveness of clinical prediction models/tools (clinical history, cardiovascular risk factors, physical examination) in evaluating people with stable chest pain of suspected cardiac origin?

4.2.1 Clinical evidence review

4.2.1.1 Methods

A systematic review of the literature search was conducted as specified in the review protocol (Appendix C). The protocol was developed in consultation with the topic experts and reviewed by the core committee members before the review was carried out. The following outcomes were considered important for decision making: area under the ROC curve (AUC, c-statistic, c-index), sensitivity and specificity.

A number of protocol refinements (see Appendix C) were made during the evidence review phase in consultation with the topic experts. The refinements were informed by the committee discussions on the diagnostic test accuracy question and were made to ensure that the evidence base was not restricted by study design nor based solely on higher prevalence populations, for example, those selected for invasive coronary angiography. To this end, we also included studies that used computed tomography coronary angiography (CTCA) as a reference standard to more closely reflect the population in whom pre-test probability scoring is most appropriate. We have presented the results in separate subgroups based on the reference standard used.

It was also agreed with the committee to restrict the literature search to studies published from 2009. This was because the previous guideline development group had reviewed evidence for clinical prediction of CAD and selected a model adapted from the Duke Clinical Score as the best available model for inclusion in NICE CG95 (2010). That model was developed in the USA in 1993 in a cohort of patients aged 30-70 years undergoing invasive coronary angiography for investigation of chest pain. Its applicability in a contemporary UK setting may be questionable, given changes in the distribution of coronary risk factors over the past 20 years. It was therefore felt important to focus the review on identifiying and evaluating the performance of different clinical prediction models which have been validated in recent studies published since the original guideline was developed. The reason for this decision is detailed in Appendix C. On this basis, a systematic search (see Appendix D) identified 7,985 articles. The titles and abstracts were screened and 48 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (Appendix C). Of these, 24 were excluded as they did not meet the criteria and 24 met the criteria and were included.

A review flowchart is provided in Appendix E and the excluded studies (with reasons for exclusion) are shown in Appendix F. Data from the included studies were extracted into standardised evidence tables.

4.2.1.21 Results

The 24 studies meeting the review inclusion criteria are summarised in Table 7. Extracted data for each study are presented in the evidence tables Appendix G.3. A total of 39 different prediction models were evaluated across these studies. Evidence synthesis and appraisal was restricted only to those validated models in common use (reported in 2 or more studies), or to novel models (single study reported with development and validation cohorts).

Table 8 summarises the 15 validated models included in the review in terms of the patient data required for their computation and the number of studies that evaluated the model. Some studies compared the performance of more than one model within the same patient cohort. Evidence for the predictive accuracy of each model was evaluated separately.

Table 7: Summary of included studies

Study reference (including study design)	Study population	Validated prediction models	Non-validated prediction models (included in evidence tables but not appraised in GRADE tables)	Reference standard for CAD diagnosis	Accuracy measures	Setting
Caselli 2015(a) Cross-sectional	N=429 Stable chest pain and intermediate probability of CAD	FRS	Bio-humoral Euro-SCORE	'CTA risk score' (based on CTCA images and calcium scoring)	AUC	14 European centres (part of EVINCI study), including UK
Caselli 2015(b) Cross-sectional	N=527 Stable chest pain and intermediate probability of CAD	Updated D-F (Genders) EVINCI model (integrated clinical + bio-humoral model)	Bio-humoral model 2	Functional testing (+ coronary angiography in subsample)	AUC Sensitivity and specificity	14 European centres (part of EVINCI study), including UK
Cetin 2014 Cross-sectional	N=407 Symptoms of CAD and / or abnormal stress test		$CHADS_2$ CHA_2DS_2-VASc CHA_2DS_2-VASc-HS score	Invasive coronary angiography (ICA)	AUC	Turkey (single centre)
Chen 2014 Cross-sectional	N=551 Exertional chest tightness / pain referred for elective ICA	Severe Predicting Score D-F		ICA	AUC	China (single centre)
Dharampal (2013) Cross-sectional	N=1,975 Stable chest pain or referred for ICA for suspected CAD		Clinical evaluation model Clinical evaluation model plus CT coronary calcium score	ICA (and/or CTCA)	AUC	The Netherlands (single centre)

Study reference (including study design)	Study population	Validated prediction models	Non-validated prediction models (included in evidence tables but not appraised in GRADE tables)	Reference standard for CAD diagnosis	Accuracy measures	Setting
Gaibazzi (2015) Cross-sectional	N=445 Chest pain or abnormal stress test referred for ICA	FRS Diagnostic Imaging in Coronary Artery Disease (DICAD) score	FRS + Echocardiographic calcium score (eCS) FRS + Carotid intima-media thickness (cIMT) FRS + Carotid plaques (cPL)	ICA	AUC	Italy (8 centres)
Genders (2010) Cross-sectional	N=254 Chest pain or abnormal functional test referred for ICA	D-F Duke Clinical Score (Pryor et al. 1993) Morise 1994 Morise 1997	D-F + CT calcium score (CTCS) Duke Clinical Score + CTCS Morise 1994 + CTCS Morise 1997 + CTCS	ICA	AUC	The Netherlands (single centre)
Genders (2011) Cross-sectional	N=2,260 Chest pain suggestive of CAD, referred for ICA	D-F Updated D-F (Genders)		ICA	AUC	10 countries (14 centres), including UK
Genders (2012) Cross-sectional	N=4,426 Stable chest pain referred for CTCA (97%) or ICA for suspected CAD	Duke Clinical Score Updated D-F (Genders) Clinical model (updated D-F + risk factors) Diagnostic Imaging in		ICA (or imputed data from CTCA)	AUC	11 countries (18 centres), including UK

Study reference (including study design)	Study population	Validated prediction models	Non-validated prediction models (included in evidence tables but not appraised in GRADE tables)	Reference standard for CAD diagnosis	Accuracy measures	Setting
		Coronary Artery Disease (DICAD) score				
Hong (2012) Cross-sectional	N=140 Women with chest pain referred for CTCA	Morise 1997 D-F		CTCA	AUC Sensitivity and specificity	USA (single centre)
Hwang (2012) Cross-sectional	N=252 Underwent CTCA for atypical or non-anginal chest pain	FRS		CTCA	AUC Sensitivity and specificity	Korea (single centre)
Jensen (2012) Cross-sectional	N=633 Referred for ICA with chest pain suggestive of CAD	D-F Updated D-F (Genders) Duke Clinical Score Morise 1997 CORSCORE		ICA	AUC	Denmark (single centre)
Kotecha (2010) Cross-sectional	N=539 Referred for ICA (76% with chest pain)	FRS SCORE – high risk regions	Conventional risk factors model (Risk) Conventional risk factors + hs-CRP and BNP (Risk+)	ICA	AUC	Australia (3 centres)
Kumamaru (2014)	N=3,996 Referred for CTCA with chest	Duke Clinical Score		CTCA / ICA	AUC	Japan (single centre)

Study reference (including study design)	Study population	Validated prediction models	Non-validated prediction models (included in evidence tables but not appraised in GRADE tables)	Reference standard for CAD diagnosis	Accuracy measures	Setting
Cross-sectional	pain suggestive of CAD					
Park (2011) Cross-sectional	N=138 Referred for ICA with stable chest pain or abnormal stress test; aged 30-75yrs	Age-adjusted FRS (AFRS)	AFRS + inverse-Flow-mediated dilation (iFMD; an ultrasound parameter) AFRS + Brachial ankle pulse wave velocity (baPWV) AFRS + baPWV + iFMD	ICA	AUC	Korea (single centre)
Pickett (2013) Cross-sectional	N=1,027 Referred for CTCA (75% with chest pain)	D-F Morise 1997		CTCA	AUC	USA (single centre)
Rademaker (2014) Cross-sectional	N=178 Women with chest pain referred for CTCA	D-F Duke Clinical Score Updated D-F (Genders) Morise 1997	Updated D-F + gestational diabetes + oestrogen status	CTCA	AUC	The Netherlands (single centre)
Rosenberg (2010) Cross-sectional	N=526 Referred for ICA with history of chest pain / anginal equivalent symptoms	D-F Combined D-F + Gene expression algorithm		ICA	AUC Sensitivity and specificity	USA (39 centres)

Study reference (including study design)	Study population	Validated prediction models	Non-validated prediction models (included in evidence tables but not appraised in GRADE tables)	Reference standard for CAD diagnosis	Accuracy measures	Setting
Schmilovich (2014) Cross-sectional	N=199 Referred for CTCA with chest pain	D-F	D-F + Diagonal earlobe crease (DELC)	CTCA	AUC Sensitivity and specificity	USA (single centre)
Versteylen (2011) Cross-sectional	N=1,296 Patients with chest pain who had CTCA	D-F FRS PROCAM risk score SCORE		CTCA	AUC	The Netherlands (one centre)
Wasfy (2012) Cross-sectional	N=114 Patients referred for CTCA with chest pain	D-F Duke Clinical Score		CTCA	AUC	USA (one centre)
Winther (2016) Cross-sectional	N=228 Referred for CTCA or ICA for suspected CAD (84% had typical or atypical chest pain)	Updated D-F (Genders)	D-F + CAD-score (acoustic measure) D-F + CAD score (acoustic measure) + coronary calcium score	ICA (and/or CTCA)	AUC	Denmark (single centre)
Yalcin (2012) Cross-sectional	N=350 Patients who had ICA (chest pain not reported)	FRS Modified FRS (MFRS) PROCAM SCORE - high-risk		ICA	AUC Sensitivity and specificity	Turkey (one centre)

Study reference (including study design)	Study population	Validated prediction models	Non-validated prediction models (included in evidence tables but not appraised in GRADE tables)	Reference standard for CAD diagnosis	Accuracy measures	Setting
		regions SCORE – low-risk regions				
Yang (2015) Cross-sectional	N=7,333 Referred for CTCA for suspected CAD (approximately 70% had typical or atypical chest pain)	Updated D-F (Genders) HRA score		CTCA	AUC	12 sites across 6 countries: USA, Canada, Korea, Austria, Italy, Switzerland, Germany.

CAD = coronary artery disease; FRS = Framingham Risk Score; CTCA = computed tomography coronary angiography; AUC = area under the curve; D-F = Diamond and Forrester model; ICA = invasive coronary angiography; HRA score =high risk anatomy score

Studies not in bold were excluded from evidence synthesis and appraisal because they either assessed the predictive accuracy only of a non-validated model(s) or because they used a threshold for diagnosing CAD which differed from that used in the majority of studies (≥50% stenosis in any major epicardial artery assessed using CTCA or ICA).

Table 8: Summary of validated probability models in the included studies

		Patient data required to assess CAD probability score								
CAD probability model (date published/ updated; development setting)	**No. of included studies in which model was used**	**Age**	**Sex**	**Chest pain symptoms / typicality**	**Smoking status**	**Family history of CAD**	**Diabetes**	**Hypertension / BP**	**Cholesterolaemia / blood lipids**	**Other variables**
Diamond-Forrester[1] (1979; USA)	11	✓ (30-69yrs)	✓	✓						
Framingham Risk Score[2] (2008; USA)	7	✓ (20-79yrs)	✓		✓		✓ (Version-specific)	✓	✓	
Duke Clinical Score[3] (1993; USA)	6	✓ (30-70yrs)	✓	✓	✓		✓		✓	• History of MI; • ECG
Updated D-F (Genders) (2011;10 countries inc. UK)[4]	6	✓	✓	✓						

		Patient data required to assess CAD probability score								
CAD probability model (date published/ updated; development setting)	**No. of included studies in which model was used**	**Age**	**Sex**	**Chest pain symptoms / typicality**	**Smoking status**	**Family history of CAD**	**Diabetes**	**Hypertension / BP**	**Cholesterolaemia / blood lipids**	**Other variables**
Morise[5] (1997; USA)	5	✓	✓	✓	✓	✓	✓	✓	✓	• Oestrogen status (women) • Obesity (BMI>27)
SCORE[6] (2012;12 European countries)	3	✓	✓		✓			✓	✓	
DICAD (2012; 11 countries inc. UK)[7]	2	✓	✓	✓	✓		✓	✓	✓	• BMI • CT coronary calcium score
PROCAM[8] (2002) Germany	2	✓ (35-65)	✓ (Male only)		✓		✓	✓	✓	• Family history of MI
Morise[9] (1994; USA)	1	✓	✓	✓			✓		✓	
CORSCORE (2012; Denmark)[10]	1	✓	✓	✓	✓			✓	✓	• History of MI

CAD probability model (date published/ updated; development setting)	No. of included studies in which model was used	Patient data required to assess CAD probability score								
		Age	Sex	Chest pain symptoms / typicality	Smoking status	Family history of CAD	Diabetes	Hypertension / BP	Cholesterolaemia / blood lipids	Other variables
SPS[11] (2014; China)	1	✓	✓				✓		✓	• AVC on echo • ECG
EVINCI[12] (2015; 14 European centres, including UK)	1	✓	✓	✓					✓	• AST • hs-CRP
Combined D-F + Gene expression algorithm[13] (2010; USA)	1	✓	✓	✓						• Blood-based test for expression values for 23 genes
HRA score[14] (2015; 6 countries across N. America, Europe & Asia)	1	✓	✓	✓	✓	✓	✓	✓	✓	• History of peripheral vascular disease
Updated D-F (Genders) + risk factors (2011; 10 countries inc. UK)[15]	1	✓	✓	✓	✓		✓	✓	✓	• BMI

✓= information required to compute patient's probability of CAD
Dark shading = variable not included in the prediction model

1. *D-F: Derived from symptomatic patients referred for ICA and autopsy studies; applicable to patients aged 30-69yrs; developed to predict CAD ≥50% stenosis (Diamond and Forrester, 1979)*
2. *FRS: Developed to estimate the 10-year risk of developing cardiovascular disease events; studies that used modified or age-adjusted versions are included (Wilson et al. 1998; D'Agostino et al. 2008)*
3. *Duke Clinical Score: Established and validated in symptomatic patients referred for ICA; developed to predict CAD ≥75% stenosis (Pryor et al. 1993)*
4. *Updated D-F: Developed in symptomatic patients referred for ICA or CTCA to update D-F for application in contemporary adult patient cohorts,(including >69 years (included study: Genders et al. 2011)*
5. *Morise 1997: updated version of Morise 1994, refining adjustment for gender in the original model.*
6. *SCORE: Developed to predict 10-year risk of fatal CVD in non-diabetic asymptomatic populations based on data from 12 European cohorts (Conroy et al. 2003; Perk et al. 2012)*
7. *Diagnostic Imaging in Coronary Artery Disease (DICAD): developed to examine the incremental diagnostic value of adding coronary calcium score to probability model based on risk factors (- included study: Genders 2012)*
8. *PROCAM: Developed for predicting 10-year risk of acute coronary events; based on cohort of mean aged 35-65 (Assmann et al. 2002)*
9. *Morise 1994: developed to predict probability of coronary artery disease, including diabetes and dyslipidaemia in addition to the variables used in D-F.*
10. *CORSCORE: a novel risk scoring system for predicting CAD (included study: Jensen 2012)*
11. *SPS: a novel risk scoring system to guide early invasive coronary angiography in angina patients using analysis of clinical risk factors, electrocardiography (ECG), and echocardiography (included study: Chen 2014)*
12. *EVINCI: developed to assess the incremental value of circulating biomarkers over the Genders model to predict functionally significant CAD(included study: Casselli 2015b)*
13. *Combined D-F and gene expression algorithm (included study: Rosenberg 2010).*
14. *HRA score: Developed to predict patients' pre-test probability of high-risk coronary anatomy (as opposed to obstructive CAD) using large, prospective international registry of patients referred for CTCA (- included study: Yang 2015)*
15. *Updated D-F (Genders) + risk factors model: developed to examine incremental diagnostic value of adding additional independent risk factors to the extended D-F mode (- included study: Genders 2012)*

4.2.1.3 Evidence synthesis and quality appraisal

Area under the curve (AUC)

The included studies all reported the area under the ROC curve (AUC) statistic for each model. A ROC curve plots the sensitivity of a model against its specificity across the full range of possible thresholds scores. Accuracy, in terms of being able to discriminate between cases and non-cases, is measured by the area under the ROC curve (AUC). An area of 1 represents a perfect prediction; an area of 0.5 represents a worthless prediction (equivalent to 'chance'). An area under the curve (AUC) value of 0.7 to 0.8 indicates acceptable model discrimination; values of 0.8 to 0.9 indicate excellent discrimination, and values greater than 0.9 indicate outstanding discrimination (Hosmer 2000). For the purpose of this review, we made the assumption that a model for predicting CAD in unselected patients with stable chest pain would have acceptable clinical utility if it had an AUC of 0.7 or above.

Where a model was examined in two or more studies, we have reported the individual AUC with 95%CIs reported by each study, and a summary median and range of AUCs for the study sample. Where a model was examined in a single study we have reported the AUC with 95%CIs.

Some studies also reported an overall sensitivity and specificity for a model, but it was not usually possible to verify these figures with reference to the relevant 2x2 data as it was not clear what threshold level had been used to dichotomise probability scores to indicate presence or absence of CAD. Therefore only AUC data were included in the evidence synthesis. These data are shown in the GRADE profiles in Appendix I.2.

CAD threshold

The most common threshold to define a diagnosis of obstructive CAD in the evidence base was ≥50% stenosis in any major epicardial coronary artery, as determined by invasive coronary angiography (ICA) or computed tomography coronary angiography (CTCA). Because CTCA may be considered a less robust diagnostic reference standard than ICA, evidence for the different probability models is presented separately according to the reference standard used (GRADE table I.2.1 for studies using ICA-based studies, GRADE table I.2.2 for CTCA-based studies).

Quality assessment

The QUADAS-2 quality assessment checklist for diagnostic studies was used to evaluate the quality of each included study, as recommended in the NICE guideline manual (2014). Because applicability to the review question varied between models depending on the variables included, and the likelihood of that information being available at a typical index clinic visit, QUADAS-2 ratings were applied on a model-by-model basis within studies.

The rating strategy used to derive a rating is shown in Table 4. An overall summary rating for each study of 'no serious', 'serious' or 'very serious' for both 'risk of bias' and 'applicability' was derived from the QUADAS-2 ratings for each domain as follows:

- No serious: 0 or 1 domain rated as 'unclear', no domains rated as 'high'.
- Serious: 2 domains rated as 'unclear' or 1 domain rated as 'high'.
- Very serious: 3 or more domains rated as unclear or 2 or more domains rated as 'high'.

The rationale for the ratings for each study can be found in the comments section of individual evidence tables (Appendix G.3). A summary individual study quality ratings for

each domain, and summary ratings for 'risk of bias' and 'applicability' are shown in Appendix H.2.

4.2.1.4 GRADE quality assessment

A GRADE quality assessment was carried out for each model applying a modification of the principles for assessing evidence on diagnostic test accuracy described by the GRADE working group (see: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3364356/). Evidence from cross sectional studies begins with a quality rating of high and is 'downgraded' to moderate, low or very-low quality according to serious or very serious sources of uncertainty in four domains: risk of bias, indirectness, inconsistency and imprecision. 'No serious', 'serious' or 'very serious' judgements were made in each domain as follows:

Risk of bias: Risk of bias was rated according to the most common summary rating (see Section 2.3.1.3) derived from the QUADAS 'risk of bias' elements for the studies contributing to the effect estimate.

Indirectness: Indirectness was rated according to the most common summary rating (see Section 2.3.1.3) derived from the QUADAS 'applicability' elements for the studies contributing to the effect estimate.

Inconsistency: As we did not statistically pool the reported AUC data, it was not possible to statistically assess the degree of heterogeneity of contributing studies. We have therefore set this as 'Not applicable' in the GRADE profiles.

Imprecision: The GRADE working group has not published criteria for assessing imprecision in relation to AUC statistics. For the current review, the AUC classification categories referred to above were used. Arbitrary minimal important difference levels of 0.7 and 0.8 were chosen for the assessment of imprecision, to be applied to the range of AUC scores reported across contributing studies (or to the 95% confidence interval where a model was evaluated by a single study).

- If AUC range (or 95% CIs around AUC for a single study) crossed one MID (0.7 or 0.8) – downgrade one level (serious imprecision)
- If AUC range (or 95% CIs around AUC for a single study) crossed both MIDs (0.7 and 0.8) – downgrade 2 levels (very serious imprecision).

For full GRADE profiles please see Appendix I.2.

An overall summary of findings for the five most evaluated probability models is presented in Appendix J.2.

4.2.2 Health economics evidence review

4.2.2.1 Methods

Evidence of cost effectiveness

The committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits rather than the total implementation cost.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought. The health economist undertook a systematic review of the published economic literature. Economic modelling was not prioritised for this review question.

Economic literature search

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to diagnostic strategies stable chest pain of suspected cardiac origin in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 2 June 2015. The health economic search strategies are detailed in appendix K.

The health economist also sought out relevant studies identified by the surveillance review or Committee members.

Economic literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts.

Inclusion and Exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the excluded economic studies table (appendix M).

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual 2014*.

4.2.2.2 Results of the economic literature review

1464 articles were identified in the search. 1464 of these were excluded based on title and abstract alone. 0 full text articles were obtained.

The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in appendix L.

4.2.2.3 Economic modelling

Economic modelling was not prioritised for this review question

4.2.31 Evidence statements

4.2.3.12 Clinical evidence statements

Invasive coronary angiography to diagnose CAD at 50% stenosis

Twelve cross-sectional studies evaluated 15 different prediction models. Accuracy of all the models that were validated in more than one study was in the AUC range 0.7 and 0.8 (indicating good overall discrimination between CAD and non-CAD)

Moderate quality evidence was found for the following prediction models:

- Genders (updated Diamond-Forrester) model: over 3 studies (5,287 patients) the median AUC was 0.77 (range: 0.71 to 0.79);
- Age-adjusted Framingham Risk Score: a single study reported an AUC of 0.86 (95%CI 0.80 to 0.93).

Low quality evidence was found for the following prediction models:

- Framingham Risk Score: over 3 studies (1,334 patients) the median AUC was 0.74 (range: 0.67 to 0.76);
- Modified Framingham Risk Score: a single study (350 patients) reported an AUC of 0.73 (95%CI 0.67 to 0.79)
- SCORE model: over 2 studies (889 patients) the median AUC was 0.70 (range: 0.65 to 0.75);
- PROCAM: a single study (350 patients) reported an AUC of 0.69 (95%CI 0.62 to 0.75);
- Morise 1994: a single study (254 patients) reported an AUC of 0.83 (95%CI 0.78 to 0.88)
- Genders model + risk factors ('Clinical model'): a single study (4,426 patients) reported an AUC of 0.79 (95%CI not reported)

Very low quality evidence was found for the following prediction models:

- Diamond-Forrester model: over 5 studies (3,473 patients) the median AUC was 0.73 (range: 0.64 to 0.81);
- Duke Clinical Score: over 2 studies (6,242 patients) the median AUC was 0.75 (range: 0.59 to 0.84);
- Morise 1997 model: over 2 studies (887 patients) the median AUC was 0.76 (range: 0.68 to 0.84);
- Diagnostic Imaging for CAD (DICAD) model: over 2 studies (4,871 patients) the median AUC was 0.78 (range 0.67 to 0.88);
- CORSCORE: a single study (633 patients) reported an AUC of 0.73 (95%CI not reported);
- Severe Predicting Score (SPS): a single study (204 patients) reported an AUC of 0.71 (95%CI not reported);
- Combined Diamond-Forrester plus gene algorithm score: a single study (525 patients) reported an AUC of 0.72 (95%CI 0.68 to 0.76).

Computed tomography coronary angiography to diagnose CAD at 50% stenosis

Eight cross-sectional studies evaluated 7 different prediction models. Accuracy of all the models that were validated in more than one study was in the AUC range 0.6 and 0.7 (indicating reasonable overall discrimination between CAD and non-CAD).

High quality evidence was found for the following prediction models:

- PROCAM: a single study (1,296 patients) reported an AUC of 0.64 (95%CI 0.61 to 0.78).

Moderate quality evidence was found for the following prediction models:

- Diamond-Forrester model: over 5 studies (2,800 patients) the median AUC was 0.61 (range 0.56 to 0.72);
- Framingham Risk Score: over 2 studies (1,548 patients) the median AUC was 0.69 (range: 0.68 to 0.71);
- SCORE: a single study (1,296 patients) reported an AUC of 0.64 (95%CI 0.61 to 0.68)

Low quality evidence was found for the following prediction models:

- Duke Clinical Score: over 2 studies (1,385 patients) the median AUC was 0.65 (range: 0.59 to 0.71);
- Genders (updated Diamond-Forrester) model: over 2 studies (632 patients) the median AUC was 0.69 (0.61 to 0.76);
- Morise 1997 model: over 3 studies (1,345 patients) the median AUC was 0.68 (range: 0.67 to 0.77)

4.2.3.27 Health economic evidence statements

No studies were included in the economic systematic review.

4.2.49 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The committee agreed that area under the ROC curve (AUC) was the best measure of the overall performance of the probability models, because it is an index of how well a model discriminates between a positive or negative diagnosis of coronary artery disease (CAD), as measured by the reference standard. The committee acknowledged that AUC was preferable to sensitivity and specificity reported for a single threshold score since the models in question are not intended to be used as diagnostic tests but for estimating diagnostic likelihood.
Quality of evidence	The committee agreed with the decision to evaluate accuracy at the threshold level of 50% stenosis (measured by ICA or CTCA), as reported in the majority of studies. Pre-test probability models are not primarily intended to estimate likelihood of more severe disease (≥70% stenosis). They also agreed with the decision not to pool AUC data given the small number of studies assessing the same model, lack of consistent reporting of 95% confidence intervals (required for meta-analysis) and differences in study population that may be a potential source of heterogeneity (for example, prevalence of CAD diagnosed by ICA, ranged from 34% to 80% in studies evaluating the original Diamond-Forrester model). They acknowledged that, while an imperfect summary measure, the median and range of AUCs reported for the most commonly validated models were all very similar across studies (see Appendix J.2). This indicated that the models all performed reasonably well (AUCs between 0.7 and 0.8) and with similar consistency in contemporary cohorts of patients with chest pain where ICA was used as the reference standard. The committee discussed the lower discriminatory performance of the same models in studies where CTCA was the reference standard (AUCs between

	Committee discussions
	0.6 and 0.7). These studies differ from the ICA studies not only in terms of the diagnostic reference standard used abut also the types of patients in which the models are applied (that is, a more diverse prevalence population). It is unclear whether these or other unmeasured differences are responsible for the variation in performance of the models. Evidence for relatively high AUCs reported for some less commonly validated models was discussed and discounted. This was because they were either based on single study data, so replication of findings could not be assessed (e.g. the AFRS and Morise 1994 model), or the model was not directly applicable to the review protocol because it requires information that would not be routinely available at the typical index clinic visit (e.g. the DICAD model incorporates CT calcium score data). External validity concerns, relating to the study populations in which models were tested, were accounted for in GRADE ratings of 'indirectness' (QUADAS concerns about population applicability were judged 'serious' if studies had recruited patients on the basis of referral for ICA, 'unclear' if recruited patients had all been referred for CTCA). However, the committee expressed concern about the external validity of the most commonly validated models themselves. Those specifically developed to predict CAD were all derived from high prevalence cohorts (that is, patients referred for invasive coronary angiography). This limits their generalisability to the unselected population of patients referred from primary care, in which the models are all likely to over-estimate true rates of prevalence. In support of this, a topic expert cited a study by Cheng et al. (2011) which found that the original Diamond-Forrester model significantly over-estimated actual prevalence of CAD in an international multicentre register of patients referred for CTCA across all three categories of chest pain type (typical, atypical and non-anginal chest pain), and all sex and age subgroups.
Trade-off between benefits and harms	A pre-test probability model has clinical utility if it identifies subgroups in whom the need for further testing can be discounted; that is, when a diagnosis of CAD can be accurately ruled out (<10% probability) or ruled in (>90% probability) on the basis of clinical assessment alone. Where there is diagnostic uncertainty (probabilities between 10-90%), and testing strategies are known to be differentially cost-effective at different levels of risk, an accurate model provides a useful means for stratifying patients to ensure appropriate testing. The committee identified potential negative consequences of using a model that systematically over-estimates the probability of CAD relative to its true prevalence. Decisions about further testing based on inflated estimates may result in too many patients undergoing unnecessary tests and in overuse of more aggressive testing than is clinically warranted.
Trade-off between net health benefits and resource use	No studies were included in the economic systematic review. The cost difference between clinical prediction tools is thought to be minimal because they all involve a few simple questions based on readily available information from the patient.
Other considerations	The committee reviewed a table of probability data generated using the updated Diamond-Forrester model developed by Genders et al. (2011), as published in the European Cardiology Society guidelines (The Task Force on the management of stable coronary artery disease of the European Society of Cardiology, 2013) – see Table 9 below.

Committee discussions

Table 9: The probability of coronary artery disease in differing categories of chest pain (adapted from Genders 2011, published with author's permission by The Task Force on the management of stable coronary artery disease in the European Society of Cardiology guidelines 2013).

	Non-anginal pain		Atypical angina		Typical angina	
Age	Men	Women	Men	Women	Men	Women
30-39	18	5	29	10	59	28
40-49	25	8	38	14	69	37
50-59	34	12	49	20	77	47
60-69	44	17	59	28	84	58
70-79	54	24	69	37	89	68
≥80	65	32	78	47	93	76

It was agreed that the Genders model showed an overall good level of discrimination in the review of evidence (median 0.77), performing relatively consistently across 3 recent studies (range: 0.71 to 0.79). The committee acknowledged that the model is likely to provide more realistic probability estimates than the one currently recommended in CG95 because:

- it was derived using sophisticated logistic regression techniques in a large contemporary multicentre cohort which included UK patients;
- it extends the age range to include probability estimates for patients over 70 years of age.

However, the Committee considered it unnecessary and potentially confusing to include the Genders probability table in the amended guideline in the same way that a table of pre-test probabilities was included in CG95 for the following reasons:

- the data table shows that the only age and sex subgroups with a probability <10% (indicated in green in table 9) are patients with non-anginal chest pain features in whom further diagnostic testing would not be routinely undertaken;
- in patients with typical or atypical chest pain features, only one subgroup (men with typical angina over the age of 80) has a pre-test probability >90% (indicated in red in table 9);

	Committee discussions
	• all other age and sex subgroups for all chest pain types fall within the 'uncertain' (10-90%) range, so would all be appropriate for further diagnostic testing; • the evidence for review question 1 (see section 2.2.5) strongly favoured CTCA as the first line testing strategy for all patients with 10-90% probability of CAD, negating the need for low / intermediate / high risk pre-test stratification. The committee agreed that it would not be necessary to make a separate recommendation for no further testing in male patients with typical angina over 80 years of age. This is because the Genders model is likely to over-estimate probabilities of CAD across all patient subgroups for the reasons noted above. True prevalence in this subgroup will therefore be lower than the 93% noted in the data table and so CTCA should be performed to establish a definitive diagnosis. The committee discussed the diagnostic management of patients younger than 30 years of age (outside the lower age range included in the pre-test probability studies reviewed). Topic experts noted that there is a risk in clinical practice of over-investigating younger patients with stitch-like pain brought on by exercise and relieved by rest (technically 'atypical angina', according to the accepted definition). However, it was acknowledged that a recommendation specifically relating to younger patients could not be made as no evidence was available for review. The topic experts were keen to clarify in the updated recommendations that patients with non-anginal chest pain on clinical assessment should not be investigated routinely for CAD regardless of pre-test probability, unless there are indications to suggest the chest pain may in fact be of cardiac origin. Currently this information is noted only in small print beneath the probability table included in CG95 and covers information on resting ECG ST-T changes or Q waves. As the committee are recommending deletion of this table with no replacement data table, a clear recommendation is required or this accompanying guidance would also be removed. The committee deliberated on this. The topic experts advised that, in their experience, resting ECG ST-T changes or Q waves would warrant further testing in people assessed as having non-anginal chest pain, with CTCA as the first line strategy. The resulting recommendation (see recommendation 15 listed in section 4.2.5) may therefore be considered consensus-based rather than evidence-based. However, it clarifies advice included in the original guideline and reflects accepted clinical practice. The committee considered the impact of basing a diagnostic testing strategy on the description of the pain and the implications for those who have poor language or communication skills as well as non-English speakers or communication disorders but considered that the current recommendations (rec 1.1.1.6) would cover these situations. The committee concluded that diagnostic testing for all patients assessed as having typical or atypical angina should be offered. This was because the best available contemporary evidence (from Genders et al. 2011), taking into account limitations in external validity of the model, suggests that all patients in these two chest pain categories will have probabilities of CAD in the 10-90% range.

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4.2.5 Recommendations

People presenting with stable chest pain

1. Diagnose or exclude stable angina based on:

- clinical assessment alone **or**
- clinical assessment plus diagnostic testing (that is, anatomical testing for obstructive CAD or functional testing for myocardial ischaemia or both). **[2016]**

Clinical assessment

2. Take a detailed clinical history documenting:

- the age and sex of the person
- the characteristics of the pain, including its location, radiation, severity, duration and frequency, and factors that provoke and relieve the pain
- any associated symptoms, such as breathlessness
- any history of angina, MI, coronary revascularisation, or other cardiovascular disease and
- any cardiovascular risk factors. **[2010]**

3. Carry out a physical examination to:

- identify risk factors for cardiovascular disease
- identify signs of other cardiovascular disease
- identify non-coronary causes of angina (for example, severe aortic stenosis, cardiomyopathy) **and**
- exclude other causes of chest pain. **[2010]**

Making a diagnosis based on clinical assessment

4. Assess the typicality of chest pain as follows:

- Presence of three of the features below is defined as typical angina.
- Presence of two of the three features below is defined as atypical angina.
- Presence of one or none of the features below is defined as non-anginal chest pain.

Anginal pain is:

- constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms
- precipitated by physical exertion
- relieved by rest or GTN within about 5 minutes. **[2010, amended 2016]**

5. Do not define typical and atypical features of anginal chest pain and non-anginal chest pain differently in men and women. [2010]

6. Do not define typical and atypical features of anginal chest pain and non-anginal chest pain differently in ethnic groups. [2010]

7. **Take the following factors, which make a diagnosis of stable angina more likely, into account when estimating people's likelihood of angina:**
    - age
    - whether the person is male
    - cardiovascular risk factors including:
        - a history of smoking
        - diabetes
        - hypertension
        - dyslipidaemia
        - family history of premature CAD
        - other cardiovascular disease
    - history of established CAD, for example, previous MI, coronary revascularisation. **[2010]**

8. **Unless clinical suspicion is raised based on other aspects of the history and risk factors, exclude a diagnosis of stable angina if the pain is non-anginal (see recommendation 4). Features which make a diagnosis of stable angina unlikely are when the chest pain is:**
    - continuous or very prolonged and/or
    - unrelated to activity and/or
    - brought on by breathing in and/or
    - associated with symptoms such as dizziness, palpitations, tingling or difficulty swallowing.

    Consider causes of chest pain other than angina (such as gastrointestinal or musculoskeletal pain). **[2010, amended 2016]**

9. **Consider investigating other causes of angina, such as hypertrophic cardiomyopathy, in people with typical angina-like chest pain and a low likelihood of CAD. [2010, amended 2016]**

10. **Arrange blood tests to identify conditions which exacerbate angina, such as anaemia, for all people being investigated for stable angina. [2010]**

11. **Only consider chest X-ray if other diagnoses, such as a lung tumour, are suspected. [2010]**

12. **If a diagnosis of stable angina has been excluded at any point in the care pathway, but people have risk factors for cardiovascular disease, follow the appropriate guidance, for example the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification and the NICE guideline on hypertension in adults: diagnosis and management [2010]**

13. **For people in whom stable angina cannot be diagnosed or excluded on the basis of the clinical assessment alone, take a resting 12-lead ECG as soon as possible after presentation. [2010]**

14. **Do not rule out a diagnosis of stable angina on the basis of a normal resting 12-lead ECG. [2010]**

15. **Do not offer diagnostic testing to people with non-anginal chest pain on clinical assessment (see recommendation 4) unless there are resting ECG ST-T changes or Q waves. [new 2016]**

16. **A number of changes on a resting 12-lead ECG are consistent with CAD and may indicate ischaemia or previous infarction. These include:**
    - pathological Q waves in particular
    - LBBB
    - ST-segment and T wave abnormalities (for example, flattening or inversion).

    Note that the results may not be conclusive.

    Consider any resting 12-lead ECG changes together with people's clinical history and risk factors. **[2010]**

17. **For people with confirmed CAD (for example, previous MI, revascularisation, previous angiography) in whom stable angina cannot be diagnosed or excluded based on clinical assessment alone, see recommendation 1.3.4.8 about functional testing. [2010]**

18. **Consider aspirin only if the person's chest pain is likely to be stable angina, until a diagnosis is made. Do not offer additional aspirin if there is clear evidence that people are already taking aspirin regularly or are allergic to it. [2010]**

19. **Follow local protocols for stable angina while waiting for the results of investigations if symptoms are typical of stable angina. [2010]**

Diagnostic testing for people in whom stable angina cannot be diagnosed or excluded by clinical assessment alone

20. **Include the typicality of anginal pain features (see recommendation 4) in all requests for diagnostic investigations and in the person's notes. [2010, amended 2016]**

21. **Use clinical judgement and take into account people's preferences and comorbidities when considering diagnostic testing. [2010]**

22. **For people with confirmed CAD (for example, previous MI, revascularisation, previous angiography), offer non-invasive functional testing when there is uncertainty about whether chest pain is caused by myocardial ischaemia. See the section on non-invasive functional imaging for myocardial ischaemia for further guidance on non-invasive functional testing. An exercise ECG may be used instead of functional imaging [2010]**

Additional diagnostic investigations

23. **Offer invasive coronary angiography as a second-line investigation when the results of non-invasive functional imaging are inconclusive. [2016]**

Use of non-invasive functional testing for myocardial ischaemia

24. When offering non-invasive functional imaging for myocardial ischaemia use:

- myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT) or
- stress echocardiography or
- first-pass contrast-enhanced magnetic resonance (MR) perfusion or
- MR imaging for stress-induced wall motion abnormalities.

Take account of locally available technology and expertise, the person and their preferences, and any contraindications (for example, disabilities, frailty, limited ability to exercise) when deciding on the imaging method. [This recommendation updates and replaces recommendation 1.1 of Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction (NICE technology appraisal guidance 73)]. **[2016]**

25. Use adenosine, dipyridamole or dobutamine as stress agents for MPS with SPECT and adenosine or dipyridamole for first-pass contrast-enhanced MR perfusion. [2010]

26. Use exercise or dobutamine for stress echocardiography or MR imaging for stress-induced wall motion abnormalities. [2010]

27. Do not use MR coronary angiography for diagnosing stable angina. [2010]

28. Do not use exercise ECG to diagnose or exclude stable angina for people without known CAD. [2010]

Making a diagnosis following investigations

Box 1 Definition of significant coronary artery disease

Significant coronary artery disease (CAD) found during CT coronary angiography is ≥ 70% diameter stenosis of at least one major epicardial artery segment or ≥ 50% diameter stenosis in the left main coronary artery:

Factors intensifying ischaemia

Such factors allow less severe lesions (for example ≥ 50%) to produce angina:

- Reduced oxygen delivery: anaemia, coronary spasm
- Increased oxygen demand: tachycardia, left ventricular hypertrophy
- Large mass of ischaemic myocardium: proximally located lesions
- Longer lesion length.

Factors reducing ischaemia which may render severe lesions (≥ 70%) asymptomatic

- Well-developed collateral supply
- Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply. **[2016]**

29. Confirm a diagnosis of stable angina and follow local guidelines for angina[b] when:

- significant CAD (see box 1) is found during invasive or 64-slice (or above) CT coronary angiography, **or**
- reversible myocardial ischaemia is found during non-invasive functional imaging. **[2016]**

30. Investigate other causes of chest pain when:

- significant CAD (see box 1) is not found during invasive coronary angiography or 64-slice (or above) CT coronary angiography, **or**
- reversible myocardial ischaemia is not found during non-invasive functional imaging **[2016]**

31. Consider investigating other causes of angina, such as hypertrophic cardiomyopathy or syndrome X, in people with typical angina-like chest pain if investigation excludes flow-limiting disease in the epicardial coronary arteries. [2010]

4.2.6 Research recommendations

The committee did not make any research recommendations for this review question.

[b] Stable angina. NICE guideline CG126 (2011).

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6 Glossary and abbreviations

Please refer to the NICE glossary.

Additional terms used in this document are listed below.

Table 10: Glossary

Term	Description
Acute myocardial infarction	A life-threatening condition that occurs when blood flow to the heart is abruptly cut off, usually as a result of blockage of one or more coronary arteries, causing tissue damage. The Universal definition of the Joint ESC/ACCF/AHA/WHF Task Force is used in this guideline. (Thygesen, K., Alpert, J. S., and White, H. D., 2007). When there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia, any one of the following criteria meets the diagnosis for myocardial infarction in patients presenting with acute chest pain or discomfort: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following: • Symptoms of ischaemia • ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block (LBBB) • Development of pathological Q waves in the ECG • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Angina Pectoris	A heart condition that occurs when the blood supply to the muscles of the heart is restricted, usually due to coronary artery disease.
Atherosclerosis	A build up of plaque on the inside of blood vessels.
Cardiovascular event	An acute coronary, cerebrovascular or peripheral arterial event.
Cardiovascular risk	The risk of a cardiovascular event occurring.
Clinical classification	A method of allocating patients into different groups based on clinical characteristics.
Clinical risk stratification	A method of allocating patients to different levels of risk of them suffering an adverse event, based on their clinical characteristics.
Computed tomography (CT)	Type of scan using special x-ray equipment that allows the creation of detailed images.
Computed tomography (CT) perfusion	Evaluation of blood flow to the myocardium using CT imaging.
Coronary angiography	An invasive diagnostic test which provides

Term	Description
	anatomical information about the degree of stenosis (narrowing) in a coronary artery. It involves manipulation of cardiac catheters from an artery in the arm or top of the leg. A contrast medium is injected into the coronary arteries, and the flow of contrast in the artery is monitored by taking a rapid series of X-rays. It is considered the 'gold standard' for providing anatomical information and defining the site and severity of coronary artery lesions (narrowing's).
Coronary artery	An artery which supplies the myocardium (heart muscle).
Coronary artery disease	Coronary artery disease is a condition in which atheromatous plaque builds up inside the coronary artery. This leads to narrowing of the arteries which may be sufficient to restrict blood flow and cause myocardial ischaemia.
Calcium scoring	Calcium scoring is a technique by which the extent of calcification in the coronary arteries is measured and scored.
Cardiac Magnetic Resonance (CMR)	See MRI
Cost-benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment as a net gain results.
Cost-consequences analysis	A type of economic evaluation where various health outcomes are reported in addition to the costs for each intervention under consideration. There is however no formal synthesis of the costs and health effects.
Cost-effectiveness acceptability curve (CEAC)	A CEAC plots the probability of an intervention being cost-effective compared with alternative intervention(s), for a range of maximum monetary values, that decision-makers might be willing to pay, for a particular unit change in outcome.
Cost-effectiveness analysis	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of incremental costs per unit of effectiveness.
Cost-minimisation analysis	An economic evaluation that finds the least costly alternative therapy. This type of analysis implicitly assumes that the health benefits of the competing interventions are equivalent.
Cost-utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Discounting	Discounting is the process by which economist make allowances for society's time preference for costs and benefits. All else being equal, society places a higher value on the same unit

Term	Description
	of cost and benefit today than it does for the same unit in the future. For example, society prefers to receive £100 today as opposed to £100 in n years time. The differential is expressed in terms of the discount factor DF, where DF = 1/ (1+ r)n and where r is the discount rate, and n is the number of years forward from the current year.
Dominance	A heath intervention is said to be dominant if it is both more effective and less costly than an alternative intervention.
EBCT	Electron Beam Computed Tomography.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Electrocardiogram (ECG)	An ECG records the rhythm and electrical activity of the heart. A number of electrodes (small sticky patches) are placed on limbs and chest and are connected to a machine that records the electrical signals of each heartbeat.
Equivocal	Where a diagnostic test result is indeterminate because it can be interpreted in one of 2 or more ways.
Exercise ECG (sometimes known as an exercise test or stress ECG)	An investigation which measures the electrical activity from the heart during exercise, usually used to look for signs of myocardial ischaemia.
Extended dominance	Where a combination of two alternative strategies dominates a third.
Evidence statements	A summary of the evidence distilled from a review of the available clinical literature.
Evidence-based questions (EBQs)	Questions which are based on a conscientious, explicit and judicious use of current best evidence.
Functional flow reserve (FFR)	A test that measures differences in pressure behind and after stenosis of a blood vessel.
Health Economic Model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporates evidence from a variety of sources in order to estimate costs and health outcomes.
Health economics	The branch of economics concerned with the allocation of society's scarce health resources, between alternative healthcare treatments/programmes, in an attempt to improve the health of the population.
Health related quality of life	An attempt to summarise an individual's or the population's quality of life resulting from the combined effect of their physical, mental, and social well-being.
Haemodynamic instability	A clinical state of perfusion failure with clinical features of circulatory shock and or severe heart failure, and requiring pharmacological or mechanical support to maintain normal blood

Term	Description
	pressure and or adequate cardiac output. It may also be used to describe a clinical state when one or more physiological measurements, for example blood pressure and or pulse, are outside the normal range.
Incremental cost-effectiveness ratio (ICER)	The difference in the costs of two alternative treatment strategies/programmes, divided by the difference in the effectiveness outcomes of the treatment strategies/programmes for a defined population of interest. That is; Cost treatment B – Cost treatment A_____ Effectiveness treatment B - Effectiveness treatment B
Ischemia	Insufficient blood supply
Life years	The number of years lived by an individual or a population. For example, if a population of 50 patients live for an average addition 2 years each as the result of receiving a healthcare intervention, then the intervention has provided 100 life years gained.
Magnetic Resonance Imaging (MRI)	MRI is a diagnostic procedure that uses radio waves in a strong magnetic field. The pattern of electromagnetic energy released is detected and analysed by a computer to generate detailed images of the heart.
Meta regression analysis	An approach for aggregating data from different clinical trials which examine the same question and report the same outcomes, and relating sources of variation in treatment effects to specific study characteristics.
Multiple logistic regression analysis	In a clinical study, an approach to examine which variables independently explain an outcome.
Multislice CT coronary angiography	Multi-slice CT coronary angiography is a non-invasive investigation which provides coronary calcium scoring and anatomical information about the degree of stenosis (narrowing) in the coronary arteries. The scanner has a special X-ray tube and rotation speed and as the technology has advanced the number of slices in each rotation has increased. A dual source scanner has two pairs of X-ray sources and multi-slice detectors mounted at 90 degrees to each other.
Myocardial infarction	See Acute Myocardial Infarction.
Myocardial perfusion scintigraphy with SPECT (MPS)	MPS involves injecting small amounts of radioactive tracer to evaluate perfusion of the myocardium via the coronary arteries at stress and at rest. The distribution of the radioactive tracer is imaged using a gamma camera. In SPECT the camera rotates round the patient and the raw data processed to obtain tomographic images of the myocardium. Cardiovascular stress may be induced by either pharmacological agents or exercise.

Term	Description
Myocardial perfusion imaging	Evaluation of perfusion (blood flow) to the myocardium.
Opportunity cost	The cost in terms of health benefits foregone by allocating resources to one intervention over an alternative intervention. The definition implicitly acknowledges the concept of scarcity of healthcare resources.
Positron emission tomography (PET)	A nuclear test that involves the evaluation of organ functions using a special type of camera that detects radioactive tracers.
Probabilistic sensitivity analysis (PSA)	The process of measuring the degree of uncertainty around outcomes in an economic evaluation by assigning probability distributions to all of the key parameters in the evaluation, and then simultaneously generating values from each of these distributions using techniques of random number generation such as Monte Carlo methods.
Quality adjusted life year (QALY)	An index of survival weighted to account for quality of life. The year of life is weighted by a utility value U (where 0 ≤ U ≤ 1). U reflects the health related quality of life, such that a U of zero represents the worst possible quality of life (equivalent to being dead), and a U of 1 represents perfect health. For example, 1 QALY is achieved if one patient lives in perfect health for one year, or alternatively if 2 people live in perfect health for 6 months each. Alternatively, a person living with a quality of life represented by a U value of 0.5 for 2 years is also representative of 1 QALY value. QALYs have the advantage of incorporating changes in both quantity (longevity/survival) and quality of life (morbidity as represented by psychological, physical and social functioning for example). QALYs are core to cost-utility analysis where the QALY is used as the measure of effectiveness in the economic evaluation.
Sensitivity	Sensitivity is the proportion of people with the disease who have a positive test. Sensitivity reflects how good the test is at identifying people with the disease. A measure of the diagnostic accuracy in including individuals with the condition. Number of True Positives divided by (Number of True Positives + Number of False Negatives) □ True positive: People correctly diagnosed with the condition □ False positive: Healthy people wrongly diagnosed with the condition □ True negative: Healthy people correctly identified as healthy □ False negative: People wrongly identified as healthy
Sensitivity analysis	A means of exploring the uncertainty in the results of an economic evaluation/model by varying the parameter values of the included

Term	Description
	variables one at a time (univariate sensitivity analysis) or simultaneously (multi-variate sensitivity analysis).
Significant coronary artery disease	Significant CAD found during invasive coronary angiography is ≥ 70% diameter stenosis of at least one major epicardial artery segment or 50% ≥ diameter stenosis in the left main coronary artery a). Factors intensifying ischaemia. Such factors allow less severe lesions (say ≥ 50%) to produce angina Reduced oxygen delivery: anaemia, coronary spasm Increased oxygen demand: tachycardia, left ventricular hypertrophy Large mass of ischaemic myocardium: proximally located lesions and longer lesion length b). Factors reducing ischaemia. Such factors may render severe lesions (≥ 70%) asymptomatic Well developed collateral supply Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply. c). Angina without epicardial coronary artery disease. When angina occurs in patients with angiographically “normal” coronary arteries (syndrome X) pathophysiological mechanisms are often unclear.
Specialist	A healthcare professional who has expert knowledge of and skills in a particular clinical area, especially one who is certified by a higher medical educational organization.
Specificity	Specificity is the proportion of people free of disease who have a negative test. Specificity reflects how good the test is at identifying people without the disease. A measure of the diagnostic accuracy in excluding individuals without the condition. Number of True Negatives divided by (Number of True Negatives + Number of False Positives) True positive: People correctly diagnosed with the condition False positive: Healthy people wrongly diagnosed with the condition True negative: Healthy people correctly identified as healthy False negative: People wrongly identified as healthy
Stable angina	Unlike acute coronary syndromes, there are no case definitions of stable angina that have been agreed internationally. Working definition angina is a symptom of myocardial ischaemia that is recognized clinically by its character, its location and its

Term	Description
	relation to provocative stimuli. Relation to coronary artery disease: Angina is usually caused by obstructive coronary artery disease that is sufficiently severe to restrict oxygen delivery to the cardiac myocytes. Generally speaking angiographic luminal obstruction estimated at ≥70% is regarded as "severe" and likely to be a cause of angina, but this will depend on other factors listed below that influence ischaemia independently of lesion severity. Factors intensifying ischaemia. Such factors allow less severe lesions (say ≥50%) to produce angina Reduced oxygen delivery: anaemia, coronary spasm Increased oxygen demand: tachycardia, left ventricular hypertrophy Large mass of ischaemic myocardium: proximally located and longer lesions Factors reducing ischaemia. Such factors may render severe lesions (≥ 70%) asymptomatic Well developed collateral supply Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply. Angina without epicardial coronary artery disease. When angina with evidence of ischaemia occurs in patients with angiographically "normal" coronary arteries (syndrome X) pathophysiological mechanisms are often unclear.
Stable chest pain	Chest pain occurring intermittently, whose frequency and intensity does not vary significantly day to day and which often occurs with a predictable pattern. May also be described as a chest discomfort.
Stenosis	Abnormal narrowing of a blood vessel
Stress echocardiograph	Echocardiography is an ultrasound examination of the heart. Exercise or pharmacological stress may be used to look for reversible systolic regional wall motion abnormalities consistent with the development of myocardial ischaemia. No to be abbreviated to or confused with ECG.
Stress ECG	See exercise ECG above.
Stress magnetic resonance imaging (stress MRI)	MRI is a diagnostic procedure that uses radio waves in a strong magnetic field. The pattern of electromagnetic energy released is detected and analysed by a computer to generate detailed images of the heart. Stress MRI is a specific application in which a contrast agent is used to detect myocardial blood flow at stress and at rest. Pharmacological stress is used to induce cardiovascular stress.
Unstable angina	This often presents in the same way as myocardial infarction but without biomarker evidence of myocardial necrosis.

Term	Description
	The working definition for this guideline is: new onset chest pain / discomfort, or abrupt deterioration in previously stable angina, with chest pain / discomfort occurring frequently and with little or no exertion, and often with prolonged episodes.
Unstable chest pain	Chest pain which occurs with increasing frequency, often with increasing intensity, and which occurs with no predictable pattern. May also be described as a chest discomfort.
Utility	A variable usually taking a value between zero (death) and unity (perfect health) which reflects health related quality of life, and which is used in the calculation of QALYs.
Willingness to pay (WTP)	The amount of money that an individual or society is willing to pay in order to achieve a specified level of health benefit. For example, it is generally recognised that the current willingness to pay for an incremental QALY gain in the NHS is somewhere between £20,000 and £30,000.

1 **Table 11: Abbreviations**

Abbreviation	Description
2VD	two-vessel disease
3VD	three-vessel disease
ACER	average cost-effectiveness ratio
AMI	acute myocardial infarction
AUC	Area under the curve
BB	beta-blocker
BPM	beats per minute
CA	coronary angiography
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCB	calcium-channel blocker
CHD	coronary heart disease
CI	confidence interval
CMR	cardiac magnetic resonance
DTM	decision tree model
EBCT	electron beam computed tomography
ECG	electrocardiography
ECHO	echocardiography
ExECG	exercise ECG
FFR	functional flow reserve
FN	false negative
FP	false positive
HR	Heart rate
ICA	Invasive coronary angiography
ICER	incremental cost-effectiveness ratio
LAD	left anterior descending

Abbreviation	Description
LBBB	left bundle branch block
LMS	left main stem
LR	likelihood ratio
MI	myocardial infarction
MIBI	technetium-99m sestamibi
MPI	myocardial perfusion imaging
MPS	myocardial perfusion scintigraphy
MRI	magnetic resonance imaging
MVD	multivessel disease
NICE	National Institute for Health and Care Excellence
PCI	percutaneous coronary intervention
PET	positron-emission tomography
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality-adjusted life-year
QoL	quality of life
QUADAS	quality assessment of diagnostic accuracy studies
RCT	randomised controlled trial
ROC	receiver operating characteristic
SA	sensitivity analysis
SPECT	single photon emission computed tomography
SVD	single-vessel disease
TN	true negative
TP	true positive

1

2

1 Appendices

2 Appendix A: Committee members and 3 NICE teams

A.1 4 Core members

Name	Role
Damien Longson (Chair)	Consultant Liaison Psychiatrist, Manchester Mental Health and Social Care Trust
Catherine Briggs (until February 2016)	GP Principal, Bracondale Medical Centre, Stockport
John Cape	Director of Psychological Therapies Programme, University College London
Alun Davies (until February 2016)	Professor of Vascular Surgery and Honorary Consultant Surgeon, Charing Cross & St Mary's Hospital & Imperial College NHS Trust
Alison Eastwood	Professor, Centre for Reviews and Dissemination, University of York
Sarah Fishburn	Lay Member
Jim Gray	Consultant Medical Microbiologist, The Birmingham Children's Hospital NHS Foundation Trust
Kath Nuttall (until November 2015)	Director, Lancashire & South Cumbria Cancer Network (- April 2013)
Tilly Pillay	Consultant Neonatologist, Staffordshire, Shropshire and Black Country Newborn Network, Royal Wolverhampton Hospitals Trust
Nick Screaton	Radiologist, Papworth Hospital NHS Foundation Trust
Lindsay Smith	Principal in General Medical Practice, Somerset
Philippa Williams	Lay Member
Sophie Wilne	Paediatric Oncologist, Nottingham Children's Hospital

A.2 5 Topic experts

Name	Role
Ivan Benett	GPwSI
Rick Body	Consultant in Emergency Medicine
Brian Hanrahan (until May 2015	Lay member
Andrew Kelion	Cardiologist
Carl Roobottom	Radiologist
Adam Timmis	Cardiologist

A.3 6 NICE project team

Name	Role
Mark Baker	Clinical Advisor
Steven Barnes	Technical Lead
Christine Carson	Guideline Lead
Ann Louise Clayton	Editor
Jessica Fielding	Public Involvement Advisor
Rupert Franklin	Guideline Commissioning Manager (from November 2015)

Bhash Naidoo	Technical Lead (Health Economics)
Louise Shires	Guideline Commissioning Manager (to November 2015)
Trudie Willingham	Guideline Co-ordinator

A.41 Clinical guidelines update team

Name	Role
Cheryl Hookway	Technical Analyst (until December 2015)
Nicki Mead	Technical Analyst (December 2015 onwards)
Paul Crosland	Health Economist
Emma Banks	Co-ordinator
Hugh McGuire	Technical Advisor (December 2015 onwards)
Jane Birch	Project Manager (July – September 2015)
Kathryn Hopkins	Technical Analyst Quality Assurance (September – December 2015), Technical Analyst (December 2015 onwards)
Lorraine Taylor	Associate Director (September 2015 onwards)
Nick Lowe	Administrator (until January 2016)
Nicole Elliott	Associate Director (until September 2015)
Phil Alderson	Clinical Advisor
Rebecca Parsons	Project manager (until June 2015)
Susannah Moon	Programme Manager (July 2015 onwards)
Toni Tan	Technical Advisor (until September 2015)

2

Appendix B: Declarations of interest

The standing committee and topic experts interests have been declared and collated and are available here (Link to be populated in time for consultation)

1 Appendix C: Review protocol

C.12 Review question 1

	Final Protocol	Refinements
Review Question	In people with stable chest pain of suspected cardiac origin, what is the accuracy, clinical utility and cost effectiveness of: a. non-invasive diagnostic tests b. invasive diagnostic tests c. calcium scoring	None
Objectives	For people in whom stable angina cannot be diagnosed or excluded by clinical assessment alone, non-invasive and invasive testing may be carried out. The type of testing undertaken depends on the estimated likelihood of coronary artery disease (CAD). Once such test used is coronary computed tomographic angiography (CCTA). The surveillance review specifically highlighted new evidence around the role of CCTA. Whilst this diagnostic test was the focus of the surveillance review, it was agreed that all modalities in this section required updating, including functional testing.	None
Type of Review	Diagnostic	None
Language	English only	None
Study Design	Test-and-Treat RCTs, cross-sectional studies, (as recommended in Cochrane DTA Handbook and QUADAS-2).	Prospective studies (ideally with consecutive enrolment). Retrospective studies excluded. Interval between index and reference tests not to exceed 3 months. No minimum sample size.
Status	Full text only	None
Population	Adults presenting with stable chest pain/discomfort of recent onset of suspected cardiac origin	**Include:** Suspected CAD - even if the study does not specifically mention chest pain. Pre-study Screening tests as part of inclusion: a. ECG – only include if all participants undergo subsequent index/reference tests. (i.e. exclude studies where only people with either normal or abnormal findings were recruited). b. Other screening tests for inducible ischemia such as stress tests (protocol index tests or otherwise) – as above. **Exclude:** Known CAD (any part of study population) excluded. Sub group populations (e.g. purely

	Final Protocol	Refinements
		women or diabetics). Populations Left bundle branch block (LBBB) and Cardiac syndrome X
Index tests	Anatomic Tests (stenosis/vessel flow) 1. Coronary angiography 2. CT a. Coronary angiography (CTCA) / Coronary computed tomographic angiography (CCTA), b. multi-slice CT (MSCT) c. new generation cardiac computed tomography (NGCCT) (excluding Aquilion ONE, Brilliance iCT, Discovery CT750 HD and Somatom Definition Flashas these are covered in NICE Diagnosic Guidance –DG3 3. Calcium scoring Functional Tests (myocardial ischaemia/wall motion) 4. Stress echocardiography 5. Stress magnetic resonance imaging (MRI) (Stress Cardiac MR (CMR) for wall motion 6. Stress MRI (Stress CMR) for perfusion imaging, 7. Myocardial perfusion scintigraphy (MPS) using positron emission tomography (PET) or SPECT (single photon emission computed tomography). 8. CT Fractional flow reserve CTFFR 9. CT myocardial perfusion 10. Positron emission tomography (PET) scan	A minimum specification (64-slice CT) was applied for index tests 2 and 3. Stress echo was split into two tests (4a Perfusion and 4b Wall motion) Studies performing SPECT using planar imaging and obsolete cameras known as gamma cameras will not be included. The following tests do not fall within the specified index tests of interest therefore are not included: MR Angiography (MRA) Magnetocardiography Electron Beam CT (EBCT) Intravascular ultrasound (IVUS) Cardiogoniometry and cardiokymography Gadolinium diethylene triamine pentaacetic acid enhanced multidetector CT (MDCT) 2D echo without stress MRI without stress
Comparator/ Reference test	Coronary angiography (at all percentage stenosis levels, reported separately to include 50% and 70% stenosis). In the unlikely case of coronary angiography as the index test ((1) above), studies evaluating any other reference standards will be included.	None
Outcomes/ Statistical reporting	Diagnostic accuracy measurements for example sensitivity, specificity, likelihood ratios, ROC curves.	CAD is the clinical outcome of interest. Only include studies that provide per patient analysis (per vessel or per segment analysis only - exclude). Included studies must have all four numbers for 2x2 table OR enough data to be able to back calculate. Adverse events/side effects to be documented as outcomes of interest.
Other criteria for inclusion / exclusion of studies	Exclusion Criteria: Children, adults with acute chest pain, adults with chest pain not suspected to be of cardiac origin, cohort studies, case-control studies and case series/case reports, conference abstracts. Animal studies will be excluded from the search results.	As stated beside each individual protocol parameter
Review strategies	*Databases for searches will include: Medline, Medline in Process, Embase, Cochrane CDSR, CENTRAL, DARE and HTA. *No date limit will be set.	Based on presentation of interim results and summary ROC curves, it was decided that these were not useful as individual studies had different thresholds for

	Final Protocol	Refinements
	*Economic searches will include Medline, Medline in Process, Embase, NHS EED and HTA, with economic evaluations and quality of life filters applied. (Legacy records will be retrieved from NHS EED). *Data on all included studies will be extracted into evidence tables *A list of excluded studies will be provided following sifting of the database *Test accuracy measurements as stated in 'Outcomes' will be reported and summarised in evidence statements. *QUADAS-2 and GRADE for DTA studies will be used to appraise and present the evidence. *Where data is appropriate and homogenous, bivariate model of meta-analysis or just the summary of ROC curves will be conducted, depending on the quality and suitability of the included data. *Where appropriate and if with sufficient data, latent class analysis may be conducted.	diagnosing CAD (according to diagnostic test) and 95% CIs could not be easily evaluated. ROC curves are thus not produced in the full results. Forest plots are provided.

C.21 Review question 2

	Details	Protocol refinements
Review Question	What is the accuracy, clinical utility and cost effectiveness of clinical prediction models/tools (clinical history, cardiovascular risk factors, physical examination) in evaluating people with stable chest pain of suspected cardiac origin?	None
Objectives	Diagnosis of stable chest pain involves clinical assessment, including assessment of pre-test probability of having coronary artery disease (CAD). New evidence relating to a revised version of the Diamond and Forrester model was identified during surveillance. This revised model may have an impact on the recommended diagnostic pathways, based on a person's estimated likelihood of CAD.	None
Type of Review	Diagnostic prediction	None
Language	English only	None
Study Design	Diagnostic prediction studies (cross-sectional)	Ideally studies will be prospective (with consecutive enrolment). Studies where probability scores are calculated retrospectively from the patient record will be included.
Status	Full text only	None

	Details	Protocol refinements
Population	Adults presenting with stable chest pain/discomfort of suspected cardiac origin (CAD)	**Include:** Suspected CAD - even if the study does not specifically mention chest pain. **Exclude:** Known CAD (any part of study population) excluded.
Predictors / risk factors	a) clinical history, *or* b) cardiovascular risk factors, *or* c) physical examination, *or* any combination of a) b) or c).	**Include:** Any clinical factors if the information is likely to be available at a typical index clinic visit.
Reference standard	Coronary angiography (CA) *or* Computed tomography coronary angiography (CTCA)	**Include:** Computed tomography coronary angiography (CTCA) in order to include studies in potentially more diverse and therefore generalisable populations
Outcomes	ROC curve - AUC (c-statistic, c-index) Sensitivity and specificity	CAD is the clinical outcome of interest.
Other criteria for inclusion / exclusion of studies	**Exclusions:** Population - children, - adults with acute chest pain, - adults with chest pain not suspected to be of cardiac origin. Methodology: - studies assessing prospective or retrospective *long-term* accuracy of a prediction model / tool (including cohort and case-control studies) - conference abstracts will be excluded. - animal studies will be excluded.	None
Search strategies	Sources will include: Medline, Medline in Process, Embase, Cochrane CDSR, CENTRAL, DARE and HTA. (Legacy records will be retrieved from DARE). Economic searches will include Medline, Medline in Process, Embase, NHS EED and HTA, with economic evaluations and quality of life filters applied. Note: in the actual search we will still need to search for (a), (b) and (c) per original question, but we will only include studies on models that incorporated some or all of these, but not studies on individual risk factors only.	Date limit: studies published from 2009 onwards. An adaptation of the Duke Clinical Score had been selected by the original guideline development group, on the basis of the best available evidence, for inclusion in NICE CG95 (2010). The remit of this update was to identify evidence for models with

	Details	Protocol refinements
		better predictive ability in contemporary patient cohorts published since the previous review.
Review strategies	**Selection of papers:** i) Selection based on titles and abstracts A full double-sifting of titles and abstracts will not be conducted due to the nature of the review question (narrow question with clearly defined straightforward inclusion and exclusion criteria). ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion will not be conducted due to the nature of the review question (as mentioned above). Uncertainties around study inclusion/exclusion will be discussed with the technical adviser. Other mechanisms will be in place for QA: - The committee will be sent the list of included and excluded studies prior to the committee meeting, and the committee will be requested to cross check whether any studies have been excluded inappropriately, and whether there are any relevant studies they have known of which haven't been picked up by the searches. **Data extraction and appraisal:** Data on all included studies will be extracted into evidence tables. Measurements of accuracy as stated in 'Outcomes' will be reported and summarised in evidence statements. Depending on the study designs used for the clinical predicting model/tool in the included studies, the following will be used to appraise the quality of the evidence i) Hayden's (QUIPS) checklist; ii) QUADAS-2 checklist; iii) GRADE for diagnostic test accuracy question. Where included data are appropriate and homogenous, bivariate model of meta-analysis will be conducted, depending on the nature and suitability of the data identified.	

Appendix D: Search strategy

D.1 Review question 1

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 12. The search strategy is shown in Table 13. The same strategy was translated for the other databases listed.

Table 12: Clinical search summary

Database	Date searched	Number retrieved
CDSR (Wiley)	21/05/2015	1
Database of Abstracts of Reviews of Effects – DARE (Wiley)	21/05/2015	59
HTA database (Wiley)	21/05/2015	5
CENTRAL (Wiley)	21/05/2015	658
MEDLINE (Ovid)	21/05/2015	8484
MEDLINE (Ovid) Additional search to cover missing Medline records between January and October 2015	19/10/2015	12
MEDLINE In-Process (Ovid)	21/05/2015	297
EMBASE (Ovid)	21/05/2015	9058
PubMed	03/06/2015	124

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The aim of the search was to identify evidence for the clinical question being asked.

The PubMed translation consisted of an abbreviated strategy run at the end of the process designed to capture references that had not yet appeared in the Medline in Process database.

Table 13: Clinical search terms

Line number/Search term/Number retrieved
1 Chest Pain/ (9704)
2 Angina Pectoris/ (30738)
3 Angina, Stable/ (513)

Line number/Search term/Number retrieved
4 Microvascular Angina/ (894)
5 (angina* or stenocardia* or angor pectoris or cardiac syndrome x).tw. (45788)
6 ((chest* or thorax* or thorac*) adj4 (pain* or discomfort or distress or ache*)).tw. (27441)
7 *Coronary Artery Disease/ (33104)
8 (coronary adj (arterioscleros?s or atheroscleros?s or artery or arteries) adj disease*).tw. (59084)
9 or/1-8 (148196)
10 *Echocardiography, stress/ (1378)
11 (Echocardiograph* adj4 (stress* or dobutamine)).tw. (4251)
12 *Tomography, Emission-Computed, Single-Photon/ (13061)
13 *Tomography, Emission-Computed/ or *Tomography, X-Ray Computed/ (103454)
14 *Positron-Emission Tomography/ (18848)
15 ((single photon or single-photon) adj2 emission*).tw. (14546)
16 ((positron-emission or positron emission) adj tomography).tw. (34398)
17 (pet adj scan*).tw. (6670)
18 *Myocardial Perfusion Imaging/ (1828)
19 (Myocardial adj (scintigraph* or perfusion*)).tw. (12467)
20 ((thallium or sestamibi or tetrofosmin or technetium) adj2 SPECT).tw. (1402)
21 *Magnetic Resonance Imaging/ (111714)
22 ((cardiac or stress) adj2 magnetic adj2 resonance adj2 imag*).tw. (2950)
23 ("cardiac MR" or CMR).tw. (4268)
24 (stress adj3 perfusion*).tw. (1736)
25 ((Multi-slice or Multi slice) adj CT).tw. (374)
26 ("new generation" adj4 tomograph*).tw. (36)
27 (fractional adj flow adj reserve).tw. (859)
28 (coronary adj2 computed adj2 tomographic adj2 angiograph*).tw. (474)

Line number/Search term/Number retrieved
29 (MSCT or MRI or CCTA or CTCA or NGCCT or SPECT or PET or MPS or CTFFR).tw. (208754)
30 (stress adj2 (ECG or EKG or electrocardiogra* or electrokardiogra*)).tw. (957)
31 *Coronary Angiography/ (14643)
32 (coronary adj angiograph*).tw. (22871)
33 ((CAC or calcium) adj scor*).tw. (2109)
34 or/10-33 (398920)
35 9 and 34 (26371)
36 animals/ not humans/ (3947089)
37 35 not 36 (26165)
38 limit 37 to english language (22297)
39 "Sensitivity and Specificity"/ (287798)
40 (sensitivity or specificity or accuracy).tw. (866529)
41 "Predictive Value of Tests"/ (151270)
42 (predictive adj1 value*).tw. (68061)
43 (roc adj1 curve*).tw. (15164)
44 (false adj2 (positiv* or negativ*)).tw. (55601)
45 (observer adj variation*).tw. (938)
46 (likelihood adj1 ratio*).tw. (8859)
47 Diagnosis, Differential/ (388741)
48 Likelihood Functions/ (17912)
49 exp Diagnostic Errors/ (97914)
50 or/39-49 (1600741)
51 38 and 50 (8484)

1

D.2 Review question 1 – supplementary test and treat randomised controlled trials search

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 12. The search strategy is shown in Table 13. The same strategy was translated for the other databases listed.

Table 14: Clinical search summary

Database	Date searched	Number retrieved
MEDLINE (Ovid)	24/02/2016	5,608 (+251)
MEDLINE In-Process (Ovid)	24/02/2016	134
Embase (Ovid)	24/02/2016	4,909
Cochrane Database of Systematic Reviews (CDSR)	24/02/2016	6
Cochrane Central Register of Controlled Trials (CENTRAL)	24/02/2016	3,119
Database of Abstracts of Reviews of Effect (DARE)	24/02/2016	113
Health Technology Assessment (HTA Database)	24/02/2016	58

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The aim of the search was to identify evidence for the clinical question being asked.

The PubMed translation consisted of an abbreviated strategy run at the end of the process designed to capture references that had not yet appeared in the Medline in Process database.

Table 15: Clinical search terms

Line number/Search term/Number retrieved
1 Chest Pain/ (10469)
2 Angina Pectoris/ (31376)
3 Angina, Stable/ (621)
4 Microvascular Angina/ (918)
5 (angina* or stenocardia* or angor pectoris or cardiac syndrome x).tw. (46631)
6 ((chest* or thorax* or thorac*) adj4 (pain* or discomfort or distress or ache*)).tw. (28316)
7 *Coronary Artery Disease/ (37212)
8 (coronary adj (arterioscleros?s or atheroscleros?s or artery or arteries) adj disease*).tw.

Line number/Search term/Number retrieved
(60888)
9 or/1-8 (154405)
10 *Echocardiography, stress/ (1454)
11 (Echocardiograph* adj4 (stress* or dobutamine)).tw. (4362)
12 *Tomography, Emission-Computed, Single-Photon/ (13414)
13 *Tomography, Emission-Computed/ or *Tomography, X-Ray Computed/ (107998)
14 *Positron-Emission Tomography/ (20362)
15 ((single photon or single-photon) adj2 emission*).tw. (14844)
16 ((positron-emission or positron emission) adj tomography).tw. (35629)
17 (pet adj scan*).tw. (6816)
18 *Myocardial Perfusion Imaging/ (1989)
19 (Myocardial adj (scintigraph* or perfusion*)).tw. (12721)
20 ((thallium or sestamibi or tetrofosmin or technetium) adj2 SPECT).tw. (1416)
21 *Magnetic Resonance Imaging/ (115537)
22 ((cardiac or stress) adj2 magnetic adj2 resonance adj2 imag*).tw. (3184)
23 ("cardiac MR" or CMR).tw. (4551)
24 (stress adj3 perfusion*).tw. (1770)
25 ((Multi-slice or Multi slice) adj CT).tw. (385)
26 ("new generation" adj4 tomograph*).tw. (38)
27 (fractional adj flow adj reserve).tw. (974)
28 (coronary adj2 computed adj2 tomographic adj2 angiograph*).tw. (508)
29 (MSCT or MRI or CCTA or CTCA or NGCCT or SPECT or PET or MPS or CTFFR).tw. (218079)
30 (stress adj2 (ECG or EKG or electrocardiogra* or electrokardiogra*)).tw. (969)
31 *Coronary Angiography/ (15341)
32 (coronary adj angiograph*).tw. (23541)
33 ((CAC or calcium) adj scor*).tw. (2238)

Line number/Search term/Number retrieved	
34	or/10-33 (415267)
35	9 and 34 (27278)
36	animals/ not humans/ (4154861)
37	35 not 36 (27075)
38	limit 37 to english language (23138)
39	Randomized Controlled Trial.pt. (406217)
40	Controlled Clinical Trial.pt. (90055)
41	Clinical Trial.pt. (496612)
42	exp Clinical Trials as Topic/ (287467)
43	Placebos/ (33017)
44	Random Allocation/ (85417)
45	Double-Blind Method/ (132981)
46	Single-Blind Method/ (21293)
47	Cross-Over Studies/ (37183)
48	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (797809)
49	(random$ adj3 allocat$).tw. (22413)
50	placebo$.tw. (160059)
51	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (130117)
52	(crossover$ or (cross adj over$)).tw. (59727)
53	or/39-52 (1466709)
54	animals/ not humans/ (4154861)
55	53 not 54 (1365632)
56	Meta-Analysis.pt. (61300)
57	Meta-Analysis as Topic/ (14478)
58	Review.pt. (2007715)
59	exp Review Literature as Topic/ (8358)

Line number/Search term/Number retrieved	
60	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (72449)
61	(review$ or overview$).ti. (295382)
62	(systematic$ adj5 (review$ or overview$)).tw. (67938)
63	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4981)
64	((studies or trial$) adj2 (review$ or overview$)).tw. (27292)
65	(integrat$ adj3 (research or review$ or literature)).tw. (6137)
66	(pool$ adj2 (analy$ or data)).tw. (15992)
67	(handsearch$ or (hand adj3 search$)).tw. (5804)
68	(manual$ adj3 search$).tw. (3484)
69	or/56-68 (2181002)
70	animals/ not humans/ (4154861)
71	69 not 70 (2041729)
72	55 or 71 (3150571)
73	38 and 72 (5859)
74	limit 73 to ed=20150522-20160224 (251)
75	73 not 74 (5608)

D.31 Review question 2

2

3 Databases that were searched, together with the number of articles retrieved from each
4 database are shown in table 6. The search strategy is shown in table 7.

5 **Table 16: Clinical search summary**

Databases	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	25/11/2015	Ovid MEDLINE(R) 1946 to November Week 2 2015	4,285
MEDLINE In-Process (Ovid)	25/11/2015	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 24, 2015>	515
Embase (Ovid)	25/11/2015	Embase <1974 to 2015 Week 47>	4,983
Cochrane Database of Systematic Reviews (CDSR)	26/11/2015	Cochrane Database of Systematic Reviews : Issue 11 of 12, November 2015	83

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	26/11/2015	Cochrane Central Register of Controlled Trials : Issue 10 of 12, October 2015	1,516
Database of Abstracts of Reviews of Effect (DARE)	26/11/2015	Database of Abstracts of Reviews of Effect : Issue 2 of 4, April 2015	81
Health Technology Assessment (HTA Database)	26/11/2015	Health Technology Assessment Database : Issue 4 of 4, October 2015	4
PubMed	25/11/2015	-	912

1

2 The MEDLINE search strategy is presented below. This was translated for use in all of the
3 other databases listed. The aim of the search was to identify evidence for the clinical
4 question being asked.

5 The PubMed translation consisted of an abbreviated strategy run at the end of the process
6 designed to capture references that had not yet appeared in the Medline in Process
7 database.

8 **Table 17: Clinical search terms**

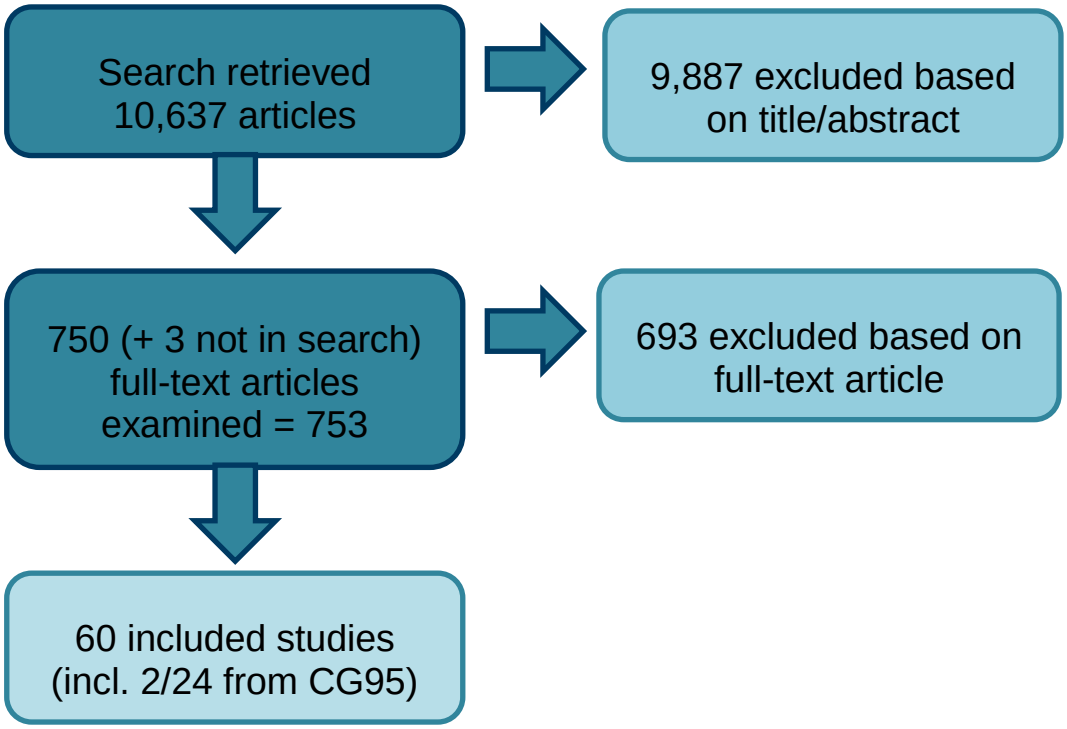
Line number/Search term/Number retrieved
1 Chest Pain/ (10195)
2 Angina Pectoris/ (31364)
3 Angina, Stable/ (593)
4 Microvascular Angina/ (920)
5 (angina* or stenocardia* or angor pectoris or cardiac syndrome x).tw. (46911)
6 ((chest* or thorax* or thorac*) adj4 (pain* or discomfort or distress or ache*)).tw. (28562)
7 *Coronary Artery Disease/ (35245)
8 (coronary adj (arterioscleros?s or atheroscleros?s or artery or arteries) adj disease*).tw. (61335)
9 or/1-8 (153833)
10 *Risk Assessment/ (20773)
11 *Risk Factors/ (968)
12 *Medical-History Taking/ (4613)
13 *Physical Examination/ (10186)
14 *Risk/ (2965)
15 (history adj tak*).tw. (3907)
16 (pretest* adj (probab* or likel*)).tw. (1176)
17 (risk* adj4 assess*).tw. (76129)
18 cardiovascular risk factor*.tw. (23581)
19 ((physic* or clinic*) adj4 exam*).tw. (137040)
20 ((medic* or famil* or patient* or clinic*) adj histor*).tw. (85616)
21 (probab* adj4 disease*).tw. (9104)
22 Framingham*.tw. (6555)
23 clinic* predict*.tw. (5265)
24 or/10-23 (355981)
25 9 and 24 (11361)
26 Animals/ not Humans/ (4055381)
27 25 not 26 (11336)
28 limit 27 to english language (9869)

Line number/Search term/Number retrieved	
29	limit 28 to ed=20090101-20151125 (4285)

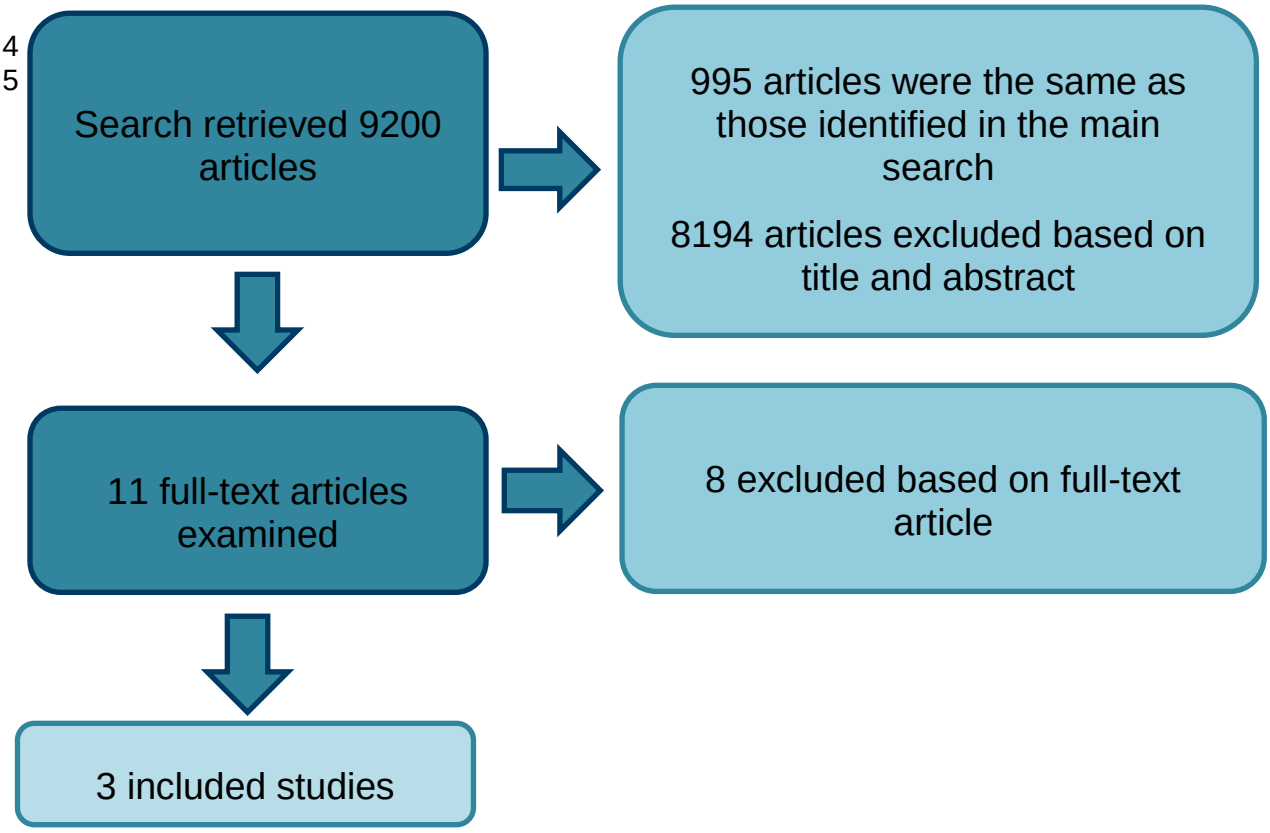
1

Appendix E: Review flowchart

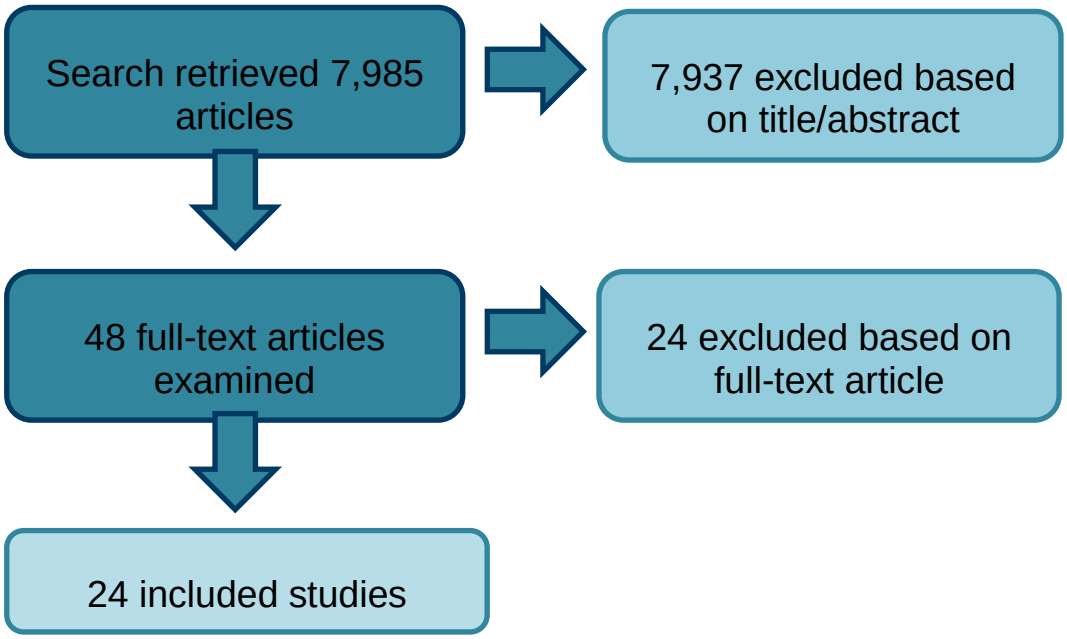
E.1 Review question 1



E.2 Review question 1 – supplementary test and treat randomised controlled trials review



E.31 Review question 2



1 Appendix F:Excluded studies

F.12 Review question 1

3 **Table 18: Clinical excluded studies table**

Author	Reason for exclusion
Abdulla,J., Abildstrom,S.Z., Gotzsche,O., Christensen,E., Kober,L., Torp-Pedersen,C., 64-Multislice detector computed tomography coronary angiography as potential alternative to conventional coronary angiography: A systematic review and meta-analysis, European Heart JournalEur.Heart J., 28, 3042-3050, 2007	Population (Included patients with known disease)
Abdulla,Jawdat, Pedersen,Kasper S., Budoff,Matthew, Kofoed,Klaus F., Influence of coronary calcification on the diagnostic accuracy of 64-slice computed tomography coronary angiography: a systematic review and meta-analysis, The international journal of cardiovascular imaging Int J Cardiovasc Imaging, 28, 943-953, 2012	Population (included patients with known CAD)
Abdulla,Jawdat, Sivertsen,Jacob, Kofoed,Klaus Fuglsang, Alkadhi,Hatem, Labounty,Troy, Abildstrom,Steen Z., Kober,Lars, Christensen,Erik, Torp-Pedersen,Christian, Evaluation of aortic valve stenosis by cardiac multislice computed tomography compared with echocardiography: a systematic review and meta-analysis, The Journal of heart valve disease J Heart Valve Dis, 18, 634-643, 2009	Population (insufficient description of population included)
Abidov,A., Gallagher,M.J., Chinnaiyan,K.M., Mehta,L.S., Wegner,J.H., Raff,G.L., Clinical effectiveness of coronary computed tomographic angiography in the triage of patients to cardiac catheterization and revascularization after inconclusive stress testing: results of a 2-year prospective trial, Journal of Nuclear CardiologyJ.Nucl.Cardiol., 16, 701-713, 2009	Population (included patients with previous inconclusive stress imagining tests)
Abitbol,Elsa, Monin,Jean Luc, Garot,Jerome, Monchi,Mehrane, Russel,Stephanie, Duval,Anne Marie, Gueret,Pascal, Relationship between the ischemic threshold at the onset of wall-motion abnormality on semisupine exercise echocardiography and the extent of coronary artery disease, Journal of the American Society of Echocardiography : official publication of the American Society of EchocardiographyJ Am Soc Echocardiogr, 17, 121-125, 2004	Mixed population - includes known CAD.
Achenbach,S., Moshage,W., Ropers,D., Nossen,J., Daniel,W.G., Value of electron-beam computed tomography for the noninvasive detection of high-grade coronary-artery stenoses and occlusions, The New England journal of medicine N Engl J Med, 339, 1964-1971, 1998	Non protocol index test (Electron Beam CT)
Achenbach,S., Ropers,U., Kuettner,A., Anders,K., Pflederer,T., Komatsu,S., Bautz,W., Daniel,W.G., Ropers,D., Randomized comparison of 64-slice single- and dual-source computed tomography coronary angiography for the detection of coronary artery disease, JACC.Cardiovascular imaging JACC Cardiovasc Imaging, 1, 177-186, 2008	Study design: not all patients had same test
Achenbach,Stephan, Goroll,Tobias, Seltmann,Martin, Pflederer,Tobias, Anders,Katharina, Ropers,Dieter, Daniel,Werner G., Uder,Michael, Lell,Michael,	New Generation CT scanner (non protocol/DG3).

Author	Reason for exclusion
Marwan,Mohamed, Detection of coronary artery stenoses by low-dose, prospectively ECG-triggered, high-pitch spiral coronary CT angiography, JACC.Cardiovascular imagingJACC Cardiovasc Imaging, 4, 328-337, 2011	
Adams,George L., Trimble,Mark A., Brosnan,Rhoda B., Russo,Cheryl A., Rusband,Dan, Honeycutt,Emily F., Shaw,Linda K., Hurwitz,Lynn M., Turkington,Timothy G., Hanson,Michael W., Pagnanelli,Robert A., Borges-Neto,Salvador, Evaluation of combined cardiac positron emission tomography and coronary computed tomography angiography for the detection of coronary artery disease, Nuclear Medicine CommunicationsNUCL.MED.COMMUN., 29, 593-598, 2008	Not all participants had both index test and reference standard
Adil,M., Hafizullah,M., Jan,H., Paracha,M.M., Qazi,S., Diagnostic yield of stress echocardiography in coronary artery disease patients, Journal of Postgraduate Medical InstituteJ.Postgrad.Med.Inst., 25, 331-337, 2011	Mixed population - includes known CAD
Afridi,I., Quinones,M.A., Zoghbi,W.A., Cheirif,J., Dobutamine stress echocardiography: sensitivity, specificity, and predictive value for future cardiac events, American Heart JournalAm.Heart J., 127, 1510-1515, 1994	Population (included patients with known CAD)
Agati,L., Renzi,M., Sciomer,S., Vizza,D.C., Voci,P., Penco,M., Fedele,F., Dagianti,A., Transesophageal dipyridamole echocardiography for diagnosis of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 19, 765-770, 1992	Mixed population - includes studies with prior MI.
Agatston,A.S., Janowitz,W.R., Hildner,F.J., Zusmer,N.R., Viamonte,M.Jr, Detrano,R., Quantification of coronary artery calcium using ultrafast computed tomography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 15, 827-832, 1990	Population (mixed - included patients with known CAD)
Aggeli,C., Felekos,I., Roussakis,G., Kazazaki,C., Lagoudakou,S., Pietri,P., Tousoulis,D., Pitsavos,C., Stefanadis,C., Value of real-time three-dimensional adenosine stress contrast echocardiography in patients with known or suspected coronary artery disease, European Journal of EchocardiographyEur.J.Echocardiogr., 12, 648-655, 2011	Mixed population - includes known CAD.
Aggeli,Constadina, Giannopoulos,Georgios, Misovoulos,Platon, Roussakis,George, Christoforatou,Euaggelia, Kokkinakis,Christos, Brili,Stela, Stefanadis,Christodoulos, Real-time three-dimensional dobutamine stress echocardiography for coronary artery disease diagnosis: validation with coronary angiography, Heart (British Cardiac Society), 93, 672-675, 2007	Per-vessel analysis only.
Ahmad,M., Dubiel,J.P., Haibach,H., Cold pressor thallium-201 myocardial scintigraphy in the diagnosis of coronary artery disease, The American journal of cardiologyAm J Cardiol, 50, 1253-1257, 1982	Population (included patients with known disease - possible bypass surgery candidates)
Akalin,Erdal Nihat, Yaylali,Olga, Kirac,Fatma Suna, Yuksel,Dogangun, Kilic,Mustafa, The Role of Myocardial Perfusion Gated SPECT Study in Women with Coronary Artery Disease: A Correlative Study, Molecular imaging and radionuclide therapyMol Imaging Radionucl Ther, 21, 69-74, 2012	Study in women only (non protocol sub group).
Akhtar,M., Vakharia,K.T., Mishell,J., Gera,A., Ports,T.A., Yeghiazarians,Y., Michaels,A.D., Randomized study of the	Non protocol index test

Author	Reason for exclusion
safety and clinical utility of rotational vs. standard coronary angiography using a flat-panel detector, Catheterization and cardiovascular interventionsCatheter Cardiovasc Interv, 66, 43-49, 2005	
Akram,Kamran, O'Donnell,Robert E., King,Spencer, Superko,H.Robert, Agatston,Arthur, Voros,Szilard, Influence of symptomatic status on the prevalence of obstructive coronary artery disease in patients with zero calcium score, Atherosclerosis, 203, 533-537, 2009	Population (included patients who were asymptomatic)
Akram,Kamran, Voros,Szilard, Absolute coronary artery calcium scores are superior to MESA percentile rank in predicting obstructive coronary artery disease, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 24, 743-749, 2008	Design (retrospective)
Al Moudi,M., Sun,Z., Lenzo,N., Diagnostic value of SPECT, PET and PET/CT in the diagnosis of coronary artery disease: A systematic review, Biomedical Imaging and Intervention JournalBiomed.Imaging Intervent.J, 7, e9-, 2011	Mixed population - includes patients with confirmed CAD
Al Moudi,Mansour, Sun,Zhong Hua, Diagnostic value of (18)F-FDG PET in the assessment of myocardial viability in coronary artery disease: A comparative study with (99m)Tc SPECT and echocardiography, Journal of geriatric cardiology : JGCJ Geriatr Cardiol, 11, 229-236, 2014	mixed population - includes known CAD
Al,Moudi M., Sun,Z.-H., Diagnostic value of 18F-FDG PET in the assessment of myocardial viability in coronary artery disease: A comparative study with 99mTc SPECT and echocardiography, Journal of Geriatric CardiologyJ.Geriatr.Cardiol., 11, 229-236, 2014	Mixed population includes known CAD
Alazraki,N.P., Krawczynska,E.G., DePuey,E.G., Ziffer,J.A., Vansant,J.P., Pettigrew,R.I., Taylor,A., King,S.B., Garcia,E.V., Reproducibility of thallium-201 exercise SPECT studies, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 35, 1237-1244, 1994	Mixed population - predominantly known CAD.
Alberto,Conti, Margherita,Luzzi, Cristina,Nanna, Chiara,Gallini, Egidio,Costanzo, Luca,Vaggelli, Luigi,Padeletti, Gian,Franco Gensini, Effectiveness of nuclear scan strategy in low-risk chest pain patients: novel insights from the real world, Nuclear Medicine CommunicationsNUCL.MED.COMMUN., 32, 1223-1230, 2011	Population (indirect - not all patients had both tests)
Alessandri,N., Di Matteo,A., Rondoni,G., Petrassi,M., Tufani,F., Ferrari,R., Laghi,A., Heart imaging: the accuracy of the 64-MSCT in the detection of coronary artery disease, European Review for Medical and Pharmacological SciencesEur.Rev.Med.Pharmacol.Sci., 13, 163-171, 2009	Population (unclear)
Alexopoulos,Dimitrios, Toulgaridis,Theodoros, Davlouros,Periklis, Christodoulou,John, Stathopoulos,Christos, Hahalis,George, Coronary calcium detected by digital cinefluoroscopy and coronary artery disease in patients undergoing coronary arteriography: effects of age and sex, International journal of cardiologyInt.J.Cardiol., 87, 159-166, 2003	Reference standard (non protocol) Population (included patients with known CAD)
Alkadhi,H., Stolzmann,P., Desbiolles,L., Baumueller,S., Goetti,R., Plass,A., Scheffel,H., Feuchtner,G., Falk,V., Marincek,B., Leschka,S., Low-dose, 128-slice, dual-source CT coronary angiography: accuracy and radiation dose of the high-pitch and the step-and-shoot mode, Heart (British	Non protocol new generation scanner (Definition Flash) (DG3)

Author	Reason for exclusion
Cardiac Society), 96, 933-938, 2010	
Allman,K.C., Berry,J., Sucharski,L.A., Stafford,K.A., Petry,N.A., Wysor,W., Schwaiger,M., Determination of extent and location of coronary artery disease in patients without prior myocardial infarction by thallium-201 tomography with pharmacologic stress, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 33, 2067-2073, 1992	Study design: retrospective
Almasi,Alireza, Pouraliakbar,Hamidreza, Sedghian,Ahmad, Karimi,Mohammad Ali, Firouzi,Ata, Tehrai,Mahmood, The value of coronary artery calcium score assessed by dual-source computed tomography coronary angiography for predicting presence and severity of coronary artery disease, Polish journal of radiology / Polish Medical Society of Radiology, 79, 169-174, 2014	Non protocol new generation scanner used.
Altinmakas,S., Dagdeviren,B., Turkmen,M., Gursurer,M., Say,B., Tezel,T., Ersek,B., Usefulness of pulse-wave Doppler tissue sampling and dobutamine stress echocardiography for identification of false positive inferior wall defects in SPECT, Japanese Heart JournalJpn.Heart J., 41, 141-152, 2000	Mixed population - includes known CAD.
Amadei,G., Patruno,M., Baggioni,G.F., Dipyridamole echocardiography detection of coronary artery disease in aortic stenosis, Cardiovascular ImagingCARDIOVASC.IMAGING, 8, 331-333, 1996	Not available via British Library or Royal Society of Medicine
Amanullah,A.M., Kiat,H., Friedman,J.D., Berman,D.S., Adenosine technetium-99m sestamibi myocardial perfusion SPECT in women: diagnostic efficacy in detection of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 27, 803-809, 1996	Mixed population - includes prior MI
Anwar,Ashraf M., Accuracy of two-dimensional speckle tracking echocardiography for the detection of significant coronary stenosis, Journal of Cardiovascular UltrasoundJ.Cardiovasc.Ultrasound, 21, 177-182, 2013	2D echo without stress is not a protocol index test
Aoyagi,K., Inoue,T., Yamauchi,Y., Iwasaki,T., Endo,K., Does myocardial thallium-201 SPECT combined with electron beam computed tomography improve the detectability of coronary artery disease?--comparative study of diagnostic accuracy, Annals of Nuclear MedicineAnn.Nucl.Med., 12, 197-204, 1998	Mixed population - includes known CAD.
Arbab-Zadeh,Armin, Miller,Julie M., Rochitte,Carlos E., Dewey,Marc, Niinuma,Hiroyuki, Gottlieb,Ilan, Paul,Narinder, Clouse,Melvin E., Shapiro,Edward P., Hoe,John, Lardo,Albert C., Bush,David E., de Roos,Albert, Cox,Christopher, Brinker,Jeffrey, Lima,Joao A.C., Diagnostic accuracy of computed tomography coronary angiography according to pre-test probability of coronary artery disease and severity of coronary arterial calcification. The CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) International Multicenter Study, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 59, 379-387, 2012	Mixed population - includes known disease
Arsanjani,R., Nakazato,R., Shalev,A., Gomez,M., Gransar,H., Leipsic,J., Berman,D., Min,J., Sinai,C., Diagnostic accuracy, image quality and patient comfort for coronary CT angiography performed using low versus high iodine content contrast: A prospective multicenter randomized controlled trial, Journal of the American College of	Conference abstract.

Author	Reason for exclusion
CardiologyJ.Am.Coll.Cardiol., 61, E1104-, 2013	
Arsanjani,Reza, Xu,Yuan, Dey,Damini, Fish,Matthews, Dorbala,Sharmila, Hayes,Sean, Berman,Daniel, Germano,Guido, Slomka,Piotr, Improved accuracy of myocardial perfusion SPECT for the detection of coronary artery disease using a support vector machine algorithm, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 54, 549-555, 2013	Study design: case control study
Atar,D., Ali,S., Steensgaard-Hansen,F., Saunamaki,K., Ramanujam,P.S., Egeblad,H., Haunso,S., The diagnostic value of exercise echocardiography in ischemic heart disease in relation to quantitative coronary arteriography, International Journal of Cardiac ImagingInt J Card Imaging, 11, 1-7, 1995	Population (unclear - only referred for CA, could be due to many reasons)
Avakian,S.D., Grinberg,M., Meneguetti,J.C., Ramires,J.A., Mansur,A.P., SPECT dipyridamole scintigraphy for detecting coronary artery disease in patients with isolated severe aortic stenosis, International journal of cardiologyInt.J.Cardiol., 81, 21-27, 2001	Population (indirect/specific)
Aviram,Galit, Finkelstein,Ariel, Herz,Itzhak, Lessick,Jonathan, Miller,Hylton, Graif,Moshe, Keren,Gad, Clinical value of 16-slice multi-detector CT compared to invasive coronary angiography, International Journal of Cardiovascular InterventionsInt.J.Cardiovasc.Interventions, 7, 21-28, 2005	16 Slice scanner (minimum 64 slice)
Ayaram,David, Bellolio,M.Fernanda, Murad,M.Hassan, Laack,Torrey A., Sadosty,Annie T., Erwin,Patricia J., Hollander,Judd E., Montori,Victor M., Stiell,Ian G., Hess,Erik P., Triple rule-out computed tomographic angiography for chest pain: a diagnostic systematic review and meta-analysis, Academic emergency medicine : official journal of the Society for Academic Emergency MedicineAcad Emerg Med, 20, 861-871, 2013	Mixed population - includes known CAD
Azzarelli,S., Galassi,A.R., Foti,R., Mammana,C., Musumeci,S., Giuffrida,G., Tamburino,C., Accuracy of 99mTc-tetrofosmin myocardial tomography in the evaluation of coronary artery disease, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 6, 183-189, 1999	Population (included patients with known CAD)
Babar,Imran M., Aleem,Khan M., Naeem,Aslam M., Irfanullah,J., Diagnosis of coronary artery disease by stress echocardiography and perfusion scintigraphy, Journal of the College of Physicians and Surgeons PakistanJ.Coll.Phys.Surg.Pak., 13, 465-470, 2003	Included studies were on mixed populations (included known CAD)
Baer,F.M., Voth,E., Theissen,P., Schneider,C.A., Schicha,H., Sechtem,U., Coronary artery disease: findings with GRE MR imaging and Tc-99m-methoxyisobutyl-isonitrile SPECT during simultaneous dobutamine stress, Radiology, 193, 203-209, 1994	Non protocol reference standard
Banerjee,A., Newman,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, International Journal of Clinical PracticeInt.J.Clin.Pract., 66, 477-492, 2012	mixed populations included
Banerjee,S.K., Haque,K.M.H.S., Sharma,A.K., Ahmed,C.M., Iqbal,A.T.M., Nisa,L., Role of exercise tolerance test (ETT) and gated single photon emission computed tomography-myocardial perfusion imaging (SPECT-MPI) in predicting severity of ischemia in patients with chest pain, Bangladesh	Population (included patients with known CAD)

Author	Reason for exclusion
Medical Research Council BulletinBangladesh Med.Res.Counc.Bull., 31, 27-35, 2005	
Barone-Rochette,Gilles, Leclere,Melanie, Calizzano,Alex, Vautrin,Estelle, Celine,Gallazzini Crepin, Broisat,Alexis, Ghezzi,Catherine, Baguet,Jean Philippe, Machecourt,Jacques, Vanzetto,Gerald, Fagret,Daniel, Stress thallium-201/rest technetium-99m sequential dual-isotope high-speed myocardial perfusion imaging validation versus invasive coronary angiography, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 22, 513-522, 2015	Design (non consecutive)
Bartunek,J., Marwick,T.H., Rodrigues,A.C.T., Vincent,M., Van,Schuerbeeck E., Sys,S.U., de,Bruyne B., Dobutamine-induced wall motion abnormalities: Correlations with myocardial fractional flow reserve and quantitative coronary angiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 27, 1429-1436, 1996	Pre-selected population with known single vessel disease
Baumgart,D., Schmermund,A., Goerge,G., Haude,M., Ge,J., Adamzik,M., Sehnert,C., Altmaier,K., Groenemeyer,D., Seibel,R., Erbel,R., Comparison of electron beam computed tomography with intracoronary ultrasound and coronary angiography for detection of coronary atherosclerosis, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 30, 57-64, 1997	Non protocol index tests (Electron Beam CT with Intracoronary ultrasound)
Bayrak,Fatih, Guneysu,Tahsin, Gemici,Gokmen, Sevinc,Deniz, Mutlu,Bulent, Aytaclar,Semih, Degertekin,Muzaffer, Diagnostic performance of 64-slice computed tomography coronary angiography to detect significant coronary artery stenosis, Acta CardiologicaActa Cardiol., 63, 11-17, 2008	Mixed population, includes MI/Unstable angina
Becker,Alexander, Leber,Alexander, White,Carl W., Becker,Christoph, Reiser,Maximilian F., Knez,Andreas, Multislice computed tomography for determination of coronary artery disease in a symptomatic patient population, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 23, 361-367, 2007	Design (non consecutive enrolment)
Becker,Christoph R., Knez,Andreas, Leber,Alexander, Treede,Hendrik, Ohnesorge,B., Schoepf,U.Joseph, Reiser,Maximilian F., Detection of coronary artery stenoses with multislice helical CT angiography, Journal of Computer Assisted TomographyJ.Comput.Assisted Tomogr., 26, 750-755, 2002	Population (indirect)
Beleslin,B.D., Ostojic,M., Stepanovic,J., Djordjevic-Dikic,A., Stojkovic,S., Nedeljkovic,M., Stankovic,G., Petrasinovic,Z., Gojkovic,L., Vasiljevic-Pokrajcic,Z., Stress echocardiography in the detection of myocardial ischemia. Head-to-head comparison of exercise, dobutamine, and dipyridamole tests, Circulation, 90, 1168-1176, 1994	Mixed population - includes previous MI.
Benjelloun,L., Benjelloun,H., Laudet,M., Itti,R., Discriminant analysis of thallium-201 myocardial scintigrams, Nuclear Medicine CommunicationsNUCL.MED.COMMUN., 6, 149-157, 1985	Population (unclear - don't know what they have been referred to CA for)
Benoit,T., Vivegnis,D., Lahiri,A., Itti,R., Braat,S., Rigo,P., Tomographic myocardial imaging with technetium-99m tetrofosmin. Comparison with tetrofosmin and thallium planar imaging and with angiography, European Heart JournalEur.Heart J., 17, 635-642, 1996	Study design (open label) and mixed population (includes known CAD)

Author	Reason for exclusion
Berman,D.S., Kiat,H., Friedman,J.D., Wang,F.P., Van Train,K., Matzer,L., Maddahi,J., Germano,G., Separate acquisition rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion single-photon emission computed tomography: a clinical validation study, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 22, 1455-1464, 1993	Mixed population - includes previous MI.
Berry,E., Kelly,S., Hutton,J., Harris,K.M., Roderick,P., Boyce,J.C., Cullingworth,J., Gathercole,L., O'Connor,P.J., Smith,M.A., A systematic literature review of spiral and electron beam computed tomography: With particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease, Health Technology AssessmentHealth Technol.Assess., 3, iii-118, 1999	Non protocol index tests (Electron Beam CT)
Bettencourt,Nuno, Chiribiri,Amedeo, Schuster,Andreas, Ferreira,Nuno, Sampaio,Francisco, Pires-Morais,Gustavo, Santos,Lino, Melica,Bruno, Rodrigues,Alberto, Braga,Pedro, Azevedo,Luis, Teixeira,Madalena, Leite-Moreira,Adelino, Silva-Cardoso,Jose, Nagel,Eike, Gama,Vasco, Direct comparison of cardiac magnetic resonance and multidetector computed tomography stress-rest perfusion imaging for detection of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 61, 1099-1107, 2013	Non protocol reference standard (FFR)
Bettencourt,Nuno, Ferreira,Nuno Dias, Leite,Daniel, Carvalho,Monica, Ferreira,Wilson da Silva, Schuster,Andreas, Chiribiri,Amedeo, Leite-Moreira,Adelino, Silva-Cardoso,Jose, Nagel,Eike, Gama,Vasco, CAD detection in patients with intermediate-high pre-test probability: low-dose CT delayed enhancement detects ischemic myocardial scar with moderate accuracy but does not improve performance of a stress-rest CT perfusion protocol, JACC.Cardiovascular imagingJACC Cardiovasc Imaging, 6, 1062-1071, 2013	Non protocol reference standard (FFR)
Bettencourt,Nuno, Ferreira,Nuno, Chiribiri,Amedeo, Schuster,Andreas, Sampaio,Francisco, Santos,Lino, Melica,Bruno, Rodrigues,Alberto, Braga,Pedro, Teixeira,Madalena, Leite-Moreira,Adelino, Silva-Cardoso,Jose, Portugal,Pedro, Gama,Vasco, Nagel,Eike, Additive value of magnetic resonance coronary angiography in a comprehensive cardiac magnetic resonance stress-rest protocol for detection of functionally significant coronary artery disease: a pilot study, Circulation.Cardiovascular imagingCirc Cardiovasc Imaging, 6, 730-738, 2013	Non protocol reference standard
Bjornstad,K., Aakhus,S., Hatle,L., Comparison of digital dipyridamole stress echocardiography and upright bicycle stress echocardiography for identification of coronary artery stenosis, Cardiology, 86, 514-520, 1995	Population (included patients with known disease)
Blinder,George, Benhorin,Jesaia, Koukoui,Daniel, Zimam,Roman, Hiller,Nurith, The value of electrocardiography-gated multi-slice computed tomography in the evaluation of patients with chest pain, The Israel Medical Association journal : IMAJIsr Med Assoc J, 7, 419-423, 2005	Includes known CAD
Bogaert,J., Kuzo,R., Dymarkowski,S., Beckers,R., Piessens,J., Rademakers,F.E., Coronary artery imaging with real-time navigator three-dimensional turbo-field-echo MR	Non protocol reference test.

Author	Reason for exclusion
coronary angiography: Initial experience, Radiology, 226, 707-716, 2003	
Boomsma,M.M., Niemeyer,M.G., Van Der Wall,E.E., van Eck-Smit,B.L., Zwinderman,A.H., Boomsma,J.H., Pauwels,E.K., Tc-99m tetrofosmin myocardial SPECT perfusion imaging: comparison of rest-stress and stress-rest protocols, International Journal of Cardiac ImagingInt J Card Imaging, 14, 105-111, 1998	Population (included patients with known and suspected CAD and patients with previous MI)
Bordeleau,Edith, Lamonde,Alexandre, Prenovault,Julie, Belblidia,Assia, Cote,Gilles, Lesperance,Jacques, Soulez,Gilles, Chartrand-Lefebvre,Carl, Accuracy and rate of coronary artery segment visualization with CT angiography for the non-invasive detection of coronary artery stenoses, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 23, 771-780, 2007	Design (retrospective)
Borges-Neto,S., Mahmarian,J.J., Jain,A., Roberts,R., Verani,M.S., Quantitative thallium-201 single photon emission computed tomography after oral dipyridamole for assessing the presence, anatomic location and severity of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 11, 962-969, 1988	Mixed population - includes known CAD.
Boshchenko,Alla A., Vrublevsky,Alexander V., Karpov,Rostislav S., Transthoracic echocardiography in the detection of chronic total coronary artery occlusion, European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of CardiologyEur J Echocardiogr, 10, 62-68, 2009	Non protocol index test (Echo without stress)
Botvinick,E.H., Shames,D.M., Gershengorn,K.M., Carlsson,E., Ratshin,R.A., Parmley,W.W., Myocardial stress perfusion scintigraphy with rubidium-81 versus stress electrocardiography, The American journal of cardiologyAm J Cardiol, 39, 364-371, 1977	Obsolete (planar) imaging technique. Exclude on TE advice.
Breen,J.F., Sheedy II,P.F., Schwartz,R.S., Stanson,A.W., Kaufmann,R.B., Moll,P.P., Rumberger,J.A., Coronary artery calcification detected with ultrafast CT as an indication of coronary artery disease. Work in progress, Radiology, 185, 435-439, 1992	Mixed population
Broderick,L.S., Shemesh,J., Wilensky,R.L., Eckert,G.J., Zhou,X., Torres,W.E., Balk,M.A., Rogers,W.J., Conces,D.J.J., Kopecky,K.K., Measurement of coronary artery calcium with dual-slice helical CT compared with coronary angiography: evaluation of CT scoring methods, interobserver variations, and reproducibility, AJR.American journal of roentgenologyAJR Am J Roentgenol, 167, 439-444, 1996	Does not answer research question - Testing results of specific old and new algorithms
Budoff,M.J., Georgiou,D., Brody,A., Agatston,A.S., Kennedy,J., Wolfkiel,C., Stanford,W., Shields,P., Lewis,R.J., Janowitz,W.R., Rich,S., Brundage,B.H., Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: a multicenter study, Circulation, 93, 898-904, 1996	Mixed population - includes known CAD
Budoff,M.J., Oudiz,R.J., Zalace,C.P., Bakhsheshi,H., Goldberg,S.L., French,W.J., Rami,T.G., Brundage,B.H., Intravenous three-dimensional coronary angiography using contrast enhanced electron beam computed tomography, The American journal of cardiologyAm J Cardiol, 83, 840-845, 1999	Non protocol index test

Author	Reason for exclusion
Budoff,Matthew J., Achenbach,Stephan, Duerinckx,Andre, Clinical utility of computed tomography and magnetic resonance techniques for noninvasive coronary angiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 42, 1867-1878, 2003	Study design - Review (non systematic)
Budoff,Matthew J., Lu,Bin, Shinbane,Jerold S., Chen,Lynn, Child,Janis, Carson,Sivi, Mao,SongShou, Methodology for improved detection of coronary stenoses with computed tomographic angiography, American Heart JournalAm.Heart J., 148, 1085-1090, 2004	Non protocol index test
Bunce,Nicholas H., Reyes,Eliana, Keegan,Jennifer, Bunce,Catey, Davies,Simon W., Lorenz,Christine H., Pennell,Dudley J., Combined coronary and perfusion cardiovascular magnetic resonance for the assessment of coronary artery stenosis, Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic ResonanceJ Cardiovasc Magn Reson, 6, 527-539, 2004	Time flow (too long between tests)
Cademartiri,F., Runza,G., Marano,R., Luccichenti,G., Gualerzi,M., Brambilla,L., Galia,M., Krestin,G.P., Coruzzi,P., Midiri,M., Belgrano,M., Diagnostic accuracy of 16-row multislice CT angiography in the evaluation of coronary segments, La Radiologia medicaRadiol Med, 109, 91-97, 2005	Not available via British Library or Royal Society of Medicine
Cademartiri,Filippo, Maffei,Erica, Palumbo,Anselmo Alessandro, Malago,Roberto, La Grutta,Ludovico, Meiijboom,W.Bob, Aldrovandi,Annachiara, Fusaro,Michele, Vignali,Luigi, Menozzi,Alberto, Brambilla,Valerio, Coruzzi,Paolo, Midiri,Massimo, Kirchin,Miles A., Mollet,Nico R.A., Krestin,Gabriel P., Influence of intra-coronary enhancement on diagnostic accuracy with 64-slice CT coronary angiography, European RadiologyEur.Radiol., 18, 576-583, 2008	Population (included patients with known CAD)
Cademartiri,Filippo, Marano,Riccardo, Luccichenti,Giacomo, Mollet,Nico, Runza,Giuseppe, Galia,Massimo, Belgrano,Manuel, Gualerzi,Massimo, Brambilla,Lorenzo, Coruzzi,Paolo, Midiri,Massimo, Image assessment with multislice CT coronary angiography, La Radiologia medicaRadiol Med, 109, 198-207, 2005	Not available via British Library or Royal Society of Medicine
Cademartiri,Filippo, Mollet,Nico, Lemos,Pedro A., McFadden,Eugene P., Marano,Riccardo, Baks,Timo, Stijnen,Theo, de Feyter,Pim J., Krestin,Gabriel P., Standard versus user-interactive assessment of significant coronary stenoses with multislice computed tomography coronary angiography, The American journal of cardiologyAm J Cardiol, 94, 1590-1593, 2004	16 slice CT (minimum 64 slice)
Caiati,Carlo, Lepera,Mario Erminio, Carretta,Domenico, Santoro,Daniela, Favale,Stefano, Head-to-head comparison of peak upright bicycle and post-treadmill echocardiography in detecting coronary artery disease: a randomized, single-blind crossover study, Journal of the American Society of Echocardiography : official publication of the American Society of EchocardiographyJ Am Soc Echocardiogr, 26, 1434-1443, 2013	Mixed population - includes known CAD.
Caldwell,J.H., Hamilton,G.W., Sorensen,S.G., The detection of coronary artery disease with radionuclide techniques: A comparison of rest-exercise thallium imaging and ejection	Mixed population - includes known CAD.

Author	Reason for exclusion
fraction response, Circulation, 61, 610-619, 1980	
Callister TQ, Cooil B, Raya SP et al. (1998) Coronary artery disease: Imoproved reproducibility of Calcium Scoring with an Electron-Beam CT Volumetric method. Radiology. 208:807-814.	Non protocol index test.
Carmo,Miguel Mota, Ferreira,Teresa, Quininha,Jorge, Ferreira,Jose, Non-invasive coronary artery evaluation with multidetector computed tomography, Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of CardiologyRev Port Cardiol, 24, 667-679, 2005	Mixed population - includes previous CABG.
Carrascosa,Patricia Marina, Capunay,Carlos Maria, Parodi,Juan Carlos, Padilla,Lucio Tiburcio, Johnson,Peter, Carrascosa,Jorge Manuel, Chandra,Shalabh, Smith,Dava, Belardi,Jorge, General utilities of multislice tomography in the cardiac field, Herz, 28, 44-51, 2003	Population (included patients with known CAD)
Carrascosa,Patricia, Capunay,Carlos, Bettinotti,Marcelo, Goldsmit,Alejandro, Deviggiano,Alejandro, Carrascosa,Jorge, Garcia,Mario J., Feasibility of gadolinium-diethylene triamine pentaacetic acid enhanced multidetector computed tomography for the evaluation of coronary artery disease, Journal of Cardiovascular Computed TomographyJ.Cardiovasc.Comput.Tomogr., 1, 86-94, 2007	Mixed population - includes known CAD
Carrascosa,Patricia, Capunay,Carlos, Deviggiano,Alejandro, Bettinotti,Marcelo, Goldsmit,Alejandro, Tajer,Carlos, Carrascosa,Jorge, Garcia,Mario J., Feasibility of 64-slice gadolinium-enhanced cardiac CT for the evaluation of obstructive coronary artery disease, Heart (British Cardiac Society), 96, 1543-1549, 2010	Includes known CAD
Carrascosa,Patricia, Deviggiano,Alejandro, Capunay,Carlos, De Zan,Macarena C., Goldsmit,Alejandro, Rodriguez-Granillo,Gaston A., Effect of intracycle motion correction algorithm on image quality and diagnostic performance of computed tomography coronary angiography in patients with suspected coronary artery disease, Academic RadiologyAcad.Radiol., 22, 81-86, 2015	New Generation Scanner used (Discovery 750)- covered by DG3
Carrascosa,Patricia, Merletti,Pablo Garcia, Capunay,Carlos, Goldsmit,Alejandro, Bettinotti,Marcelo, Carrascosa,Jorge, New approach to noninvasive coronary angiography by multidetector computed tomography: initial experience using gadolinium, Journal of Computer Assisted TomographyJ.Comput.Assisted Tomogr., 31, 441-443, 2007	Population (included patients with known CAD)
Carstensen,S., Host,U., Saunamaki,K., Kelbaek,H., Quantitative analysis of dobutamine-atropine stress echocardiography by fractional area change, European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of CardiologyEur J Echocardiogr, 3, 220-228, 2002	Mixed population - includes known CAD
Caymaz,O., Fak,A.S., Tezcan,H., Inanir,S., Toprak,A., Tokay,S., Turoglu,T., Oktay,A., Correlation of myocardial fractional flow reserve with thallium-201 SPECT imaging in intermediate-severity coronary artery lesions, The Journal of invasive cardiologyJ Invasive Cardiol, 12, 345-350, 2000	Unclear which test was reference standard
Celutkiene,Jelena, Zakarkaite,Diana, Skorniakov,Viktor, Zvironaite,Vida, Grabauskiene,Virginija, Burca,Jelizaveta, Ciparyte,Laura, Laucevicius,Aleksandras, Quantitative	Mixed population - includes known CAD.

Author	Reason for exclusion
approach using multiple single parameters versus visual assessment in dobutamine stress echocardiography, Cardiovascular ultrasoundCardiovasc Ultrasound, 10, 31-, 2012	
Cerci,Rodrigo, Vavere,Andrea L., Miller,Julie M., Yoneyama,Kihei, Rochitte,Carlos E., Dewey,Marc, Niinuma,Hiroyuki, Clouse,Melvin E., Laham,Roger, Bush,David E., Shapiro,Edward P., Lardo,Albert C., Cox,Christopher, Brinker,Jeffrey, Lima,Joao A.C., Arbab-Zadeh,Armin, Patterns of coronary arterial lesion calcification by a novel, cross-sectional CT angiographic assessment, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 29, 1619-1627, 2013	Mixed population - includes known CAD.
Chammas,Elie, Yatim,Ahmad, Hage,Chadi, Sokhn,Kozhaya, Tarcha,Walid, Ghanem,Georges, Evaluation of Tc-99m tetrofosmin scan for coronary artery disease diagnosis, Asian cardiovascular & thoracic annals, 10, 244-247, 2002	Population (included patients with known or suspected CAD)
Chandraratna,P.A., Kuznetsov,V.A., Mohar,D.S., Sidarous,P.F., Scheutz,J., Krinochkin,D.V., Pak,Y.A., Mohar,P., Arawgoda,U., Comparison of squatting stress echocardiography and dobutamine stress echocardiography for the diagnosis of coronary artery disease, Echocardiography (Mount Kisco, N.Y.), 29, 695-699, 2012	Reference standard (unclear)
Chao,Shu Ping, Law,Wai Yip, Kuo,Chu Jen, Hung,Huei Fong, Cheng,Jun Jack, Lo,Huey Ming, Shyu,Kou Gi, The diagnostic accuracy of 256-row computed tomographic angiography compared with invasive coronary angiography in patients with suspected coronary artery disease, European Heart JournalEur.Heart J., 31, 1916-1923, 2010	New generation scanner used (as per protocol exclusions)
Chaosuwannakit,Narumol, Kiatchoosakun,Songsak, Makarawate,Pattarapong, Diagnostic accuracy of 128-row multidetector computed tomography coronary angiography in the diagnosis of significant coronary artery stenosis, Journal of the Medical Association of Thailand = Chotmaihet thangphaetJ Med Assoc Thai, 95, 1548-1555, 2012	Design (retrospective)
Chen,Gui Bing, Wu,Hua, He,Xiao Jiang, Huang,Jin Xiong, Yu,Dan, Xu,Wei Yi, Yu,Hao, Adenosine stress thallium-201 myocardial perfusion imaging for detecting coronary artery disease at an early stage, Journal of X-ray science and technologyJ Xray Sci Technol, 21, 317-322, 2013	No threshold given for CAD with CA
Chen,Hong wei, Fang,Xiang ming, Hu,Xiao yun, Bao,Jian, Hu,Chun hong, Chen,Yin, Yang,Zhen yu, Alexander,Lerner, Wu,Xiao qing, Efficacy of dual-source CT coronary angiography in evaluating coronary stenosis: initial experience, Clinical ImagingClin.Imaging, 34, 165-171, 2010	Design (retrospective)
Chen,L.C., Ding,P.Y., Chen,J.W., Wu,M.H., Liu,J.C., Lan,G.Y., Chern,M.S., Chang,C.Y., Chang,M.S., Coronary artery calcium determined by electron beam computed tomography for predicting angiographic coronary artery disease in moderate- to high-risk Chinese patients, Cardiology, 95, 183-189, 2001	Non protocol index test (EBCT)
Chen,M.-L., Chao,I.-M., Chen,C.-H., Wu,H.-H., Chen,P.-L., Liu,S.-M., Chen,P.H., Diagnostic accuracy and safety of dipyridamole Thallium-201 single photon emission computed tomography in coronary artery disease, Acta Cardiologica SinicaActa Cardiol.Sin., 12, 126-133, 1996	Population (mixed)
Chen,Yan, Han,Ping, Liang,Bo, Liang,Huimin, Lei,Ziqiao,	Design (retrospective)

Author	Reason for exclusion
Tian,Zhiliang, Feng,Gansheng, Xiao,Jie, Comparative study on 16-slice CT coronary angiography vs conventional coronary angiography--a report of 38 cases, Journal of Huazhong University of Science and Technology.Medical sciences = Hua zhong ke ji da xue xue bao.Yi xue Ying De wen ban = Huazhong keji daxue xuebao.Yixue Yingdewen banJ Huazhong Univ Sci Technolog Med Sci, 28, 110-113, 2008	
Chen,Zhiyong, Duan,Qing, Xue,Xunjing, Chen,Lianglong, Ye,Wenbin, Jin,Lixin, Sun,Bin, Noninvasive detection of coronary artery stenoses with contrast-enhanced whole-heart coronary magnetic resonance angiography at 3.0 T, Cardiology, 117, 284-290, 2010	Non protocol index test
Cheng,Adrian S.H., Pegg,Tammy J., Karamitsos,Theodoros D., Searle,Nick, Jerosch-Herold,Michael, Choudhury,Robin P., Banning,Adrian P., Neubauer,Stefan, Robson,Matthew D., Selvanayagam,Joseph B., Cardiovascular magnetic resonance perfusion imaging at 3-tesla for the detection of coronary artery disease: a comparison with 1.5-tesla, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 49, 2440-2449, 2007	Mixed population - includes known CAD.
Cheng,L., Jing,S., Zhang,Y., A comparison study between CT angiography with 64-multislice spiral computed tomography and selective X-ray coronary angiography, Experimental and Therapeutic MedicineExp.Ther.Med., 5, 969-971, 2013	Study design - case control.
Cheng,L., Jing,S., Zhang,Y., A comparison study between CT angiography with 64-multislice spiral computed tomography and selective X-ray coronary angiography, Experimental and Therapeutic MedicineExp.Ther.Med., 5, 969-971, 2013	Study design - case control
Cheng,Liuquan, Gao,Yuangui, Guaricci,Andrea I., Mulukutla,Suresh, Sun,Wei, Sheng,Fugeng, Foo,Thomas K., Prince,Martin R., Wang,Yi, Breath-hold 3D steady-state free precession coronary MRA compared with conventional X-ray coronary angiography, Journal of magnetic resonance imaging : JMRIJ Magn Reson Imaging, 23, 669-673, 2006	Non protocol index test
Cheng,Liuquan, Ma,Lin, Schoenhagen,Paul, Ye,Huiyi, Lou,Xin, Gao,Yuangui, Zhao,Xihai, Wang,Xinjiang, Dong,Wei, Comparison of three-dimensional volume-targeted thin-slab FIESTA magnetic resonance angiography and 64-multidetector computed tomographic angiography for the identification of proximal coronary stenosis, International journal of cardiologyInt.J.Cardiol., 167, 2969-2976, 2013	No per patient analysis reported
Chiou,Kuan Rau, Huang,Wei Chun, Lin,Shoa Lin, Hsieh,Pu Lin, Liu,Chun Peng, Tsay,Daw Guey, Chiang,Hung Ting, Real-time dobutamine stress myocardial contrast echocardiography for detecting coronary artery disease: correlating abnormal wall motion and disturbed perfusion, The Canadian journal of cardiologyCan J Cardiol, 20, 1237-1243, 2004	Includes known CAD
Cho,Hyun Ok, Nam,Chang Wook, Cho,Yun Kyeong, Yoon,Hyuck Jun, Park,Hyoung Seob, Kim,Hyungseop, Chung,In Sung, Doh,Joon Hyung, Koo,Bon Kwon, Hyun,Dae Woo, Hur,Seung Ho, Kim,Yoon Nyun, Kim,Kwon Bae, Characteristics of function-anatomy mismatch in patients with coronary artery disease, Korean Circulation JournalKorean	Mixed population - includes people with known coronary lesions

Author	Reason for exclusion
Circ.J., 44, 394-399, 2014	
Choi,Jin Oh, Cho,Sung Won, Song,Young Bin, Cho,Soo Jin, Song,Bong Gun, Lee,Sang Chol, Park,Seung Woo, Longitudinal 2D strain at rest predicts the presence of left main and three vessel coronary artery disease in patients without regional wall motion abnormality, European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of CardiologyEur J Echocardiogr, 10, 695-701, 2009	Non protocol index test (2D echo without stress)
Chow,B.J.W., Freeman,M.R., Bowen,J.M., Levin,L., Hopkins,R.B., Provost,Y., Tarride,J.-E., Dennie,C., Cohen,E.A., Marcuzzi,D., Iwanochko,R., Moody,A.R., Paul,N., Parker,J.D., O'Reilly,D.J., Xie,F., Goeree,R., Ontario multidetector computed tomographic coronary angiography study: Field evaluation of diagnostic accuracy, Archives of Internal MedicineArch.Intern.Med., 171, 1021-1029, 2011	Mixed population. Includes known valve disease/congenital heart disease.
Chow,Benjamin J.W., Abraham,Arun, Wells,George A., Chen,Li, Ruddy,Terrence D., Yam,Yeung, Govas,Nayia, Galbraith,Phoebe Diane, Dennie,Carole, Beanlands,Rob S., Diagnostic accuracy and impact of computed tomographic coronary angiography on utilization of invasive coronary angiography, Circulation.Cardiovascular imagingCirc Cardiovasc Imaging, 2, 16-23, 2009	Study design - retrospective
Chow,Benjamin J.W., Dennie,Carole, Hoffmann,Udo, So,Derek, de Kemp,Robert A., Ruddy,Terrence D., Beanlands,Rob S., Comparison of computed tomographic angiography versus rubidium-82 positron emission tomography for the detection of patients with anatomical coronary artery disease, The Canadian journal of cardiologyCan J Cardiol, 23, 801-807, 2007	Mixed population - includes known disease.
Chow,Benjamin J.W., Kass,Malek, Gagne,Owen, Chen,Li, Yam,Yeung, Dick,Alexander, Wells,George A., Can differences in corrected coronary opacification measured with computed tomography predict resting coronary artery flow?, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 57, 1280-1288, 2011	Study design - retrospective
Chowdhury,F.U., Vaidyanathan,S., Bould,M., Marsh,J., Trickett,C., Dodds,K., Clark,T.P.R., Sapsford,R.J., Dickinson,C.J., Patel,C.N., Thorley,P.J., Rapid-acquisition myocardial perfusion scintigraphy (MPS) on a novel gamma camera using multipinhole collimation and miniaturized cadmium-zinc-telluride (CZT) detectors: prognostic value and diagnostic accuracy in a 'real-world' nuclear cardiology service, European Heart Journal Cardiovascular ImagingEur.Heart J.Cardiovasc.Imaging, 15, 275-283, 2014	Study Design - retrospective
Christensen,Henrik Wulff, Haghfelt,Torben, Vach,Werner, Johansen,Allan, Hoilund-Carlsen,Poul Flemming, Observer reproducibility and validity of systems for clinical classification of angina pectoris: comparison with radionuclide imaging and coronary angiography, Clinical Physiology and Functional ImagingClin.Physiol.Funct.Imaging, 26, 26-31, 2006	Population (included patients with known CAD)
Chua,S.-K., Hung,H.-F., Cheng,J.-J., Tseng,M.-T., Law,W.-Y., Kuo,C.-J., Chiu,C.-Z., Chang,C.-M., Lee,S.-H., Lo,H.-M., Lin,S.-C., Liou,J.-Y., Shyu,K.-G., Diagnostic performance of 64-versus 256-slice computed tomography coronary angiography compared with conventional coronary angiography in patients with suspected coronary artery disease, Acta Cardiologica SinicaActa Cardiol.Sin., 29, 151-	Study design - retrospective. Protocol exclusion (New generation scanner used).

Author	Reason for exclusion
159, 2013	
Chung,W.Y., Choi,B.J., Lim,S.H., Matsuo,Y., Lennon,R.J., Gulati,R., Sandhu,G.S., Holmes,D.R.,Jr., Rihal,C.S., Lerman,A., Three dimensional quantitative coronary angiography can detect reliably ischemic coronary lesions based on fractional flow reserve, J Korean Med Sci, 30, 716-724, 2015	Non protocol index
Ciavolella,M., Tomai,F., Vicchio,D., Ruscitti,G., Giannitti,C., Scali,D., Schad,N., Reale,A., Single-day combined evaluation of regional myocardial perfusion and function at rest and peak exercise with 99mTc-MIBI in patients with coronary artery disease, International Journal of Cardiac ImagingInt J Card Imaging, 9, 299-311, 1993	Population (included patients with known CAD)
Cohen,J.L., Chan,K.L., Jaarsma,W., Bach,D.S., Muller,D.W.M., Starling,M.R., Armstrong,W.F., Arbutamine echocardiography: Efficacy and safety of a new pharmacologic stress agent to induce myocardial ischemia and detect coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 26, 1168-1175, 1995	Mixed population - includes known CAD.
Cohen,J.L., Greene,T.O., Ottenweller,J., Binenbaum,S.Z., Wilchfort,S.D., Kim,C.S., Dobutamine digital echocardiography for detecting coronary artery disease, The American journal of cardiologyAm J Cardiol, 67, 1311-1318, 1991	Includes known CAD.
Cohen,J.L., Ottenweller,J.E., George,A.K., Duvvuri,S., Comparison of dobutamine and exercise echocardiography for detecting coronary artery disease, The American journal of cardiologyAm J Cardiol, 72, 1226-1231, 1993	Population (included patients with previous MI)
Conti,Alberto, Mariannini,Yuri, Canuti,Erica, Petrova,Tetyana, Innocenti,Francesca, Zanobetti,Maurizio, Gallini,Chiara, Costanzo,Egidio, Nuclear scan strategy and outcomes in chest pain patients value of stress testing with dipyridamole or adenosine, World journal of nuclear medicineWorld j.nucl.med., 13, 94-101, 2014	Mixed population - includes acute chest pain
Cramer,M.J., Verzijlbergen,J.F., Niemeyer,M.G., Van Der Wall,E.E., Zwinderman,A.H., Ascoop,C.A., Pauwels,E.K., 99Tcm-sestamibi SPECT with combined dipyridamole and exercise stress in coronary artery disease, Nuclear Medicine CommunicationsNUCL.MED.COMMUN., 15, 554-559, 1994	Population (included patients with previous MI)
Cramer,M.J., Verzijlbergen,J.F., Van Der Wall,E.E., Vermeersch,P.H., Niemeyer,M.G., Zwinderman,A.H., Ascoop,C.A., Pauwels,E.K., Comparison of adenosine and high-dose dipyridamole both combined with low-level exercise stress for 99Tcm-MIBI SPET myocardial perfusion imaging, Nuclear Medicine CommunicationsNUCL.MED.COMMUN., 17, 97-104, 1996	Population (included patients with previous MI)
Cramer,M.J., Verzijlbergen,J.F., Wall,E.E., Niemeyer,M.G., Zwinderman,A.H., Ascoop,C.A., Pauwels,E.J., Head-to-head comparison between technetium-99m-sestamibi and thallium-201 tomographic imaging for the detection of coronary artery disease using combined dipyridamole-exercise stress, Coronary Artery DiseaseCoron.Artery Dis., 5, 787-791, 1994	Population (included patients with previous MI)
Cury,Ricardo C., Cattani,Cesar A.M., Gabure,Luiz A.G., Racy,Douglas J., de Gois,Jose M., Siebert,Uwe, Lima,Sergio S., Brady,Thomas J., Diagnostic performance of stress perfusion and delayed-enhancement MR imaging in patients	Mixed population - includes previous MI.

Author	Reason for exclusion
with coronary artery disease, Radiology, 240, 39-45, 2006	
Cury,Roberto C., Magalhaes,Tiago A., Borges,Anna C., Shiozaki,Afonso A., Lemos,Pedro A., Junior,Jose Soares, Meneghetti,Jose Claudio, Cury,Ricardo C., Rochitte,Carlos E., Dipyridamole stress and rest myocardial perfusion by 64-detector row computed tomography in patients with suspected coronary artery disease, The American journal of cardiologyAm J Cardiol, 106, 310-315, 2010	Only participants with positive SPECT were included
Cwajg,J., Xie,F., O'Leary,E., Kricsfeld,D., Dittrich,H., Porter,T.R., Detection of angiographically significant coronary artery disease with accelerated intermittent imaging after intravenous administration of ultrasound contrast material, American Heart JournalAm.Heart J., 139, 675-683, 2000	Design (retrospective)
Daghighi,M.H., Javadrashid,R., Ghaffari,S., Sadighi,A., PourIssa,M., Abdkarimi,M.H., Ghorashi,S., Nezami,N., 64-Slice multidetector computed tomographic angiography and invasive coronary angiography in diagnosis of significant coronary artery stenosis, Journal of Surgical RadiologyJ.Surg.Radiol., 3, 204-209, 2012	Population (all patients had CAD signs/symptoms. 50% stable angina. 15% atypical chest pain)
Danad,Ibrahim, Raijmakers,Pieter G., Appelman,Yolande E., Harms,Hendrik J., de Haan,Stefan, van den Oever,Mijntje L.P., Heymans,Martijn W., Tulevski,Igor I., van Kuijk,Cornelis, Hoekstra,Otto S., Lammertsma,Adriaan A., Lubberink,Mark, van Rossum,Albert C., Knaapen,Paul, Hybrid imaging using quantitative H215O PET and CT-based coronary angiography for the detection of coronary artery disease, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 54, 55-63, 2013	Non protocol reference standard
Danad,Ibrahim, Raijmakers,Pieter G., Harms,Hendrik J., Heymans,Martijn W., van Royen,Niels, Lubberink,Mark, Boellaard,Ronald, van Rossum,Albert C., Lammertsma,Adriaan A., Knaapen,Paul, Impact of anatomical and functional severity of coronary atherosclerotic plaques on the transmural perfusion gradient: a [15O]H2O PET study, European Heart JournalEur.Heart J., 35, 2094-2105, 2014	Reference standard (non protocol)
Danad,Ibrahim, Uusitalo,Valtteri, Kero,Tanja, Saraste,Antti, Raijmakers,Pieter G., Lammertsma,Adriaan A., Heymans,Martijn W., Kajander,Sami A., Pietila,Mikko, James,Stefan, Sorensen,Jens, Knaapen,Paul, Knuuti,Juhani, Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease: cutoff values and diagnostic accuracy of quantitative [(15)O]H2O PET imaging, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 64, 1464-1475, 2014	Analysis (missing data) Reference standard (non protocol)
Danias,Peter G., Roussakis,Arkadios, Ioannidis,John P.A., Diagnostic performance of coronary magnetic resonance angiography as compared against conventional X-ray angiography: a meta-analysis, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 44, 1867-1876, 2004	Population (included patients with known disease)
Dart,J., Yuda,S., Cain,P., Case,C., Marwick,T.H., Use of myocardial backscatter as a quantitative tool for dobutamine echocardiography: Feasibility, response to ischemia and accuracy compared with coronary angiography, International Journal of Cardiovascular ImagingInt.J.Card.Imaging, 18, 325-336, 2002	Population (included patients with known CAD)

Author	Reason for exclusion
Davin,Laurent, Lancellotti,Patrizio, Bruyere,Pierre Julien, Gach,Olivier, Pierard,Luc, Legrand,Victor, Diagnostic accuracy of computed tomography coronary angiography in routine practice, Acta CardiologicaActa Cardiol., 62, 339-344, 2007	CT scanner 16 slice only
de Graaf,Fleur R., Schuijf,Joanne D., van Velzen,Joella E., Boogers,Mark J., Kroft,Lucia J., de Roos,Albert, Reiber,Johannes H.C., Sieders,Allard, Spano,Fabrizio, Jukema,J.Wouter, Schalij,Martin J., van der Wall,Ernst E., Bax,Jeroen J., Diagnostic accuracy of 320-row multidetector computed tomography coronary angiography to noninvasively assess in-stent restenosis, Investigative RadiologyInvest.Radiol., 45, 331-340, 2010	Index test overlaps with DG3 (New Generation Scanner)
de Graaf,Fleur R., Schuijf,Joanne D., van Velzen,Joella E., Kroft,Lucia J., de Roos,Albert, Reiber,Johannes H.C., Boersma,Eric, Schalij,Martin J., Spano,Fabrizio, Jukema,J.Wouter, van der Wall,Ernst E., Bax,Jeroen J., Diagnostic accuracy of 320-row multidetector computed tomography coronary angiography in the non-invasive evaluation of significant coronary artery disease, European Heart JournalEur.Heart J., 31, 1908-1915, 2010	Mixed population - includes known CAD. New Generation scanner used (protocol exclusion).
de Jong,Marcus C., Genders,Tessa S.S., van Geuns,Robert Jan, Moelker,Adriaan, Hunink,M.G.M., Diagnostic performance of stress myocardial perfusion imaging for coronary artery disease: a systematic review and meta-analysis, European RadiologyEur.Radiol., 22, 1881-1895, 2012	Mixed populations - includes known CAD.
de Mello,Ricardo Andrade Fernades, Nacif,Marcelo Souto, dos Santos,Alair Augusto Sarmet, Cury,Ricardo Caldeira, Rochitte,Carlos Eduardo, Marchiori,Edson, Diagnostic performance of combined cardiac MRI for detection of coronary artery disease, European Journal of RadiologyEur.J.Radiol., 81, 1782-1789, 2012	Design (retrospective)
Dedic,Admir, Rossi,A., Ten Kate,G.J.R., Neefjes,L.A., Galema,T.W., Moelker,A., Van Domburg,R.T., Schultz,C.J., Mollet,N.R., De Feyter,P.J., Nieman,K., First-line evaluation of coronary artery disease with coronary calcium scanning or exercise electrocardiography, International journal of cardiologyInt.J.Cardiol., 163, 190-195, 2013	Mixed population - includes known disease.
Deetjen,Anja G., Conradi,Guido, Mollmann,Susanne, Ekinci,Okan, Weber,Michael, Nef,Holger, Mollmann,Helge, Hamm,Christian W., Dill,Thorsten, Diagnostic value of the 16-detector row multislice spiral computed tomography for the detection of coronary artery stenosis in comparison to invasive coronary angiography, Clinical CardiologyClin.Cardiol., 30, 118-123, 2007	Mixed population. Includes known disease.
Delgado,Carlos, Vazquez,Maria, Oca,Roque, Vilar,Manuel, Trinidad,Carmen, Sanmartin,Marcelo, Myocardial ischemia evaluation with dual-source computed tomography: comparison with magnetic resonance imaging, Revista espanola de cardiologia (English ed.)Rev Esp Cardiol (Engl), 66, 864-870, 2013	Index test overlaps with DG3 (New Generation Scanner) Population (only included patients with positive stress tests)
Dendukuri,N., Chiu,K., Brophy,J.M., Validity of electron beam computed tomography for coronary artery disease: Asystematic review and meta-analysis, BMC MedicineBMC Med., 5, -, 2007	Non protocol index test (EBCT)
Detrano,R., Gianrossi,R., Mulvihill,D., Lehmann,K.,	Non protocol index test

Author	Reason for exclusion
Dubach,P., Colombo,A., Froelicher,V., Exercise-induced ST segment depression in the diagnosis of multivessel coronary disease: a meta analysis, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 14, 1501-1508, 1989	
Dewey,M., Schnapauff,D., Laule,M., Lembcke,A., Borges,A.C., Rutsch,W., Hamm,B., Rogalla,P., Multislice CT coronary angiography: Evaluation of an automatic vessel detection tool, RoFo Fortschritte auf dem Gebiet der Rontgenstrahlen und der Bildgebenden VerfahrenRoFo Fortschr.Geb.Rontgenstr.Bildgebenden Verfahren, 176, 478-483, 2004	Index test overlaps with DG3 (New Generation Scanner)
Dewey,Marc, Dubel,Hans Peter, Schink,Tania, Baumann,Gert, Hamm,Bernd, Head-to-head comparison of multislice computed tomography and exercise electrocardiography for diagnosis of coronary artery disease, European Heart JournalEur.Heart J., 28, 2485-2490, 2007	CT scanner specification - 16 slice only.
Dewey,Marc, Teige,Florian, Rutsch,Wolfgang, Schink,Tania, Hamm,Bernd, CT coronary angiography: influence of different cardiac reconstruction intervals on image quality and diagnostic accuracy, European Journal of RadiologyEur.J.Radiol., 67, 92-99, 2008	16 Slice scanner (minimum 64 slice)
Dewey,Marc, Teige,Florian, Schnapauff,Dirk, Laule,Michael, Borges,Adrian C., Wernecke,Klaus Dieter, Schink,Tania, Baumann,Gert, Rutsch,Wolfgang, Rogalla,Patrik, Taupitz,Matthias, Hamm,Bernd, Noninvasive detection of coronary artery stenoses with multislice computed tomography or magnetic resonance imaging, Annals of Internal MedicineANN.INTERN.MED., 145, 407-415, 2006	Only participants with positive stress test were included
Dewey,Marc, Zimmermann,Elke, Deissenrieder,Florian, Laule,Michael, Dubel,Hans Peter, Schlattmann,Peter, Knebel,Fabian, Rutsch,Wolfgang, Hamm,Bernd, Noninvasive coronary angiography by 320-row computed tomography with lower radiation exposure and maintained diagnostic accuracy: comparison of results with cardiac catheterization in a head-to-head pilot investigation, Circulation, 120, 867-875, 2009	New generation scanner used (protocol exclusion)
Dharampal,Anoeshka S., Papadopoulou,Stella L., Rossi,Alexia, Meijboom,W.Bob, Weustink,Annick, Dijkshoorn,Marcel, Nieman,Koen, Boersma,Eric H., de Feijter,Pim J., Krestin,Gabriel P., Diagnostic performance of computed tomography coronary angiography to detect and exclude left main and/or three-vessel coronary artery disease, European RadiologyEur.Radiol., 23, 2934-2943, 2013	Index test overlaps with DG3 (New Generation Scanner)
Di Bello,V., Gori,E., Bellina,C.R., Parodi,O., Molea,N., Santoro,G., Mariani,G., Conti,U., Magagnini,E., Marzullo,P., Incremental diagnostic value of dipyridamole echocardiography and exercise thallium 201 scintigraphy in the assessment of presence and extent of coronary artery disease, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 1, 372-381, 1994	Analysis (missing data)
Di Tanna,Gian Luca, Berti,Elena, Stivanello,Elisa, Cademartiri,Filippo, Achenbach,Stephan, Camerlingo,Maria Domenica, Grilli,Roberto, Informative value of clinical research on multislice computed tomography in the diagnosis of coronary artery disease: A systematic review, International	Population (included patients with known CAD)

Author	Reason for exclusion
journal of cardiologyInt.J.Cardiol., 130, 386-404, 2008	
Dikkers,R., Willems,T.P., Piers,L.H., de Jonge,G.J., Tio,R.A., van der Zaag-Loonen,H.J., van Ooijen,P.M.A., Zijlstra,F., Oudkerk,M., Coronary revascularization treatment based on dual-source computed tomography, European RadiologyEur.Radiol., 18, 1800-1808, 2008	Not relevant
Djordjevic-Dikic,A.D., Ostojic,M.C., Beleslin,B.D., Stepanovic,J., Petrasinovic,Z., Babic,R., Stojkovic,S.M., Stankovic,G., Nedeljkovic,M., Nedeljkovic,I., Kanjuh,V., High dose adenosine stress echocardiography for noninvasive detection of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 28, 1689-1695, 1996	Mixed population: Includes patients with previous MI
Donati,O.F., Alkadhi,H., Scheffel,H., Kuehnel,C., Hennemuth,A., Wyss,C., Azemaj,N., Plass,A., Kozerke,S., Falk,V., Leschka,S., Stolzmann,P., 3D fusion of functional cardiac magnetic resonance imaging and computed tomography coronary angiography: accuracy and added clinical value, Investigative RadiologyInvest.Radiol., 46, 331-340, 2011	Population (included patients with known stenoses)
Donati,Olivio F., Scheffel,Hans, Stolzmann,Paul, Baumuller,Stephan, Plass,Andre, Leschka,Sebastian, Alkadhi,Hatem, Combined cardiac CT and MRI for the comprehensive workup of hemodynamically relevant coronary stenoses, AJR.American journal of roentgenologyAJR Am J Roentgenol, 194, 920-926, 2010	Includes known CAD
Dong,Shaohong, Liang,Xu, Zhang,Shaoweng, Zhai,Lihua, Hu,Xuesong, Xia,Lingqiong, Wang,Zengying, Yang,Chunyu, Yuan,Nuanrong, Assessment of coronary artery disease with second harmonic myocardial perfusion contrast echocardiography, Chinese medical journalChin.Med.J., 115, 837-841, 2002	Population (included patients with known CAD)
Duvall,W.Lane, Sweeny,Joseph M., Croft,Lori B., Barghash,Maya H., Kulkarni,Nitin K., Guma,Krista A., Henzlova,Milena J., Comparison of high efficiency CZT SPECT MPI to coronary angiography, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 18, 595-604, 2011	Design (retrospective) Population (included patients with known CAD)
Duvall,W.Lane, Sweeny,Joseph M., Croft,Lori B., Ginsberg,Eric, Guma,Krista A., Henzlova,Milena J., Reduced stress dose with rapid acquisition CZT SPECT MPI in a non-obese clinical population: comparison to coronary angiography, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 19, 19-27, 2012	Retrospective design
Einstein AJ, Henzlova MJ, Rajagopalan S. (2007) Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA. 298 (3): 317-323.	Not revelvant
Elhendy,A., Geleijnse,M.L., Van Domburg,R.T., Nierop,P.R., Poldermans,D., Bax,J.J., Tencate,F.J., Nosir,Y.F., Ibrahim,M.M., Roelandt,J.R., Gender differences in the accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery disease, The American journal of cardiologyAm J Cardiol, 80, 1414-1418, 1997	Subgroup analysis only
Elhendy,Abdou, O'Leary,Edward L., Xie,Feng, McGrain,Anna C., Anderson,James R., Porter,Thomas R., Comparative	Includes known CAD

Author	Reason for exclusion
accuracy of real-time myocardial contrast perfusion imaging and wall motion analysis during dobutamine stress echocardiography for the diagnosis of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 44, 2185-2191, 2004	
Engman,M.L., An update on EBCT (Ultrafast CT) scans for coronary artery disease, Journal of insurance medicine (New York, N.Y.), 30, 175-179, 1998	Non protocol index test
Epstein,M., Gin,K., Sterns,L., Pollick,C., Dobutamine stress echocardiography: initial experience of a Canadian centre, The Canadian journal of cardiologyCan J Cardiol, 8, 273-279, 1992	Population (included patients with known or suspected CAD)
Erdogan,Nihan, Akar,Nihal, Vural,Murat, Canbay,Alper, Kayhan,Tugba, Sahin,Deniz, Diker,Erdem, Aydogdu,Sinan, Diagnostic value of 16-slice multidetector computed tomography in symptomatic patients with suspected significant obstructive coronary artery disease, Heart and VesselsHeart Vessels, 21, 278-284, 2006	16 slice CT Scanner only
Eroglu,Elif, D'hooge,Jan, Herbots,Lieven, Thijs,Daisy, Dubois,Christophe, Sinnaeve,Peter, Dens,Joseph, Vanhaecke,Johan, Rademakers,Frank, Comparison of real-time tri-plane and conventional 2D dobutamine stress echocardiography for the assessment of coronary artery disease, European Heart JournalEur.Heart J., 27, 1719-1724, 2006	Includes known CAD.
Evaluation of coronary arterial stenoses using 2D magnetic resonance coronary angiography, Minim.Invasive Ther Allied.Technol, 11, 7-15, 2002	Non protocol index test
Fagret,D., Marie,P.Y., Brunotte,F., Giganti,M., Le Guludec,D., Bertrand,A., Wolf,J.E., Piffanelli,A., Chossat,F., Bekhechi,D., Myocardial perfusion imaging with technetium-99m-Tc NOET: comparison with thallium-201 and coronary angiography, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 36, 936-943, 1995	Mixed population, includes patients with prior MI
Faisal,A.W., Abid,A.R., Azhar,M., Exercise Tolerance Test: a comparison between true positive and false positive test results, Journal of Ayub Medical College, AbbottabadJ Ayub Med Coll Abbottabad, 19, 71-74, 2007	Non protocol index test
Feldman,C., Vitola,D., Schiavo,N., Detection of coronary artery disease based on the calcification index obtained by helical computed tomography, Arquivos Brasileiros de CardiologiaArq.Bras.Cardiol., 75, 471-480, 2000	Includes known CAD/acute chest pain.
Fiechter,Michael, Ghadri,Jelena R., Gebhard,Catherine, Fuchs,Tobias A., Pazhenkottil,Aju P., Nkoulou,Rene N., Herzog,Bernhard A., Wyss,Christophe A., Gaemperli,Oliver, Kaufmann,Philipp A., Diagnostic value of 13N-ammonia myocardial perfusion PET: added value of myocardial flow reserve, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 53, 1230-1234, 2012	Includes known CAD
Fiechter,Michael, Ghadri,Jelena R., Kuest,Silke M., Pazhenkottil,Aju P., Wolfrum,Mathias, Nkoulou,Rene N., Goetti,Robert, Gaemperli,Oliver, Kaufmann,Philipp A., Nuclear myocardial perfusion imaging with a novel cadmium-zinc-telluride detector SPECT/CT device: first validation versus invasive coronary angiography, European Journal of Nuclear Medicine and Molecular	Population (included patients with known CAD)

Author	Reason for exclusion
ImagingEur.J.Nucl.Med.Mol.Imaging, 38, 2025-2030, 2011	
Fine,Jeffrey J., Hopkins,Christie B., Hall,Patrick A.X., Delphia,Robert E., Attebery,Timothy W., Newton,F.Carter, Noninvasive coronary angiography: agreement of multi-slice spiral computed tomography and selective catheter angiography, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 20, 549-552, 2004	Analysis (missing data)
Fine,Jeffrey J., Hopkins,Christie B., Ruff,Nicol, Newton,F.Carter, Comparison of accuracy of 64-slice cardiovascular computed tomography with coronary angiography in patients with suspected coronary artery disease, The American journal of cardiologyAm J Cardiol, 97, 173-174, 2006	Population (included patients with known CAD)
Fleischmann,K.E., Hunink,M.G., Kuntz,K.M., Douglas,P.S., Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance, JAMA, 280, 913-920, 1998	Includes known CAD
Fleming,R.M., Harrington,G.M., FHRWW Stress SPECT Protocol Reduces Radioactive Dosage and Increases Ischemia Detection, ANZ Nuclear MedicineANZ Nucl.Med., 41, 24-32, 2010	Population (included patients with suspected CAD) Reference standard (unclear)
Fleming,R.M., Rose,C.H., Feldmann,K.M., Comparing a high-dose dipyridamole SPECT imaging protocol with dobutamine and exercise stress testing protocols, Angiology, 46, 547-556, 1995	Analysis (missing data)
Forster,Stefan, Rieber,Johannes, Ubleis,Christopher, Weiss,Mayo, Bartenstein,Peter, Cumming,Paul, Klauss,Volker, Hacker,Marcus, Tc-99m sestamibi single photon emission computed tomography for guiding percutaneous coronary intervention in patients with multivessel disease: a comparison with quantitative coronary angiography and fractional flow reserve, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 26, 203-213, 2010	Not relevant
Freeman,M.R., Konstantinou,C., Barr,A., Greyson,N.D., Clinical comparison of 180-degree and 360-degree data collection of technetium 99m sestamibi SPECT for detection of coronary artery disease, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 5, 14-18, 1998	Design (retrospective)
Froelicher,V.F., Lehmann,K.G., Thomas,R., Goldman,S., Morrison,D., Edson,R., Lavori,P., Myers,J., Dennis,C., Shabetai,R., Do,D., Froning,J., The electrocardiographic exercise test in a population with reduced workup bias: diagnostic performance, computerized interpretation, and multivariable prediction. Veterans Affairs Cooperative Study in Health Services #016 (QUEXTA) Study Group. Quantitative Exercise Testing and Angiography, Annals of Internal MedicineANN.INTERN.MED., 128, 965-974, 1998	Non protocol index test
Frohwein,S., Klein,J.L., Lane,A., Taylor,W.R., Transesophageal dobutamine stress echocardiography in the evaluation of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 25, 823-829, 1995	Population (all male and included patients with previous MI)
Fukuoka,S., Maeno,M., Nakagawa,S., Fukunaga,T., Yamada,H., Eto,T., Feasibility of myocardial dual-isotope perfusion imaging combined with gated single photon	Population (included patients with a history of MI)

Author	Reason for exclusion
emission tomography for assessing coronary artery disease, Nuclear Medicine CommunicationsNUCL.MED.COMMUN., 23, 19-29, 2002	
Futamatsu,Hideki, Klassen,Chris, Pilla,Marco, Wilke,Norbert, Angiolillo,Dominick J., Smalheiser,Stuart, Siuciak,Alan, Suzuki,Nobuaki, Bass,Theodore A., Costa,Marco A., Diagnostic accuracy of quantitative cardiac MRI evaluation compared to stress single-photon-emission computed tomography, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 24, 293-299, 2008	Design (retrospective)
Futamatsu,Hideki, Wilke,Norbert, Klassen,Chris, Shoemaker,Steven, Angiolillo,Dominick J., Siuciak,Alan, Morikawa-Futamatsu,Kino, Suzuki,Nobuaki, von Ziegler,Franz, Bass,Theodore A., Costa,Marco A., Evaluation of cardiac magnetic resonance imaging parameters to detect anatomically and hemodynamically significant coronary artery disease, American Heart JournalAm.Heart J., 154, 298-305, 2007	Analysis (missing data)
Gaemperli,Oliver, Husmann,Lars, Schepis,Tiziano, Koepfli,Pascal, Valenta,Ines, Jenni,Walter, Alkadhi,Hatem, Luscher,Thomas F., Kaufmann,Philipp A., Coronary CT angiography and myocardial perfusion imaging to detect flow-limiting stenoses: a potential gatekeeper for coronary revascularization?, European Heart JournalEur.Heart J., 30, 2921-2929, 2009	Includes patients with known CAD
Gaibazzi,Nicola, Rigo,Fausto, Reverberi,Claudio, Detection of coronary artery disease by combined assessment of wall motion, myocardial perfusion and coronary flow reserve: a multiparametric contrast stress-echocardiography study, Journal of the American Society of Echocardiography : official publication of the American Society of EchocardiographyJ Am Soc Echocardiogr, 23, 1242-1250, 2010	Includes known CAD
Gaibazzi,Nicola, Rigo,Fausto, Squeri,Angelo, Ugo,Fabrizio, Reverberi,Claudio, Incremental value of contrast myocardial perfusion to detect intermediate versus severe coronary artery stenosis during stress-echocardiography, Cardiovascular ultrasoundCardiovasc Ultrasound, 8, 16-, 2010	Mixed population, includes previous MI
Galanti,G., Sciagra,R., Comeglio,M., Taddei,T., Bonechi,F., Giusti,F., Malfanti,P., Bisi,G., Diagnostic accuracy of peak exercise echocardiography in coronary artery disease: comparison with thallium-201 myocardial scintigraphy, American Heart JournalAm.Heart J., 122, 1609-1616, 1991	Population (included patients with known CAD
Gang,S., Min,L., Li,L., Guo-Ying,L., Lin,X., Qun,J., Hua,Z., Evaluation of CT coronary artery angiography with 320-row detector CT in a high-risk population, The British journal of radiologyBr J Radiol, 85, 562-570, 2012	New generation scanner (protocol exclusion)
Garcia,Mario J., Lessick,Jonathan, Hoffmann,Martin H.K., CATSCAN,Study,I, Accuracy of 16-row multidetector computed tomography for the assessment of coronary artery stenosis, JAMA, 296, 403-411, 2006	Population includes people with previous MI
Gaudio,C., Mirabelli,F., Alessandra,L., Nguyen,B.L., Di Michele,S., Corsi,F., Tanzilli,G., Mancone,M., Pannarale,G., Francone,M., Carbone,I., Catalano,C., Passariello,R., Fedele,F., Noninvasive assessment of coronary artery stenoses by multidetector-row spiral computed tomography: comparison with conventional angiography, European	4 slice scanner (minimum 64 slice)

Author	Reason for exclusion
Review for Medical and Pharmacological SciencesEur.Rev.Med.Pharmacol.Sci., 9, 13-21, 2005	
Gaudio,C., Pelliccia,F., Evangelista,A., Tanzilli,G., Paravati,V., Pannarale,G., Pannitteri,G., Barilla,F., Greco,C., Franzoni,F., Speziale,G., Pasceri,V., 320-row computed tomography coronary angiography vs. conventional coronary angiography in patients with suspected coronary artery disease: A systematic review and meta-analysis, International journal of cardiologyInt.J.Cardiol., 168, 1562-1564, 2013	Index test overlaps with DG3 (New Generation Scanner)
Gaudio,C., Tanzilli,G., Vittore,A., Arca,M., Barilla,F., Di Michele,S., Minardi,G., Fedele,F., Lombardi,M., Donato,L., Detection of coronary artery stenoses using breath-hold magnetic resonance coronary angiography. Comparison with conventional x-ray angiography, European Review for Medical and Pharmacological SciencesEur.Rev.Med.Pharmacol.Sci., 8, 121-128, 2004	Non protocol index test
Gaur,Sara, Achenbach,Stephan, Leipsic,Jonathon, Mauri,Laura, Bezerra,Hiram G., Jensen,Jesper Moller, Botker,Hans Erik, Lassen,Jens Flensted, Norgaard,Bjarne Linde, Rationale and design of the HeartFlowNXT (HeartFlow analysis of coronary blood flow using CT angiography: NeXt sTeps) study, Journal of Cardiovascular Computed TomographyJ.Cardiovasc.Comput.Tomogr., 7, 279-288, 2013	Non protocol reference test
Gaur,Sara, Bezerra,Hiram G., Lassen,Jens F., Christiansen,Evald H., Tanaka,Kentaro, Jensen,Jesper M., Oldroyd,Keith G., Leipsic,Jonathon, Achenbach,Stephan, Kaltoft,Anne K., Botker,Hans Erik, Norgaard,Bjarne L., Fractional flow reserve derived from coronary CT angiography: variation of repeated analyses, Journal of Cardiovascular Computed TomographyJ.Cardiovasc.Comput.Tomogr., 8, 307-314, 2014	Non protocol reference test
Gebhard,C., Fuchs,T.A., Stehli,J., et al (2015) Coronary dominance and prognosis in patients undergoing coronary computed tomographic angiography: results from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry Eur Heart J Cardiovasc Imaging	Includes known CAD.
Gebker,R., Jahnke,C., Hucko,T., Manka,R., Mirelis,J.G., Hamdan,A., Schnackenburg,B., Fleck,E., Paetsch,I., Dobutamine stress magnetic resonance imaging for the detection of coronary artery disease in women, Heart (British Cardiac Society), 96, 616-620, 2010	Study on women only
Gebker,R., Jahnke,C., Manka,R., Frick,M., Hucko,T., Kozerke,S., Schnackenburg,B., Fleck,E., Paetsch,I., High spatial resolution myocardial perfusion imaging during high dose dobutamine/atropine stress magnetic resonance using k-t SENSE, International journal of cardiologyInt.J.Cardiol., 158, 411-416, 2012	Population (included patients with known CAD)
Gebker,Rolf, Frick,M., Jahnke,C., Berger,A., Schneeweis,C., Manka,R., Kelle,S., Klein,C., Schnackenburg,B., Fleck,E., Paetsch,I., Value of additional myocardial perfusion imaging during dobutamine stress magnetic resonance for the assessment of intermediate coronary artery disease, The international journal of cardiovascular imagingInt J	Population (included patients with known CAD)

Author	Reason for exclusion
Cardiovasc Imaging, 28, 89-97, 2012	
Gebker,Rolf, Jahnke,Cosima, Manka,Robert, Hamdan,Ashraf, Schnackenburg,Bernhard, Fleck,Eckart, Paetsch,Ingo, Additional value of myocardial perfusion imaging during dobutamine stress magnetic resonance for the assessment of coronary artery disease, Circulation.Cardiovascular imagingCirc Cardiovasc Imaging, 1, 122-130, 2008	Includes known CAD
Gebker,Rolf, Jahnke,Cosima, Paetsch,Ingo, Schnackenburg,Bernhard, Kozerke,Sebastian, Bornstedt,Axel, Fleck,Eckart, Nagel,Eike, MR myocardial perfusion imaging with k-space and time broad-use linear acquisition speed-up technique: feasibility study, Radiology, 245, 863-871, 2007	Includes known CAD
Geleijnse,M.L., Elhendy,A., Fioretti,P.M., Roelandt,J.R., Dobutamine stress myocardial perfusion imaging, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 36, 2017-2027, 2000	Unclear if mixed population within individual studies. Includes studies that performed planar imaging (obsolete as per topic experts)
Geleijnse,Marcel L., Krenning,Boudewijn J., Soliman,Osama I.I., Nemes,Attila, Galema,Tjebbe W., Ten Cate,Folkert J., Dobutamine stress echocardiography for the detection of coronary artery disease in women, The American journal of cardiologyAm J Cardiol, 99, 714-717, 2007	Population (women only)
Genders,Tessa S.S., Steyerberg,Ewout W., Alkadhi,Hatem, Leschka,Sebastian, Desbiolles,Lotus, Nieman,Koen, Galema,Tjebbe W., Meijboom,W.Bob, Mollet,Nico R., de Feyter,Pim J., Cademartiri,Filippo, Maffei,Erica, Dewey,Marc, Zimmermann,Elke, Laule,Michael, Pugliese,Francesca, Barbagallo,Rossella, Sinitsyn,Valentin, Bogaert,Jan, Goetschalckx,Kaatje, Schoepf,U.Joseph, Rowe,Garrett W., Schuijf,Joanne D., Bax,Jeroen J., de Graaf,Fleur R., Knuuti,Juhani, Kajander,Sami, van Mieghem,Carlos A.G., Meijs,Matthijs F.L., Cramer,Maarten J., Gopalan,Deepa, Feuchtner,Gudrun, Friedrich,Guy, Krestin,Gabriel P., Hunink,M.G.M., CAD Consortium, A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension, European Heart JournalEur.Heart J., 32, 1316-1330, 2011	Not relevant for this review question
Genovesi,Dario, Giorgetti,Assuero, Gimelli,Alessia, Kusch,Annette, D'Aragona Tagliavia,Irene, Casagranda,Mirta, Cannizzaro,Giorgio, Giubbini,Raffaele, Bertagna,Francesco, Fagioli,Giorgio, Rossi,Massimiliano, Romeo,Annadina, Bertolaccini,Pietro, Bonini,Rita, Marzullo,Paolo, Impact of attenuation correction and gated acquisition in SPECT myocardial perfusion imaging: results of the multicentre SPAG (SPECT Attenuation Correction vs Gated) study, European Journal of Nuclear Medicine and Molecular ImagingEur.J.Nucl.Med.Mol.Imaging, 38, 1890-1898, 2011	Population (all patients had known CAD)
George,Richard T., Mehra,Vishal C., Chen,Marcus Y., Kitagawa,Kakuya, Arbab-Zadeh,Armin, Miller,Julie M., Matheson,Matthew B., Vavere,Andrea L., Kofoed,Klaus F., Rochitte,Carlos E., Dewey,Marc, Yaw,Tan S., Niinuma,Hiroyuki, Brenner,Winfried, Cox,Christopher, Clouse,Melvin E., Lima,Joao A.C., Di Carli,Marcelo, Myocardial CT perfusion imaging and SPECT for the diagnosis of coronary artery disease: a head-to-head	Mixed population - includes known disease

Author	Reason for exclusion
comparison from the CORE320 multicenter diagnostic performance study, Radiology, 272, 407-416, 2014	
Gerber,Bernhard L., Coche,Emmanuel, Pasquet,Agnes, Ketelslegers,Etienne, Vancraeynest,David, Grandin,Cecile, Van Beers,Bernard E., Vanoverschelde,Jean Louis, Coronary artery stenosis: direct comparison of four-section multi-detector row CT and 3D navigator MR imaging for detection--initial results, Radiology, 234, 98-108, 2005	No per patient analysis (Per-segment analysis only).
Gokdeniz,Tayyar, Kalaycioglu,Ezgi, Aykan,Ahmet Cagri, Boyaci,Faruk, Turan,Turhan, Gul,Ilker, Cavusoglu,Gokhan, Dursun,Ihsan, Value of coronary artery calcium score to predict severity or complexity of coronary artery disease, Arquivos Brasileiros de CardiologiaArq.Bras.Cardiol., 102, 120-127, 2014	Entire population had known CAD
Gonzalez,P., Massardo,T., Jofre,M.J., Yovanovich,J., Prat,H., Munoz,A., Arriagada,M., Anzoategui,W., Carmona,A.R., 201Tl myocardial SPECT detects significant coronary artery disease between 50% and 75% angiogram stenosis, Revista Espanola de Medicina NuclearRev.Esp.Med.Nucl., 24, 305-311, 2005	Population (included patients with previous MI. Documented post test rather than in baseline characteristics)
Goto,Kenji, Takebayashi,Hideo, Kihara,Yasuki, Yamane,Hiroki, Hagikura,Arata, Morimoto,Yoshimasa, Kikuta,Yuetsu, Sato,Katsumasa, Taniguchi,Masahito, Hiramatsu,Shigeki, Haruta,Seiichi, Impact of combined supine and prone myocardial perfusion imaging using an ultrafast cardiac gamma camera for detection of inferolateral coronary artery disease, International journal of cardiologyInt.J.Cardiol., 174, 313-317, 2014	Population (included patients with previous MI/PCI)
Gottlieb,Ilan, Miller,Julie M., Arbab-Zadeh,Armin, Dewey,Marc, Clouse,Melvin E., Sara,Leonardo, Niinuma,Hiroyuki, Bush,David E., Paul,Narinder, Vavere,Andrea L., Texter,John, Brinker,Jeffery, Lima,Joao A.C., Rochitte,Carlos E., The absence of coronary calcification does not exclude obstructive coronary artery disease or the need for revascularization in patients referred for conventional coronary angiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 55, 627-634, 2010	Duplicate population reported in a newer study. Retrospective data selection.
Greenwood,J.P., Maredia,N., Younger,J.F., Brown,J.M., Nixon,J., Everett,C.C., Bijsterveld,P., Ridgway,J.P., Radjenovic,A., Dickinson,C.J., Ball,S.G., Plein,S., Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): A prospective trial, Lancet, 379, 453-460, 2012	Includes known CAD
Groothuis,Jan G.J., Beek,Aernout M., Meijerink,Martijn R., Brinckman,Stijn L., Heymans,Martijn W., van Kuijk,Cornelis, van Rossum,Albert C., Positive predictive value of computed tomography coronary angiography in clinical practice, International journal of cardiologyInt.J.Cardiol., 156, 315-319, 2012	Excluded participants selected on the basis of positive CTCA
Groothuis,Jan G.J., Kremers,Frans P.P.J., Beek,Aernout M., Brinckman,Stijn L., Tuinenburg,Alvin C., Jerosch-Herold,Michael, van Rossum,Albert C., Hofman,Mark B.M., Comparison of dual to single contrast bolus magnetic resonance myocardial perfusion imaging for detection of significant coronary artery disease, Journal of magnetic resonance imaging : JMRIJ Magn Reson Imaging, 32, 88-93,	Analysis (missing data)

Author	Reason for exclusion
2010	
Grosse,C., Globits,S., Hergan,K., Forty-slice spiral computed tomography of the coronary arteries: assessment of image quality and diagnostic accuracy in a non-selected patient population, Acta radiologica (Stockholm, Sweden : 1987), 48, 36-44, 2007	Population (included patients with known CAD)
Gueret,P., Deux,J.F., Bonello,L., Sarran,A., Tron,C., Christiaens,L., Dacher,J.N., Bertrand,D., Leborgne,L., Renard,C., Caussin,C., Cluzel,P., Helft,G., Crochet,D., Vernhet-Kovacsik,H., Chabbert,V., Ferrari,E., Gilard,M., Willoteaux,S., Furber,A., Barone-Rochette,G., Jankowski,A., Douek,P., Mousseaux,E., Sirol,M., Niarra,R., Chatellier,G., Laissy,J.P., Diagnostic performance of computed tomography coronary angiography (from the Prospective National Multicenter Multivendor EVASCAN Study), American Journal of CardiologyAm.J.Cardiol., 111, 471-478, 2013	Population (included patients with known CAD)
Guerra,U.P., Giacomuzzi,F., Di Gregorio,F., Bax,J.J., Slavich,G.A., Fioretti,P.M., Gated Tc-99m sestamibi SPECT versus stress-rest SPECT in detecting coronary artery disease: correlation with coronary angiography in patients without myocardial infarction, Clinical Nuclear MedicineClin.Nucl.Med., 24, 921-926, 1999	Population (included patients with known CAD)
Gunalp,B., Dokumaci,B., Uyan,C., Vardareli,E., Isik,E., Bayhan,H., Ozguven,M., Ozturk,E., Value of dobutamine technetium-99m-sestamibi SPECT and echocardiography in the detection of coronary artery disease compared with coronary angiography, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 34, 889-894, 1993	Design (unclear)
Guo,Shun Lin, Guo,You Min, Zhai,Ya Nan, Ma,Bin, Wang,Ping, Yang,Ke Hu, Diagnostic accuracy of first generation dual-source computed tomography in the assessment of coronary artery disease: a meta-analysis from 24 studies, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 27, 755-771, 2011	Population (included patients with known CAD)
Haberl,R., Becker,A., Leber,A., Knez,A., Becker,C., Lang,C., Bruning,R., Reiser,M., Steinbeck,G., Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 37, 451-457, 2001	Non protocol index test (EBCT)
Haberl,Ralph, Tittus,Janine, Bohme,Eike, Czernik,Andreas, Richartz,Barbara Maria, Buck,Jurgen, Steinbigler,Peter, Multislice spiral computed tomographic angiography of coronary arteries in patients with suspected coronary artery disease: an effective filter before catheter angiography?, American Heart JournalAm.Heart J., 149, 1112-1119, 2005	4 slice scanner (minimum 64)
Halon,David A., Gaspar,Tamar, Adawi,Salim, Rubinshtein,Ronen, Schliamser,Jorge E., Peled,Nathan, Lewis,Basil S., Uses and limitations of 40 slice multi-detector row spiral computed tomography for diagnosing coronary lesions in unselected patients referred for routine invasive coronary angiography, Cardiology, 108, 200-209, 2007	mixed population: includes known CAD
Hamirani,Yasmin S., Isma'eel,Hussain, Larijani,Vahid, Drury,Paul, Lim,Wayland, Bevinal,Manzoor, Saeed,Anila, Ahmadi,Nasser, Karlsberg,Ronald P., Budoff,Matthew J., The	Population (included patients with a history of CAD)

Author	Reason for exclusion
diagnostic accuracy of 64-detector cardiac computed tomography compared with stress nuclear imaging in patients undergoing invasive cardiac catheterization, Journal of Computer Assisted TomographyJ.Comput.Assisted Tomogr., 34, 645-651, 2010	
Hamon,Michele, Biondi-Zoccai,Giuseppe G.L., Malagutti,Patrizia, Agostoni,Pierfrancesco, Morello,Remy, Valgimigli,Marco, Hamon,Martial, Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography: a meta-analysis, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 48, 1896-1910, 2006	Populations of included studies included known CAD
Hamon,Michele, Fau,Georges, Nee,Guillaume, Ehtisham,Javed, Morello,Remy, Hamon,Martial, Meta-analysis of the diagnostic performance of stress perfusion cardiovascular magnetic resonance for detection of coronary artery disease, Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic ResonanceJ Cardiovasc Magn Reson, 12, 29-, 2010	Mixed populations within included studies (known CAD)
Hamon,Michele, Morello,Remy, Riddell,John W., Hamon,Martial, Coronary arteries: diagnostic performance of 16- versus 64-section spiral CT compared with invasive coronary angiography--meta-analysis, Radiology, 245, 720-731, 2007	Includes known CAD
Han,Shu Chen, Fang,Ching Chang, Chen,Yi, Chen,Chi Liang, Wang,Shih Pu, Coronary computed tomography angiography---a promising imaging modality in diagnosing coronary artery disease, Journal of the Chinese Medical Association : JCMAJ Chin Med Assoc, 71, 241-246, 2008	Non protocol population (asymptomatic self-referred patients)
Haramati,Linda B., Levsky,Jeffrey M., Jain,Vineet R., Altman,Erik J., Spindola-Franco,Hugo, Bobra,Shalini, Doddamani,Sanjay, Travin,Mark I., CT angiography for evaluation of coronary artery disease in inner-city outpatients: an initial prospective comparison with stress myocardial perfusion imaging, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 25, 303-313, 2009	Population (only those with positive SPECT had reference standard)
Hausleiter,J., Meyer,T., Hadamitzky,M., Zankl,M., Gerein,P., Dörrler,K., Kastrati,A., Martinoff,S., Schömig,A., Non-invasive coronary computed tomographic angiography for patients with suspected coronary artery disease: the Coronary Angiography by Computed Tomography with the Use of a Submillimeter resolution (CACTUS) trial, European Heart JournalEur.Heart J., 28, 3034-3041, 2007	CT Scanner spec - used 16 slice scanner (64 slice) but data grouped together.
He,Z.X., Iskandrian,A.S., Gupta,N.C., Verani,M.S., Assessing coronary artery disease with dipyridamole technetium-99m-tetrofosmin SPECT: a multicenter trial, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 38, 44-48, 1997	Includes known CAD
Health,Quality Ontario, 64-slice computed tomographic angiography for the diagnosis of intermediate risk coronary artery disease: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 10, 1-44, 2010	Population (included patients with known CAD
Health,Quality Ontario, Cardiac magnetic resonance imaging for the diagnosis of coronary artery disease: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 10, 1-38, 2010	Included mixed population

Author	Reason for exclusion
Health,Quality Ontario, Functional cardiac magnetic resonance imaging (MRI) in the assessment of myocardial viability and perfusion: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 3, 1-82, 2003	Non protocol index test
Health,Quality Ontario, Magnetic resonance imaging (MRI) for the assessment of myocardial viability: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 10, 1-45, 2010	Population (include patients with known CAD specifically)
Health,Quality Ontario, Multi-detector computed tomography angiography for coronary artery disease: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 5, 1-57, 2005	Population (included patients with positive stress) Design (not all studies included report consecutive enrolment)
Health,Quality Ontario, Multidetector computed tomography for coronary artery disease screening in asymptomatic populations: evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 7, 1-56, 2007	Population (included asymptomatic patients)
Health,Quality Ontario, Positron emission tomography for the assessment of myocardial viability: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 10, 1-80, 2010	Non protocol reference standard
Health,Quality Ontario, Positron emission tomography for the assessment of myocardial viability: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 5, 1-167, 2005	Non protocol reference standard and Population (included patients with know CAD
Health,Quality Ontario, Single photon emission computed tomography for the diagnosis of coronary artery disease: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 10, 1-64, 2010	Population (included patients with previous MI)
Health,Quality Ontario, Stress echocardiography for the diagnosis of coronary artery disease: an evidence-based analysis, Ontario health technology assessment seriesOnt Health Technol Assess Ser, 10, 1-61, 2010	Population (included patients with previous MI)
Health,Quality Ontario, Stress echocardiography with contrast for the diagnosis of coronary artery disease: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 10, 1-59, 2010	Included non protocol study designs (retrospective)
Hecht,H.S., DeBord,L., Shaw,R., Chin,H., Dunlap,R., Ryan,C., Myler,R.K., Supine bicycle stress echocardiography versus tomographic thallium-201 exercise imaging for the detection of coronary artery disease, Journal of the American Society of Echocardiography : official publication of the American Society of EchocardiographyJ Am Soc Echocardiogr, 6, 177-185, 1993	Population (included patients with previous MI/CABG/angioplasty)
Hecht,H.S., DeBord,L., Sotomayor,N., Shaw,R., Dunlap,R., Ryan,C., Supine bicycle stress echocardiography: peak exercise imaging is superior to postexercise imaging, Journal of the American Society of Echocardiography : official publication of the American Society of EchocardiographyJ Am Soc Echocardiogr, 6, 265-271, 1993	Population (included patients with previous MI)
Heijenbrok-Kal,Majanka H., Fleischmann,Kirsten E., Hunink,M.G.M., Stress echocardiography, stress single-photon-emission computed tomography and electron beam	Population (included patients with previous MI

Author	Reason for exclusion
computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance, American Heart JournalAm.Heart J., 154, 415-423, 2007	
Heinicke,N., Benesch,B., Kaiser,T., Debl,K., Segmuller,M., Schonberger,J., Marienhagen,J., Eilles,C., Riegger,G.A.J., Holmer,S., Luchner,A., Mechanisms of regional wall motion abnormalities in contrast-enhanced dobutamine stress echocardiography, Clinical research in cardiology : official journal of the German Cardiac Society, 95, 650-656, 2006	Population (included patients with known CAD)
Hell,M.M., Dey,D., Marwan,M., Achenbach,S., Schmid,J., Schuhbaeck,A., Non-invasive prediction of hemodynamically significant coronary artery stenoses by contrast density difference in coronary CT angiography, Eur J Radiol, -, 2015	Non protocol reference test
Hennessy,T.G., Codd,M.B., Hennessy,M.S., Kane,G., McCarthy,C., McCann,H.A., Sugrue,D.D., Comparison of dobutamine stress echocardiography and treadmill exercise electrocardiography for detection of coronary artery disease, Coronary Artery DiseaseCoron.Artery Dis., 8, 689-695, 1997	Population (included patients with a history of MI)
Hennessy,T.G., Codd,M.B., McCarthy,C., Kane,G., McCann,H.A., Sugrue,D.D., Dobutamine stress echocardiography in the detection of coronary artery disease in a clinical practice setting, International journal of cardiologyInt.J.Cardiol., 62, 55-62, 1997	Population (included patients with previous MI)
Hennessy,T.G., Siobhan Hennessy,M., Codd,M.B., Kane,G., McCarthy,C., McCann,H.A., Sugrue,D.D., Detection of coronary artery disease using dobutamine stress echocardiography in patients with an abnormal resting electrocardiograph, International journal of cardiologyInt.J.Cardiol., 64, 293-298, 1998	Population (included patients with previous MI)
Heo,J., Powers,J., Iskandrian,A.E., Exercise-rest same-day SPECT sestamibi imaging to detect coronary artery disease, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 38, 200-203, 1997	Population (not all participants had reference standard and insufficiently described)
Herbst,C.P., Du Theron,T.H., Van,Aswegen A., Kleynhans,P.H.T., Otto,A.C., Minnaar,P.C., A comparison of the clinical relevance of thallium-201 and technetium-99m-methoxyisobutyl-isonitrile for the evaluation of myocardial blood flow, South African Medical JournalS.AFR.MED.J., 78, 277-280, 1990	Population (some participants selected based on inconclusive coronary angiography)
Herzog,B.A., Wyss,C.A., Husmann,L., Gaemperli,O., Valenta,I., Treyer,V., Landmesser,U., Kaufmann,P.A., First head-to-head comparison of effective radiation dose from low-dose 64-slice CT with prospective ECG-triggering versus invasive coronary angiography, Heart (British Cardiac Society), 95, 1656-1661, 2009	4 slice scanner (minimum 64 slice)
Herzog,Bernhard A., Husmann,Lars, Buechel,Ronny R., Pazhenkottil,Aju P., Burger,Irene A., Valenta,Ines, Altorfer,Ulrich, Wolfrum,Mathias, Nkoulou,Rene N., Ghadri,Jelena R., Wyss,Christophe A., Kaufmann,Philipp A., Rapid cardiac hybrid imaging with minimized radiation dose for accurate non-invasive assessment of ischemic coronary artery disease, International journal of cardiologyInt.J.Cardiol., 153, 10-13, 2011	Outcome (analysis done on predicting revascularisation not CAD)
Herzog,Christopher, Zwerner,Peter L., Doll,Josh R., Nielsen,Christopher D., Nguyen,Shaun A., Savino,Giancarlo, Vogl,Thomas J., Costello,Philip, Schoepf,U.Joseph, Significant coronary artery stenosis: comparison on per-	Population (atypical CP specifically)

Author	Reason for exclusion
patient and per-vessel or per-segment basis at 64-section CT angiography, Radiology, 244, 112-120, 2007	
Heussel,C.P., Voigtlaender,T., Kauczor,H., Braun,M., Meyer,J., Thelen,M., Detection of coronary artery calcifications predicting coronary heart disease: comparison of fluoroscopy and spiral CT, European RadiologyEur.Radiol., 8, 1016-1024, 1998	Population (included patients with post angioplasty or aortic valve disorder)
Heydari,Bobak, Leipsic,Jonathon, Mancini,G.B.J., Min,James K., Labounty,Troy, Taylor,C., Freue,Gabriela V.C., Heilbron,Brett, Diagnostic performance of high-definition coronary computed tomography angiography performed with multiple radiation dose reduction strategies, The Canadian journal of cardiologyCan J Cardiol, 27, 606-612, 2011	Index test overlaps with DG3 (New Generation Scanner)
Hida,Satoshi, Chikamori,Taishiro, Tanaka,Hirokazu, Usui,Yasuhiro, Igarashi,Yuko, Nagao,Tadashi, Yamashina,Akira, Diagnostic value of left ventricular function after stress and at rest in the detection of multivessel coronary artery disease as assessed by electrocardiogram-gated SPECT, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 14, 68-74, 2007	Population (included patients with known CAD)
Ho,F.-M., Huang,P.-J., Liau,C.-S., Lee,F.-K., Chieng,P.-U., Su,C.-T., Lee,Y.-T., Dobutamine stress echocardiography compared with dipyridamole thallium-201 single-photon emission computed tomography in detecting coronary artery disease, European Heart JournalEur.Heart J., 16, 570-575, 1995	Population (included patients with previous MI)
Hoffmann,Martin H.K., Shi,Heshui, Schmitz,Bernd L., Schmid,Florian T., Lieberknecht,Michael, Schulze,Ralph, Ludwig,Bernd, Kroschel,Ulf, Jahnke,Norbert, Haerer,Winfried, Brambs,Hans Juergen, Aschoff,Andrik J., Noninvasive coronary angiography with multislice computed tomography, JAMA, 293, 2471-2478, 2005	Population (included patients with recurrent symptoms after PCI)
Hoffmann,R., Lethen,H., Kuhl,H., Lepper,W., Hanrath,P., Extent and severity of test positivity during dobutamine stress echocardiography. Influence on the predictive value for coronary artery disease, European Heart JournalEur.Heart J., 20, 1485-1492, 1999	Population (included patients with known CAD)
Hoffmann,Udo, Moselewski,Fabian, Cury,Ricardo C., Ferencik,Maros, Jang,Ik Kyung, Diaz,Larry J., Abbara,Suhny, Brady,Thomas J., Achenbach,Stephan, Predictive value of 16-slice multidetector spiral computed tomography to detect significant obstructive coronary artery disease in patients at high risk for coronary artery disease: patient-versus segment-based analysis, Circulation, 110, 2638-2643, 2004	16 slice scanner (minimum 64 slice)
Hoilund-Carlsen,Poul Flemming, Johansen,Allan, Christensen,Henrik Wulff, Pedersen,Lise Toffner, Johnk,Ida Karina, Vach,Werner, Haghfelt,Torben, Usefulness of the exercise electrocardiogram in diagnosing ischemic or coronary heart disease in patients with chest pain, The American journal of cardiologyAm J Cardiol, 95, 96-99, 2005	Population (included patients with a mix of different types of chest pain)
Holmstrom,Miia, Vesterinen,Paula, Hanninen,Helena, Sillanpaa,Mikko A., Kivisto,Sari, Lauerma,Kirsi, Noninvasive analysis of coronary artery disease with combination of MDCT and functional MRI, Academic RadiologyAcad.Radiol., 13, 177-185, 2006	Population (included patients with known CAD)
Hong,Y.J., Kim,S.J., Lee,S.M., Min,P.K., Yoon,Y.W.,	Population (included patients with

Author	Reason for exclusion
Lee,B.K., Kim,T.H., Low-dose coronary computed tomography angiography using prospective ECG-triggering compared to invasive coronary angiography, International Journal of Cardiovascular ImagingInt.J.Card.Imaging, 27, 425-431, 2011	known CAD)
Hou,Yang, Ma,Yue, Fan,Weipeng, Wang,Yuke, Yu,Mei, Vembar,Mani, Guo,Qiyong, Diagnostic accuracy of low-dose 256-slice multi-detector coronary CT angiography using iterative reconstruction in patients with suspected coronary artery disease, European RadiologyEur.Radiol., 24, 3-11, 2014	Index test overlaps with DG3 (New Generation Scanner)
Hozumi,T., Akasaka,T., Yoshida,K., Yoshikawa,J., Noninvasive estimation of coronary flow reserve by transthoracic Doppler echocardiography with a high-frequency transducer, Journal of CardiologyJ.Cardiol., 37 Suppl 1, 43-50, 2001	Population (included patients with known CAD)
Hozumi,T., Yoshida,K., Ogata,Y., Akasaka,T., Asami,Y., Takagi,T., Morioka,S., Noninvasive assessment of significant left anterior descending coronary artery stenosis by coronary flow velocity reserve with transthoracic color Doppler echocardiography, Circulation, 97, 1557-1562, 1998	Reference standard (non protocol)
Hsu,Chien Chin, Chen,Yu Wen, Hao,Chi Long, Chong,Jun Ted, Lee,Chun I., Tan,Hau Tong, Wu,Ming Sheng, Wu,Jung Chou, Comparison of automated 4D-MSPECT and visual analysis for evaluating myocardial perfusion in coronary artery disease, The Kaohsiung journal of medical sciencesKaohsiung J Med Sci, 24, 445-452, 2008	Population (included patients with known CAD)
Huang,P.J., Ho,Y.L., Wu,C.C., Chao,C.L., Chen,M.F., Chieng,P.U., Lee,Y.T., Simultaneous dobutamine stress echocardiography and thallium-201 perfusion imaging for the detection of coronary artery disease, Cardiology, 88, 556-562, 1997	Population (included patients with previous MI)
Huang,R., Li,F., Zhao,Z., Liu,B., Ou,X., Tian,R., Li,L., Hybrid SPECT/CT for attenuation correction of stress myocardial perfusion imaging, Clinical Nuclear MedicineClin.Nucl.Med., 36, 344-349, 2011	Design (retrospective)
Huber,Armin, Sourbron,Steven, Klauss,Volker, Schaefer,Julia, Bauner,Kerstin Ulrike, Schweyer,Michael, Reiser,Maximilian, Rummeny,Ernst, Rieber,Johannes, Magnetic resonance perfusion of the myocardium: semiquantitative and quantitative evaluation in comparison with coronary angiography and fractional flow reserve, Investigative RadiologyInvest.Radiol., 47, 332-338, 2012	Mixed population - includes prior MI
Hung,Guang Uei, Lee,Kung Wei, Chen,Ching Pei, Yang,Kuang Tao, Lin,Wan Yu, Worsening of left ventricular ejection fraction induced by dipyridamole on Tl-201 gated myocardial perfusion imaging predicts significant coronary artery disease, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 13, 225-232, 2006	Design (retrospective)
Husmann,L., Wiegand,M., Valenta,I., Gaemperli,O., Schepis,T., Siegrist,P.T., Namdar,M., Wyss,C.A., Alkadhi,H., Kaufmann,P.A., Diagnostic accuracy of myocardial perfusion imaging with single photon emission computed tomography and positron emission tomography: A comparison with coronary angiography, International Journal of Cardiovascular ImagingInt.J.Card.Imaging, 24, 511-518,	Population (included patients with known CAD)

Author	Reason for exclusion
2008	
Husmann,Lars, Herzog,Bernhard A., Burger,Irene A., Buechel,Ronny R., Pazhenkottil,Aju P., von Schulthess,Patrick, Wyss,Christophe A., Gaemperli,Oliver, Landmesser,Ulf, Kaufmann,Philipp A., Usefulness of additional coronary calcium scoring in low-dose CT coronary angiography with prospective ECG-triggering impact on total effective radiation dose and diagnostic accuracy, Academic RadiologyAcad.Radiol., 17, 201-206, 2010	Population (included patients with known CAD)
Husmann,Lars, Schepis,Tiziano, Scheffel,Hans, Gaemperli,Oliver, Leschka,Sebastian, Valenta,Ines, Koepfli,Pascal, Desbiolles,Lotus, Stolzmann,Paul, Marincek,Borut, Alkadhi,Hatem, Kaufmann,Philipp A., Comparison of diagnostic accuracy of 64-slice computed tomography coronary angiography in patients with low, intermediate, and high cardiovascular risk, Academic RadiologyAcad.Radiol., 15, 452-461, 2008	Population (16 patients included had coronary angiograph to rule out CAD pre-operatively)
Husser,Oliver, Bodi,Vicente, Sanchis,Juan, Mainar,Luis, Nunez,Julio, Lopez-Lereu,Maria P., Monmeneu,Jose V., Ruiz,Vicente, Rumiz,Eva, Moratal,David, Chorro,Francisco J., Llacer,Angel, Additional diagnostic value of systolic dysfunction induced by dipyridamole stress cardiac magnetic resonance used in detecting coronary artery disease, Revista Espanola de CardiologiaRev.Esp.Cardiol., 62, 383-391, 2009	Design (retrospective)
Hwang,Hui Jeong, Lee,Hyae Min, Yang,In Ho, Lee,Jung Lok, Pak,Hyun Young, Park,Chang Bum, Jin,Eun Sun, Cho,Jin Man, Kim,Chong Jin, Sohn,Il Suk, The value of assessing myocardial deformation at recovery after dobutamine stress echocardiography, Journal of Cardiovascular UltrasoundJ.Cardiovasc.Ultrasound, 22, 127-133, 2014	Reference standard not consistently ICA
Ibrahim,O., Oteh,M., Anwar,I.R., Che Hassan,H.H., Choor,C.K., Hamzaini,A.H., Rahman,M.M., Calcium score of coronary artery stratifies the risk of obstructive coronary artery diseases, La Clinica terapeuticaClin Ter, 164, 391-395, 2013	Population (presumed history of ACS)
Imran,Muhammad B., Palinkas,Attila, Picano,Eugenio, Head-to-head comparison of dipyridamole echocardiography and stress perfusion scintigraphy for the detection of coronary artery disease: a meta-analysis. Comparison between stress echo and scintigraphy, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 19, 23-28, 2003	Population (included patients with known CAD)
Imran,Muhammad Babar, Khan,Muhammad Aleem, Aslam,Muhammad Naseem, Irfanullah,Javaid, Diagnosis of coronary artery disease by stress echocardiography and perfusion scintigraphy, Journal of the College of Physicians and Surgeons--Pakistan : JCPSPJ Coll Physicians Surg Pak, 13, 465-470, 2003	Population (individual studies included patients with known CAD)
Inoue,S., Mitsunami,K., Kinoshita,M., Comparison of electron beam computed tomography and exercise electrocardiography in detecting coronary artery disease in the elderly. [Japanese], Japanese Journal of GeriatricsJPN.J.GERIATR., 35, 626-630, 1998	Non protocol index test (EBCT). Full text in Japanese only.
Ioannidis,J.P.A., Trikalinos,T.A., Danias,P.G., Electrocardiogram-gated single-photon emission computed tomography versus cardiac magnetic resonance imaging for the assessment of left ventricular volumes and ejection	Outcome is not a diagnosis of CAD

Author	Reason for exclusion
fraction: A meta-analysis, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 39, 2059-2068, 2002	
Irmer,M., Reuland,P., Huonker,M., Berg,A., Keul,J., Combined physical and pharmacological stress for diagnosis of coronary heart disease. Comparison of stress-echo and myocardial scintigraphy, Cardiovascular ImagingCARDIOVASC.IMAGING, 8, 85-87, 1996	Population (included patients with known
Iskandrian,A.S., Heo,J., Kong,B., Lyons,E., Effect of exercise level on the ability of thallium-201 tomographic imaging in detecting coronary artery disease: analysis of 461 patients, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 14, 1477-1486, 1989	Population (not all patients had c.angio/reference standard) Time flow up to 6 months
Iskandrian,A.S., Mintz,G.S., Croll,M.N., Exercise thallium-201 myocardial scintigraphy: Advantages and limitations, Cardiology, 65, 136-152, 1980	Analysis (missing data)
Jahnke,Cosima, Paetsch,Ingo, Nehrke,Kay, Schnackenburg,Bernhard, Gebker,Rolf, Fleck,Eckart, Nagel,Eike, Rapid and complete coronary arterial tree visualization with magnetic resonance imaging: feasibility and diagnostic performance, European Heart JournalEur.Heart J., 26, 2313-2319, 2005	Reference standard (non protocol)
Jahnke,Cosima, Paetsch,Ingo, Schnackenburg,Bernhard, Bornstedt,Axel, Gebker,Rolf, Fleck,Eckart, Nagel,Eike, Coronary MR angiography with steady-state free precession: individually adapted breath-hold technique versus free-breathing technique, Radiology, 232, 669-676, 2004	Reference standard (non protocol)
Jahnke,Cosima, Paetsch,Ingo, Schnackenburg,Bernhard, Gebker,Rolf, Kohler,Uwe, Bornstedt,Axel, Fleck,Eckart, Nagel,Eike, Comparison of radial and Cartesian imaging techniques for MR coronary angiography, Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic ResonanceJ Cardiovasc Magn Reson, 6, 865-875, 2004	Non protocol index test
Janne d'Othee,Bertrand, Siebert,Uwe, Cury,Ricardo, Jadvar,Hossein, Dunn,Edward J., Hoffmann,Udo, A systematic review on diagnostic accuracy of CT-based detection of significant coronary artery disease, European Journal of RadiologyEur.J.Radiol., 65, 449-461, 2008	Unclear population (? whether known CAD) Non protocol index test (EBCT)
Jeetley,Paramjit, Hickman,Michael, Kamp,Otto, Lang,Roberto M., Thomas,James D., Vannan,Mani A., Vanoverschelde,Jean Louis, van der Wouw,Poll A., Senior,Roxy, Myocardial contrast echocardiography for the detection of coronary artery stenosis: a prospective multicenter study in comparison with single-photon emission computed tomography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 47, 141-145, 2006	Population (included patients with known CAD)
Jenkins,S.M.M., Johnston,N., Hawkins,N.M., Messow,C.M., Shand,J., Hogg,K.J., Eteiba,H., Mckillop,G., Goodfield,N.E.R., McConnachie,A., Dunn,F.G., Limited clinical utility of CT coronary angiography in a district hospital setting, QJM : monthly journal of the Association of Physicians, 104, 49-57, 2011	40 slice scanner (minimum 64 slice)
Jiang,B., Wang,J., Lv,X., Cai,W., Dual-source CT versus single-source 64-section CT angiography for coronary artery disease: A meta-analysis, Clinical RadiologyClin.Radiol., 69, 861-869, 2014	Reference standard (unclear)
Jimenez-Navarro,M., Alonso-Briales,J.H., Hernandez	Population (included patients with

Author	Reason for exclusion
Garcia,M.J., Rodriguez Bailon,I., Gomez-Doblas,J.J., de Teresa Galvan,E., Measurement of fractional flow reserve to assess moderately severe coronary lesions: correlation with dobutamine stress echocardiography, Journal of Interventional CardiologyJ.Intervent.Cardiol., 14, 499-504, 2001	unstable angina)
Jogiya,Roy, Kozerke,Sebastian, Morton,Geraint, De Silva,Kalpa, Redwood,Simon, Perera,Divaka, Nagel,Eike, Plein,Sven, Validation of dynamic 3-dimensional whole heart magnetic resonance myocardial perfusion imaging against fractional flow reserve for the detection of significant coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 60, 756-765, 2012	Non protocol reference test
Johansen,A., Høilund-Carlsen,P.F., Christensen,H.W., Vach,W., Jørgensen,H.B., Veje,A., Haghfelt,T., Diagnostic accuracy of myocardial perfusion imaging in a study population without post-test referral bias, Journal of Nuclear CardiologyJ.Nucl.Cardiol., 12, 530-537, 2005	Population (included patients with known CAD)
Johri,Amer M., Chitty,David W., Matangi,Murray, Malik,Paul, Mousavi,Parvin, Day,Andrew, Gravett,Matthew, Simpson,Chris, Can carotid bulb plaque assessment rule out significant coronary artery disease? A comparison of plaque quantification by two- and three-dimensional ultrasound, Journal of the American Society of Echocardiography : official publication of the American Society of EchocardiographyJ Am Soc Echocardiogr, 26, 86-95, 2013	non protocol index test
Josephson,M.A., Brown,B.G., Hecht,H.S., Hopkins,J., Pierce,C.D., Petersen,R.B., Noninvasive detection and localization of coronary stenoses in patients: comparison of resting dipyridamole and exercise thallium-201 myocardial perfusion imaging, American Heart JournalAm.Heart J., 103, 1008-1018, 1982	Population (included patients with previous MI)
Joutsiniemi,Esa, Saraste,Antti, Pietila,Mikko, Maki,Maija, Kajander,Sami, Ukkonen,Heikki, Airaksinen,Juhani, Knuuti,Juhani, Absolute flow or myocardial flow reserve for the detection of significant coronary artery disease?, European Heart Journal Cardiovascular ImagingEur.Heart J.Cardiovasc.Imaging, 15, 659-665, 2014	Reference standard (non protocol)
Joutsiniemi,Esa, Saraste,Antti, Pietila,Mikko, Ukkonen,Heikki, Kajander,Sami, Maki,Maija, Koskenvuo,Juha, Airaksinen,Juhani, Hartiala,Jaakko, Saraste,Markku, Knuuti,Juhani, Resting coronary flow velocity in the functional evaluation of coronary artery stenosis: study on sequential use of computed tomography angiography and transthoracic Doppler echocardiography, European Heart Journal Cardiovascular ImagingEur.Heart J.Cardiovasc.Imaging, 13, 79-85, 2012	Reference standard (non protocol)
Kaiser,Christoph, Bremerich,Jens, Haller,Sabine, Brunner-La Rocca,Hans Peter, Bongartz,Georg, Pfisterer,Matthias, Buser,Peter, Limited diagnostic yield of non-invasive coronary angiography by 16-slice multi-detector spiral computed tomography in routine patients referred for evaluation of coronary artery disease, European Heart JournalEur.Heart J., 26, 1987-1992, 2005	Population (included patients with known CAD)
Kajander,S., Joutsiniemi,E., Saraste,M., Pietila,M., Ukkonen,H., Saraste,A., Sipila,H.T., Teras,M., Maki,M., Airaksinen,J., Hartiala,J., Knuuti,J., Cardiac positron emission tomography/computed tomography imaging	Reference standard (non protocol)

Author	Reason for exclusion
accurately detects anatomically and functionally significant coronary artery disease, Circulation, 122, 603-613, 2010	
Kajander,Sami A., Joutsiniemi,Esa, Saraste,Markku, Pietila,Mikko, Ukkonen,Heikki, Saraste,Antti, Sipila,Hannu T., Teras,Mika, Maki,Maija, Airaksinen,Juhani, Hartiala,Jaakko, Knuuti,Juhani, Clinical value of absolute quantification of myocardial perfusion with (15)O-water in coronary artery disease, Circulation.Cardiovascular imagingCirc Cardiovasc Imaging, 4, 678-684, 2011	Non protocol reference test
Kajinami,K., Seki,H., Takekoshi,N., Mabuchi,H., Coronary calcification and coronary atherosclerosis: site by site comparative morphologic study of electron beam computed tomography and coronary angiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 29, 1549-1556, 1997	Reference standard (non protocol)
Kakuta,Kentaro, Dohi,Kaoru, Yamada,Tomomi, Yamanaka,Takashi, Kawamura,Masaki, Nakamori,Shiro, Nakajima,Hiroshi, Tanigawa,Takashi, Onishi,Katsuya, Yamada,Norikazu, Nakamura,Mashio, Ito,Masaaki, Detection of coronary artery disease using coronary flow velocity reserve by transthoracic Doppler echocardiography versus multidetector computed tomography coronary angiography: influence of calcium score, Journal of the American Society of Echocardiography : official publication of the American Society of EchocardiographyJ Am Soc Echocardiogr, 27, 775-785, 2014	Index test overlaps with DG3 (New Generation Scanner)
Kan,Jing, Gao,Xiaofei, Sandeep,Kumar Gami, Xu,Haimei, Zhao,Yingying, Chen,Shaoliang, Chen,Feng, Comparison of two and three dimensional quantitative coronary angiography to intravascular ultrasound in the assessment of left main coronary artery bifurcation lesions, Chinese medical journalChin.Med.J., 127, 1012-1021, 2014	Conference abstract only
Kang,Koung Mi, Choi,Sang Il, Chun,Eun Ju, Kim,Jeong A., Youn,Tae Jin, Choi,Dong Ju, Coronary vasospastic angina: assessment by multidetector CT coronary angiography, Korean Journal of RadiologyKor.J.Radiol., 13, 27-33, 2012	Not relevant Design (retrospective)
Karagiannis,Stefanos E., Bax,Jeroen J., Elhendy,Abdou, Feringa,Herman H.H., Cokkinos,Dennis V., van Domburg,Ron, Simoons,Maarten, Poldermans,Daniel, Enhanced sensitivity of dobutamine stress echocardiography by observing wall motion abnormalities during the recovery phase after acute beta-blocker administration, The American journal of cardiologyAm J Cardiol, 97, 462-465, 2006	Population (included patients with known or suspected CAD)
Kataoka,Yu, Nakatani,Satoshi, Tanaka,Norio, Kanzaki,Hideaki, Yasuda,Satoshi, Morii,Isao, Kawamura,Atsushi, Miyazaki,Shunichi, Kitakaze,Masafumi, Role of transthoracic Doppler-determined coronary flow reserve in patients with chest pain, Circulation journal : official journal of the Japanese Circulation SocietyCirc J, 71, 891-896, 2007	Population (included patients with previous MI)
Katayama,Takuji, Ogata,Nobuhiko, Tsuruya,Yoshio, Diagnostic accuracy of supine and prone thallium-201 stress myocardial perfusion single-photon emission computed tomography to detect coronary artery disease in inferior wall of left ventricle, Annals of Nuclear MedicineAnn.Nucl.Med., 22, 317-321, 2008	Design (flawed)
Kato,Shingo, Kitagawa,Kakuya, Ishida,Nanaka,	Reference standard (non

Author	Reason for exclusion
Ishida,Masaki, Nagata,Motonori, Ichikawa,Yasutaka, Katahira,Kazuhiro, Matsumoto,Yuji, Seo,Koji, Ochiai,Reiji, Kobayashi,Yasuyuki, Sakuma,Hajime, Assessment of coronary artery disease using magnetic resonance coronary angiography: a national multicenter trial, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 56, 983-991, 2010	protocol)
Kaufmann,R.B., Peyser,P.A., Sheedy,P.F., Rumberger,J.A., Schwartz,R.S., Quantification of coronary artery calcium by electron beam computed tomography for determination of severity of angiographic coronary artery disease in younger patients, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 25, 626-632, 1995	Population (included patients with known CAD) Non protocol index test
Kawaji,T., Shiomi,H., Morimoto,T., Nishikawa,R., Yano,M., Higami,H., Tazaki,J., Imai,M., Saito,N., Makiyama,T., Shizuta,S., Ono,K., Kimura,T., Noninvasive Detection of Functional Myocardial Ischemia: Multifunction Cardiogram Evaluation in Diagnosis of Functional Coronary Ischemia Study (MED-FIT), Ann Noninvasive Electrocardiol, -, 2015	Non protocol index test
Kefer,J., Coche,E., Legros,G., Pasquet,A., Grandin,C., Beers,B.E., Vanoverschelde,J.L., Gerber,B.L., Head-to-head comparison of three-dimensional navigator-gated magnetic resonance imaging and 16-slice computed tomography to detect coronary artery stenosis in patients, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 46, 92-100, 2005	Mixed/indirect population (1. Pre surgical exclusion of CAD and 2. Had positive stress test)
Khan,Razi, Rawal,Sapna, Eisenberg,Mark J., Transitioning from 16-slice to 64-slice multidetector computed tomography for the assessment of coronary artery disease: are we really making progress?, The Canadian journal of cardiologyCan J Cardiol, 25, 533-542, 2009	Population (included patients with post stent/CABG)
Khattar,R.S., Senior,R., Lahiri,A., Assessment of myocardial perfusion and contractile function by inotropic stress Tc-99m sestamibi SPECT imaging and echocardiography for optimal detection of multivessel coronary artery disease, Heart (British Cardiac Society), 79, 274-280, 1998	Population (included patients with previous MI)
Khorsand,A., Haddad,M., Graf,S., Moertl,D., Sochor,H., Porenta,G., Automated assessment of dipyridamole 201Tl myocardial SPECT perfusion scintigraphy by case-based reasoning, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 42, 189-193, 2001	study design - Restrospective
Khorsand,Aliasghar, Graf,Senta, Sochor,Heinz, Schuster,Ernst, Porenta,Gerold, Automated assessment of myocardial SPECT perfusion scintigraphy: a comparison of different approaches of case-based reasoning, Artificial Intelligence in MedicineArtif.Intell.Med., 40, 103-113, 2007	Retrospective design. Population unclear.
Kim,C., Kwok,Y.S., Heagerty,P., Redberg,R., Pharmacologic stress testing for coronary disease diagnosis: A meta-analysis, American Heart JournalAm.Heart J., 142, 934-944, 2001	Population (included patients with known CAD)
Kim,S.M., Choi,J.H., Chang,S.A., Choe,Y.H., Additional value of adenosine-stress dynamic CT myocardial perfusion imaging in the reclassification of severity of coronary artery stenosis at coronary CT angiography, Clinical RadiologyClin.Radiol., 68, e659-e668, 2013	Population (included patients with previous MI)
Kim,W.Y., Danias,P.G., Stuber,M., Flamm,S.D., Plein,S., Nagel,E., Langerak,S.E., Weber,O.M., Pedersen,E.M.,	Non protocol index test

Author	Reason for exclusion
Schmidt,M., Botnar,R.M., Manning,W.J., Coronary magnetic resonance angiography for the detection of coronary stenoses, The New England journal of medicineN Engl J Med, 345, 1863-1869, 2001	
Kitamura A, Kobayashi t, Ueda K et al. (2005) Evaluation of coronary artery calcification by multi-detector computed tomography for the detection of coronary artery stenosis in Japenese Patients. J Eipdemiol. 15(5):187-193.	Mixed population. Includes known CAD.
Klumpp,B., Hoevelborn,T., Fenchel,M., Stauder,N.I., Kramer,U., May,A., Gawaz,M.P., Claussen,C.D., Miller,S., Magnetic resonance myocardial perfusion imaging-First experience at 3.0T, European Journal of RadiologyEur.J.Radiol., 69, 165-172, 2009	Population (included patients with known or suspected CAD)
Klumpp,B., Miller,S., Seeger,A., May,A.E., Gawaz,M.P., Claussen,C.D., Kramer,U., Is the diagnostic yield of myocardial stress perfusion MRI impaired by three-vessel coronary artery disease?, Acta RadiologicaActa Radiol., 56, 143-151, 2014	Population (included patients with known CAD)
Klumpp,Bernhard D., Seeger,Achim, Doesch,Christina, Doering,Joerg, Hoevelborn,Tobias, Kramer,Ulrich, Fenchel,Michael, Gawaz,Meinrad P., Claussen,Claus D., Miller,Stephan, High resolution myocardial magnetic resonance stress perfusion imaging at 3 T using a 1 M contrast agent, European RadiologyEur.Radiol., 20, 533-541, 2010	Population (included patients with known CAD)
Klumpp,Bernhard, Miller,S., Seeger,A., May,A.E., Gawaz,M.P., Claussen,C.D., Kramer,U., Is the diagnostic yield of myocardial stress perfusion MRI impaired by three-vessel coronary artery disease?, Acta radiologica (Stockholm, Sweden : 1987), 56, 143-151, 2015	Population (included patients with known or suspected CAD)
Ko,Brian S., Wong,Dennis T.L., Cameron,James D., Leong,Darryl P., Leung,Michael, Meredith,Ian T., Nerlekar,Nitesh, Antonis,Paul, Crossett,Marcus, Troupis,John, Harper,Richard, Malaiapan,Yuvaraj, Seneviratne,Sujith K., 320-row CT coronary angiography predicts freedom from revascularisation and acts as a gatekeeper to defer invasive angiography in stable coronary artery disease: a fractional flow reserve-correlated study, European RadiologyEur.Radiol., 24, 738-747, 2014	Not relevant Index test overlaps with DG3 (New Generation Scanner)
Kong,Eun Jung, Cho,Ihn Ho, Chun,Kyung Ah, Clinical usefulness of combinatorial protocol with stress only myocardial perfusion SPECT, CTA and SPECT/CTA 3-dimensional fusion image, Annals of Nuclear MedicineAnn.Nucl.Med., 25, 387-395, 2011	Design (retrospective)
Konieczynska,Malgorzata, Tracz,Wieslawa, Pasowicz,Mieczyslaw, Przewlocki,Tadeusz, Use of coronary calcium score in the assessment of atherosclerotic lesions in coronary arteries, Kardiologia PolskaKardiol.Pol., 64, 1073-1, 2006	Population (included patients with previous MI)
Koo,Bon Kwon, Erglis,Andrejs, Doh,Joon Hyung, Daniels,David V., Jegere,Sanda, Kim,Hyo Soo, Dunning,Allison, Defrance,Tony, Lansky,Alexandra, Leipsic,Jonathan, Min,James K., Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing	Reference standard (non protocol)

Author	Reason for exclusion
Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 58, 1989-1997, 2011	
Korkeila,P., Hietanen,E., Parviainen,S., Virkki,R., Hartiala,J., Exercise thallium-201 scintigraphy in the localization of myocardial ischaemia, Clinical physiology (Oxford, England)Clin Physiol, 9, 555-565, 1989	Design (retrospective)
Korosoglou,Grigorios, Mueller,Dirk, Lehrke,Stephanie, Steen,Henning, Hosch,Waldemar, Heye,Tobias, Kauczor,Hans Ulrich, Giannitsis,Evangelos, Katus,Hugo A., Quantitative assessment of stenosis severity and atherosclerotic plaque composition using 256-slice computed tomography, European RadiologyEur.Radiol., 20, 1841-1850, 2010	Index test overlaps with DG3 (New Generation Scanner)
Kowatsch,Ingrid, Tsutsui,Jeane M., Osorio,Altamiro F.F., Uchida,Augusto H., Machiori,Gilberto G.A., Lopes,Marden L., Cesar,Luiz A.M., Ramires,Jose Antonio, Mathias,Wilson Jr, Head-to-head comparison of dobutamine and adenosine stress real-time myocardial perfusion echocardiography for the detection of coronary artery disease, Journal of the American Society of Echocardiography : official publication of the American Society of EchocardiographyJ Am Soc Echocardiogr, 20, 1109-1117, 2007	Population (included patients with known or suspected CAD)
Krenning,Boudewijn J., Nemes,Attila, Soliman,Osama I.I., Vletter,Wim B., Voormolen,Marco M., Bosch,Johan G., Ten Cate,Folkert J., Roelandt,Jos R.T.C., Geleijnse,Marcel L., Contrast-enhanced three-dimensional dobutamine stress echocardiography: between Scylla and Charybdis?, European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of CardiologyEur J Echocardiogr, 9, 757-760, 2008	Population (included patients with known CAD)
Krittayaphong,Rungroj, Mahanonda,Nithi, Kangkagate,Charuwan, Nakyen,Supaporn, Tanapibunpon,Prajak, Chaithiraphan,Suphachai, Accuracy of magnetic resonance imaging in the diagnosis of coronary artery disease, Journal of the Medical Association of Thailand = Chotmaihet thangphaetJ Med Assoc Thai, 86 Suppl 1, S59-S66, 2003	Reference standard (non protocol)
Kuettner,A., Beck,T., Drosch,T., Kettering,K., Heuschmid,M., Burgstahler,C., Claussen,C.D., Kopp,A.F., Schroeder,S., Image quality and diagnostic accuracy of non-invasive coronary imaging with 16 detector slice spiral computed tomography with 188 ms temporal resolution, Heart (British Cardiac Society), 91, 938-941, 2005	Population (included patients with known CAD)
Kuettner,Axel, Beck,Torsten, Drosch,Tanja, Kettering,Klaus, Heuschmid,Martin, Burgstahler,Christof, Claussen,Claus D., Kopp,Andreas F., Schroeder,Stephen, Diagnostic accuracy of noninvasive coronary imaging using 16-detector slice spiral computed tomography with 188 ms temporal resolution, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 45, 123-127, 2005	16 slice scanner (minimum 64 slice)
Kuettner,Axel, Trabold,Tobias, Schroeder,Stephen, Feyer,Anja, Beck,Torsten, Brueckner,Ariane, Heuschmid,Martin, Burgstahler,Christof, Kopp,Andreas F., Claussen,Claus D., Noninvasive detection of coronary lesions using 16-detector multislice spiral computed tomography technology: initial clinical results, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 44, 1230-	Population (unclear)

Author	Reason for exclusion
1237, 2004	
Kunimasa,Taeko, Sato,Yuichi, Matsumoto,Naoya, Chiku,Masaaki, Tani,Shigemasa, Kasama,Shu, Kunimoto,Satoshi, Yoda,Shunichi, Saito,Satoshi, Nagao,Ken, Detection of coronary artery disease by free-breathing, whole heart coronary magnetic resonance angiography: our initial experience, Heart and VesselsHeart Vessels, 24, 429-433, 2009	Reference standard (non protocol)
Kurata,Akira, Kawaguchi,Naoto, Kido,Teruhito, Inoue,Katsuji, Suzuki,Jun, Ogimoto,Akiyoshi, Funada,Jun ichi, Higaki,Jitsuo, Miyagawa,Masao, Vembar,Mani, Mochizuki,Teruhito, Qualitative and quantitative assessment of adenosine triphosphate stress whole-heart dynamic myocardial perfusion imaging using 256-slice computed tomography, PLoS ONE, 8, e83950-, 2013	Index test overlaps with DG3 (New Generation Scanner)
Kwok,Y., Kim,C., Grady,D., Segal,M., Redberg,R., Meta-analysis of exercise testing to detect coronary artery disease in women, The American journal of cardiologyAm J Cardiol, 83, 660-666, 1999	Population (women only)
Labounty,Troy M., Kim,Robert J., Lin,Fay Y., Budoff,Matthew J., Weinsaft,Jonathan W., Min,James K., Diagnostic accuracy of coronary computed tomography angiography as interpreted on a mobile handheld phone device, JACC.Cardiovascular imagingJACC Cardiovasc Imaging, 3, 482-490, 2010	Discussed with Topic Experts(too specific)
LaManna,M.M., Mohama,R., Slavich,I.L., Lumia,F.J., Cha,S.D., Rambaran,N., Maranhao,V., Intravenous adenosine (adenoscan) versus exercise in the noninvasive assessment of coronary artery disease by SPECT, Clinical Nuclear MedicineClin.Nucl.Med., 15, 804-805, 1990	Population (unclear)
Lambertz,H., Kreis,A., Trumper,H., Hanrath,P., Simultaneous transesophageal atrial pacing and transesophageal two-dimensional echocardiography: a new method of stress echocardiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 16, 1143-1153, 1990	Population (included patients with previous MI
Lau,George T., Ridley,Lloyd J., Schieb,Max C., Brieger,David B., Freedman,S Benedict, Wong,Louise A., Lo,Sing Kai, Kritharides,Leonard, Coronary artery stenoses: detection with calcium scoring, CT angiography, and both methods combined, Radiology, 235, 415-422, 2005	4 scanner slices (minimum 64 slice)
Laudon,D.A., Behrenbeck,T.R., Wood,C.M., Bailey,K.R., Callahan,C.M., Breen,J.F., Vukov,L.F., Computed tomographic coronary artery calcium assessment for evaluating chest pain in the emergency department: long-term outcome of a prospective blind study, Mayo Clinic ProceedingsMAYO CLIN.PROC., 85, 314-322, 2010	CAD is not the outcome reported
Layritz,Christian, Schmid,Jasmin, Achenbach,Stephan, Ulzheimer,Stefan, Wuest,Wolfgang, May,Matthias, Ropers,Dieter, Klinghammer,Lutz, Daniel,Werner G., Pflederer,Tobias, Lell,Michael, Accuracy of prospectively ECG-triggered very low-dose coronary dual-source CT angiography using iterative reconstruction for the detection of coronary artery stenosis: comparison with invasive catheterization, European Heart Journal Cardiovascular ImagingEur.Heart J.Cardiovasc.Imaging, 15, 1238-1245, 2014	New generation scanner used (protocol exclusion)
Leber,Alexander W., Johnson,Thorsten, Becker,Alexander,	Only patients with

Author	Reason for exclusion
von Ziegler,Franz, Tittus,Janine, Nikolaou,Konstantin, Reiser,Maximilian, Steinbeck,Gerhard, Becker,Christoph R., Knez,Andreas, Diagnostic accuracy of dual-source multi-slice CT-coronary angiography in patients with an intermediate pretest likelihood for coronary artery disease, European Heart JournalEur.Heart J., 28, 2354-2360, 2007	negative/unequivocal pre-study sress tests were included.
Leber,Alexander W., Knez,Andreas, von Ziegler,Franz, Becker,Alexander, Nikolaou,Konstantin, Paul,Stephan, Wintersperger,Bernd, Reiser,Maximilian, Becker,Christoph R., Steinbeck,Gerhard, Boekstegers,Peter, Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 46, 147-154, 2005	Population (included patients with previous angioplasty having scans prior to catheterization)
Lee,Jung S., Lee,Jun S., Kim,Seong Jang, Kim,In Ju, Kim,Yong Ki, Choo,Ki S., Comparison of gated blood pool SPECT and spiral multidetector computed tomography in the assessment of right ventricular functional parameters: validation with first-pass radionuclide angiography, Annals of Nuclear MedicineAnn.Nucl.Med., 21, 159-166, 2007	Not relevant
Lei,Ziqiao, Gu,Jin, Fu,Qing, Shi,Heshui, Xu,Haibo, Han,Ping, Yu,Jianming, The diagnostic evaluation of dual-source CT (DSCT) in the diagnosis of coronary artery stenoses, Pakistan Journal of Medical SciencesPak.J.Med.Sci., 29, 107-111, 2013	Design (retrospective)
Leipsic,Jonathon, Yang,Tae Hyun, Thompson,Angus, Koo,Bo Kwon, Mancini,G.B.J., Taylor,Carolyn, Budoff,Matthew J., Park,Hyung Bok, Berman,Daniel S., Min,James K., CT angiography (CTA) and diagnostic performance of noninvasive fractional flow reserve: results from the Determination of Fractional Flow Reserve by Anatomic CTA (DeFACTO) study, AJR.American journal of roentgenologyAJR Am J Roentgenol, 202, 989-994, 2014	Population (included patients with known CAD)
Leschka,S., Scheffel,H., Desbiolles,L., Plass,A., Gaemperli,O., Stolzmann,P., Genoni,M., Luescher,T., Marincek,B., Kaufmann,P., Alkadhi,H., Combining dual-source computed tomography coronary angiography and calcium scoring: added value for the assessment of coronary artery disease, Heart (British Cardiac Society), 94, 1154-1161, 2008	Includes known CAD
Leschka,Sebastian, Alkadhi,Hatem, Plass,Andre, Desbiolles,Lotus, Grunenfelder,Jurg, Marincek,Borut, Wildermuth,Simon, Accuracy of MSCT coronary angiography with 64-slice technology: first experience, European Heart JournalEur.Heart J., 26, 1482-1487, 2005	Population (included patients having c.angio prior to CABG)
Li,Dong ye, Liang,Li, Xu,Tong da, Zhang,Hui, Pan,De feng, Chen,Jun hong, Chen,Jing, Wang,Xiao ping, The value of quantitative real-time myocardial contrast echocardiography for detection of angiographically significant coronary artery disease, Clinical CardiologyClin.Cardiol., 36, 468-474, 2013	No patient level analysis (segment level only)
Li,Jian Ming, Shi,Rong Fang, Zhang,Li Ren, Li,Ting, Dong,Zhi, Combined CT angiography and SPECT myocardial perfusion imaging for the detection of functionally relevant coronary stenoses, Molecular Medicine ReportsMol.Med.Rep., 7, 1391-1396, 2013	Population (included patients with known CAD)
Li,Min, Du,Xiang Min, Jin,Zhi Tao, Peng,Zhao Hui,	Population (included patients with

Author	Reason for exclusion
Ding,Juan, Li,Li, The diagnostic performance of coronary artery angiography with 64-MSCT and post 64-MSCT: systematic review and meta-analysis, PLoS ONE, 9, e84937-, 2014	known CAD) Index test overlaps with DG3 (New Generation Scanner)
Li,S., Ni,Q., Wu,H., Peng,L., Dong,R., Chen,L., Liu,J., Diagnostic accuracy of 320-slice computed tomography angiography for detection of coronary artery stenosis: meta-analysis (Structured abstract), International journal of cardiologyInt.J.Cardiol., 168, 2699-2705, 2013	Included mix population studies
Li,Suhua, Ni,Qiongqiong, Wu,Huilan, Peng,Long, Dong,Ruimin, Chen,Lin, Liu,Jinlai, Diagnostic accuracy of 320-slice computed tomography angiography for detection of coronary artery stenosis: meta-analysis, International journal of cardiologyInt.J.Cardiol., 168, 2699-2705, 2013	Includes mixed population studies
Lim,M.C.L., Wong,T.W., Yaneza,L.O., De Larrazabal,C., Lau,J.K., Boey,H.K., Non-invasive detection of significant coronary artery disease with multi-section computed tomography angiography in patients with suspected coronary artery disease, Clinical RadiologyClin.Radiol., 61, 174-180, 2006	40 slice scanner (minimum 64 slice)
Lin,C.J., Hsu,J.C., Lai,Y.J., Wang,K.L., Lee,J.Y., Li,A.H., Chu,S.H., Diagnostic accuracy of dual-source CT coronary angiography in a population unselected for degree of coronary artery calcification and without heart rate modification, Clinical RadiologyClin.Radiol., 65, 109-117, 2010	Design (retrospective)
Lipiec,Piotr, Wejner-Mik,Paulina, Krzeminska-Pakula,Maria, Kusmierek,Jacek, Plachcinska,Anna, Szuminski,Remigiusz, Kapusta,Anna, Kasprzak,Jaroslaw D., Gated 99mTc-MIBI single-photon emission computed tomography for the evaluation of left ventricular ejection fraction: comparison with three-dimensional echocardiography, Annals of Nuclear MedicineAnn.Nucl.Med., 22, 723-726, 2008	Population (included patients with known CAD)
Liu,X.J., Wang,X.B., Gao,R.L., Lu,P., Wang,Y.Q., Clinical evaluation of 99Tcm-MIBI SPECT in the assessment of coronary artery disease, Nuclear Medicine CommunicationsNUCL.MED.COMMUN., 13, 776-779, 1992	Population (included patients with known CAD)
Lu,Bin, Lu,Jin Guo, Sun,Ming Li, Hou,Zhi Hui, Chen,Xiong Biao, Tang,Xiang, Wu,Run Ze, Johnson,Laura, Qiao,Shu bin, Yang,Yue Jin, Jiang,Shi Liang, Comparison of diagnostic accuracy and radiation dose between prospective triggering and retrospective gated coronary angiography by dual-source computed tomography, The American journal of cardiologyAm J Cardiol, 107, 1278-1284, 2011	Design (retrospective)
Lu,Bin, Shavelle,David M., Mao,SongShou, Chen,Lynn, Child,Janis, Carson,Sivi, Budoff,Matthew J., Improved accuracy of noninvasive electron beam coronary angiography, Investigative RadiologyInvest.Radiol., 39, 73-79, 2004	Non protocol index test
Luotolahti,M., Saraste,M., Hartiala,J., Exercise echocardiography in the diagnosis of coronary artery disease, Annals of MedicineANN.MED., 28, 73-77, 1996	Population (included patients with suspected CAD
Ma,Heng, Yang,Jun, Liu,Jing, Ge,Lan, An,Jing, Tang,Qing, Li,Han, Zhang,Yu, Chen,David, Wang,Yong, Liu,Jiabin, Liang,Zhigang, Lin,Kai, Jin,Lixin, Bi,Xiaoming, Li,Kuncheng, Li,Debiao, Myocardial perfusion magnetic resonance imaging using sliding-window conjugate-gradient highly constrained	Discuss with Topic Experts (too highly specific to reflect current practice)

Author	Reason for exclusion
back-projection reconstruction for detection of coronary artery disease, The American journal of cardiologyAm J Cardiol, 109, 1137-1141, 2012	
Madaj,Paul, Gopal,Ambarish, Hamirani,Yasmin, Zeb,Irfan, Elamir,Sameh, Budoff,Matthew, The degree of stenosis on cardiac catheterization compared to calcified coronary segments on multi-detector row cardiac computed tomography MDCT, Academic RadiologyAcad.Radiol., 17, 1001-1005, 2010	Outcome/analysis not performed on CAD(types of calcification)
Madhok,Rajneesh, Aggarwal,Abhinav, Comparison of 128-Slice Dual Source CT Coronary Angiography with Invasive Coronary Angiography, Journal of clinical and diagnostic research : JCDRJ Clin Diagn Res, 8, RC08-RC11, 2014	Index test overlaps with DG3 (New Generation Scanner)
Maffei,E., Martini,C., Rossi,A., Mollet,N., Lario,C., Castiglione Morelli,M., Clemente,A., Gentile,G., Arcadi,T., Seitun,S., Catalano,O., Aldrovandi,A., Cademartiri,F., Diagnostic accuracy of second-generation dual-source computed tomography coronary angiography with iterative reconstructions: a real-world experience, La Radiologia medicaRadiol Med, 117, 725-738, 2012	Index test overlaps with DG3 (New Generation Scanner)
Maffei,E., Martini,C., Tedeschi,C., Spagnolo,P., Zuccarelli,A., Arcadi,T., Guaricci,A., Seitun,S., Weustink,A., Mollet,N., Cademartiri,F., Diagnostic accuracy of 64-slice computed tomography coronary angiography in a large population of patients without revascularisation: registry data on the comparison between male and female population, La Radiologia medicaRadiol Med, 117, 6-18, 2012	Population (included patients with ACS)
Maffei,E., Palumbo,A., Martini,C., Meijboom,W., Tedeschi,C., Spagnolo,P., Zuccarelli,A., Weustink,A., Torri,T., Mollet,N., Seitun,S., Krestin,G.P., Cademartiri,F., Diagnostic accuracy of 64-slice computed tomography coronary angiography in a large population of patients without revascularisation: registry data and review of multicentre trials, La Radiologia medicaRadiol Med, 115, 368-384, 2010	Population (included patients with ACS)
Maffei,E., Palumbo,A., Martini,C., Ugo,F., Lina,D., Aldrovandi,A., Reverberi,C., Manca,C., Ardissino,D., Crisi,G., Cademartiri,F., Diagnostic accuracy of computed tomography coronary angiography in a high risk symptomatic population, Acta bio-medica, 81, 47-53, 2010	Population (included patients with ACS)
Mahmarian,J.J., Boyce,T.M., Goldberg,R.K., Cocanougher,M.K., Roberts,R., Verani,M.S., Quantitative exercise thallium-201 single photon emission computed tomography for the enhanced diagnosis of ischemic heart disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 15, 318-329, 1990	Population (included patients with known CAD)
Mahnken,A.H., Wildberger,J.E., Sinha,A.M., Dedden,K., Stanzel,S., Hoffmann,R., Schmitz-Rode,T., Gunther,R.W., Value of 3D-volume rendering in the assessment of coronary arteries with retrospectively ECG-gated multislice spiral CT, Acta radiologica (Stockholm, SwedenActa Radiol, 44, 302-309, 2003	Study design/mixed population
Mahnken,Andreas H., Wein,Berthold B., Sinha,Anil M., Gunther,Rolf W., Wildberger,Joachim E., Value of conventional chest radiography for the detection of coronary calcifications: comparison with MSCT, European Journal of RadiologyEur.J.Radiol., 69, 510-516, 2009	Design (retrospective)
Maintz,David, Aepfelbacher,Franz C., Kissinger,Kraig V.,	Non protocol index test

Author	Reason for exclusion
Botnar,Rene M., Danias,Peter G., Heindel,Walter, Manning,Warren J., Stuber,Matthias, Coronary MR angiography: comparison of quantitative and qualitative data from four techniques, AJR.American journal of roentgenologyAJR Am J Roentgenol, 182, 515-521, 2004	
Mairesse,G.H., Marwick,T.H., Vanoverschelde,J.L., Baudhuin,T., Wijns,W., Melin,J.A., Detry,J.M., How accurate is dobutamine stress electrocardiography for detection of coronary artery disease? Comparison with two-dimensional echocardiography and technetium-99m methoxyl isobutyl isonitrile (mibi) perfusion scintigraphy, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 24, 920-927, 1994	Reference standard (non protocol)
Makaryus,Amgad N., Henry,Sonia, Loewinger,Lee, Makaryus,John N., Boxt,Lawrence, Multi-Detector Coronary CT Imaging for the Identification of Coronary Artery Stenoses in a "Real-World" Population, Clinical Medicine Insights.CardiologyClin Med Insights Cardiol, 8, 13-22, 2014	Population (selected on basis of CTCA results)
Malago,R., Pezzato,A., Barbiani,C., Alfonsi,U., D'Onofrio,M., Tavella,D., Benussi,P., Pozzi Mucelli,R., Role of coronary angiography MDCT in the clinical setting: changes in diagnostic workup in the real world, La Radiologia medicaRadiol Med, 117, 939-952, 2012	Includes known disease
Manka,Robert, Wissmann,Lukas, Gebker,Rolf, Jogiya,Roy, Motwani,Manish, Frick,Michael, Reinartz,Sebastian, Schnackenburg,Bernhard, Niemann,Markus, Gotschy,Alexander, Kuhl,Christiane, Nagel,Eike, Fleck,Eckart, Marx,Nikolaus, Luescher,Thomas F., Plein,Sven, Kozerke,Sebastian, Multicenter evaluation of dynamic three-dimensional magnetic resonance myocardial perfusion imaging for the detection of coronary artery disease defined by fractional flow reserve, Circulation.Cardiovascular imagingCirc Cardiovasc Imaging, 8, -, 2015	Non protocol reference test
Mannan,M., Bashar,M.A., Mohammad,J., Jahan,M.U., Momenuzzaman,N.A.M., Haque,M.A., Comparison of coronary CT angiography with conventional coronary angiography in the diagnosis of coronary artery disease, Bangladesh Medical Research Council BulletinBangladesh Med.Res.Counc.Bull., 40, 31-35, 2014	Population not defined.
Mao,S., Budoff,M.J., Oudiz,R.J., Bakhsheshi,H., Wang,S., Brundage,B.H., Effect of exercise on left and right ventricular ejection fraction and wall motion, International journal of cardiologyInt.J.Cardiol., 71, 23-31, 1999	Non protocol index test
Maret,Eva, Engvall,Jan, Nylander,Eva, Ohlsson,Jan, Feasibility and diagnostic power of transthoracic coronary Doppler for coronary flow velocity reserve in patients referred for myocardial perfusion imaging, Cardiovascular ultrasoundCardiovasc Ultrasound, 6, 12-, 2008	Reference standard (non protocol)
Martuscelli,Eugenio, Razzini,Cinzia, D'Eliseo,Alessia, Marchei,Massimo, Pisani,Eliana, Romeo,Francesco, Limitations of four-slice multirow detector computed tomography in the detection of coronary stenosis, Italian heart journal : official journal of the Italian Federation of Cardiology, 5, 127-131, 2004	4 slice scanner (minimum 64 slice)
Martuscelli,Eugenio, Romagnoli,Andrea, D'Eliseo,Alessia, Razzini,Cinzia, Tomassini,Marco, Sperandio,Massimiliano, Simonetti,Giovanni, Romeo,Francesco, Accuracy of thin-slice	16 slice CT (minimum 64slice)

Author	Reason for exclusion
computed tomography in the detection of coronary stenoses, European Heart JournalEur.Heart J., 25, 1043-1048, 2004	
Maruyama,Takao, Takada,Masanori, Hasuike,Toshiaki, Yoshikawa,Atsushi, Namimatsu,Eiji, Yoshizumi,Tohru, Radiation dose reduction and coronary assessability of prospective electrocardiogram-gated computed tomography coronary angiography: comparison with retrospective electrocardiogram-gated helical scan, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 52, 1450-1455, 2008	Population (those being followed up after PCI)
Masuda,Y., Naito,S., Aoyagi,Y., Yamada,Z., Uda,T., Morooka,N., Watanabe,S., Inagaki,Y., Coronary artery calcification detected by CT: clinical significance and angiographic correlates, Angiology, 41, 1037-1047, 1990	Includes known CAD
Mathias,Wilson Jr, Tsutsui,Jeane M., Andrade,Jose L., Kowatsch,Ingrid, Lemos,Pedro A., Leal,Samira M.B., Khandheria,Bijoy K., Ramires,Jose F., Value of rapid beta-blocker injection at peak dobutamine-atropine stress echocardiography for detection of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 41, 1583-1589, 2003	Population (included patients with known CAD)
Matsuda,J., Miyamoto,N., Ikushima,I., Takenaga,M., Koiwaya,Y., Eto,T., Stress technetium-99m tetrofosmin myocardial scintigraphy: a new one-hour protocol for the detection of coronary artery disease, Journal of CardiologyJ.Cardiol., 32, 219-226, 1998	Reference standard (unclear)
Matsuo,Shinro, Nakamura,Yasuyuki, Matsumoto,Tetsuya, Nakae,Ichiro, Nagatani,Yukihiro, Takazakura,Ryutaro, Takahashi,Masashi, Murata,Kiyoshi, Horie,Minoru, Visual assessment of coronary artery stenosis with electrocardiographically-gated multislice computed tomography, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 20, 61-66, 2004	Index test overlaps with DG3 (New Generation Scanner)
Mazeika,P.K., Nadazdin,A., Oakley,C.M., Dobutamine stress echocardiography for detection and assessment of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 19, 1203-1211, 1992	Mixed population: Includes patients with previous MI. Analysis (missing data)
Mc Ardle,Brian A., Dowsley,Taylor F., deKemp,Robert A., Wells,George A., Beanlands,Rob S., Does rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease?: A systematic review and meta-analysis, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 60, 1828-1837, 2012	Population (included patients known or suspected CAD)
McCarthy,Richard M., Deshpande,Vibhas S., Beohar,Nirat, Meyers,Sheridan N., Shea,Steven M., Green,Jordin D., Liu,Xin, Bi,Xiaoming, Pereles,F.Scott, Finn,John Paul, Davidson,Charles J., Carr,James C., Li,Debiao, Three-dimensional breathhold magnetization-prepared TrueFISP: a pilot study for magnetic resonance imaging of the coronary artery disease, Investigative RadiologyInvest.Radiol., 42, 665-670, 2007	non protocol index test
McKavanagh,Peter, Lusk,Lisa, Ball,Peter A., Trinick,Tom R., Duly,Ellie, Walls,Gerard M., Orr,Clare, Harbinson,Mark T., Donnelly,Patrick M., A comparison of Diamond Forrester and coronary calcium scores as gatekeepers for investigations of stable chest pain, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 29, 1547-1555, 2013	Not relevant to the question

Author	Reason for exclusion
Meijboom,W.Bob, Meijs,Matthijs F.L., Schuijf,Joanne D., Cramer,Maarten J., Mollet,Nico R., van Mieghem,Carlos A.G., Nieman,Koen, van Werkhoven,Jacob M., Pundziute,Gabija, Weustink,Annick C., de Vos,Alexander M., Pugliese,Francesca, Rensing,Benno, Jukema,J.Wouter, Bax,Jeroen J., Prokop,Mathias, Doevendans,Pieter A., Hunink,Myriam G.M., Krestin,Gabriel P., de Feyter,Pim J., Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 52, 2135-2144, 2008	Population (included patients with ACS)
Meijboom,W.Bob, van Mieghem,Carlos A.G., Mollet,Nico R., Pugliese,Francesca, Weustink,Annick C., van Pelt,Niels, Cademartiri,Filippo, Nieman,Koen, Boersma,Eric, de Jaegere,Peter, Krestin,Gabriel P., de Feyter,Pim J., 64-slice computed tomography coronary angiography in patients with high, intermediate, or low pretest probability of significant coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 50, 1469-1475, 2007	Population (included patients with ACS)
Meijboom,W.Bob, van Mieghem,Carlos A.G., van Pelt,Niels, Weustink,Annick, Pugliese,Francesca, Mollet,Nico R., Boersma,Eric, Regar,Eveline, van Geuns,Robert J., de Jaegere,Peter J., Serruys,Patrick W., Krestin,Gabriel P., de Feyter,Pim J., Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 52, 636-643, 2008	Reference standard (non protocol)
Melendez,L.J., Driedger,A.A., Salcedo,J.R., et al. (1979) Exercise electrocardiography and myocardial perfusion imaging in the diagnosis of coronary artery disease: preliminary report. Canadian journal of surgery.Journal canadien de chirurgieCan J Surg: 22 p.334-336	Used obsolete image acquisition equipment
Melin,J.A., Piret,L.J., and Vanbutsele,R.J.M. (1981) Diagnostic value of exercise electrocardiography and thallium myocardial scintigraphy in patients without previous myocardial infarction: A Bayesian approach. Circulation: 63 p.1019-1024	Used obsolete image acquisition equipment
Memmola,C., Iliceto,S., Rizzon,P., Detection of proximal stenosis of left coronary artery by digital transesophageal echocardiography: feasibility, sensitivity, and specificity, Journal of the American Society of EchocardiographyJ.Am.Soc.Echocardiogr., 6, 149-157, 1993	Non protocol index test
Mendelson,M.A., Spies,S.M., Spies,W.G., Abi-Mansour,P., Fintel,D.J., Usefulness of single-photon emission computed tomography of thallium-201 uptake after dipyridamole infusion for detection of coronary artery disease, The American journal of cardiologyAm J Cardiol, 69, 1150-1155, 1992	Population (included patients with known or suspected CAD and patients with previous MI)
Menke,J., Kowalski,J., Diagnostic accuracy and utility of coronary CT angiography with consideration of unevaluable	Population (included patients with known or suspected CAD)

Author	Reason for exclusion
results: A systematic review and multivariate Bayesian random-effects meta-analysis with intention to diagnose, Eur Radiol, -, 2015	
Meyer,Mathias, Henzler,Thomas, Fink,Christian, Vliegenthart,Rozemarijn, Barraza,J.Michael Jr, Nance,John W.J., Apfaltrer,Paul, Schoenberg,Stefan O., Wasser,Klaus, Impact of coronary calcium score on the prevalence of coronary artery stenosis on dual source CT coronary angiography in caucasian patients with an intermediate risk, Academic RadiologyAcad.Radiol., 19, 1316-1323, 2012	Design (retrospective) Index test overlaps with DG3 (New Generation Scanner)
Michael,T.A.D., Rao,G., Balasingam,S., Accuracy and usefulness of atrial pacing in conjunction with transesophageal echocardiography in the detection of cardiac ischemia (a comparative study with scintigraphic tomography and coronary arteriography), American Journal of CardiologyAm.J.Cardiol., 75, 563-567, 1995	Design (non consecutive) Population (mixed)
Miller,D.D., Younis,L.T., Chaitman,B.R., Stratmann,H., Diagnostic accuracy of dipyridamole technetium 99m-labeled sestamibi myocardial tomography for detection of coronary artery disease, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 4, 18-24, 1997	Population (included patients with previous MI)
Miller,J.M., Rochitte,C.E., Dewey,M., Keyhani,S., Cardiac computed tomography-not ready for prime time, Journal of Clinical Outcomes ManagementJ.Clin.Outcomes Manage., 16, 18-19, 2009	Abstract only
Miller,Julie M., Rochitte,Carlos E., Dewey,Marc, Arbab-Zadeh,Armin, Niinuma,Hiroyuki, Gottlieb,Ilan, Paul,Narinder, Clouse,Melvin E., Shapiro,Edward P., Hoe,John, Lardo,Albert C., Bush,David E., de Roos,Albert, Cox,Christopher, Brinker,Jeffery, Lima,Joao A.C., Diagnostic performance of coronary angiography by 64-row CT, The New England journal of medicineN Engl J Med, 359, 2324-2336, 2008	Population (included patients with previous MI
Min,James K., Arsanjani,Reza, Kurabayashi,Sachio, Andreini,Daniele, Pontone,Gianluca, Choi,Byung Wook, Chang,Hyuk Jae, Lu,Bin, Narula,Jagat, Karimi,Afshin, Roobottom,Carl, Gomez,Millie, Berman,Daniel S., Cury,Ricardo C., Villines,Todd, Kang,Joon, Leipsic,Jonathon, Rationale and design of the ViCTORY (Validation of an Intracycle CT Motion CORrection Algorithm for Diagnostic AccuracY) trial, Journal of Cardiovascular Computed TomographyJ.Cardiovasc.Comput.Tomogr., 7, 200-206, 2013	Rationale and design of study only. No results.
Min,James K., Berman,Daniel S., Budoff,Matthew J., Jaffer,Farouc A., Leipsic,Jonathon, Leon,Martin B., Mancini,G.B.J., Mauri,Laura, Schwartz,Robert S., Shaw,Leslee J., Rationale and design of the DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic AngiOgraphy) study, Journal of Cardiovascular Computed TomographyJ.Cardiovasc.Comput.Tomogr., 5, 301-309, 2011	Reference standard (non protocol)
Minoves,M., Garcia,A., Magrina,J., Pavia,J., Herranz,R., Setoain,J., Evaluation of myocardial perfusion defects by means of "bull's eye" images, Clinical CardiologyClin.Cardiol., 16, 16-22, 1993	known CAD population
Mir-Akbari,H., Ripsweden,J., Jensen,J., Pichler,P., Sylven,C.,	Population (included patients with

Author	Reason for exclusion
Cederlund,K., Ruck,A., Limitations of 64-detector-row computed tomography coronary angiography: calcium and motion but not short experience, Acta radiologica (Stockholm, Sweden : 1987), 50, 174-180, 2009	previous MI or PCI)
Miszalski-Jamka,Tomasz, Kuntz-Hehner,Stefanie, Schmidt,Harald, Hammerstingl,Christoph, Tiemann,Klaus, Ghanem,Alexander, Troatz,Clemens, Luderitz,Berndt, Omran,Heyder, Real time myocardial contrast echocardiography during supine bicycle stress and continuous infusion of contrast agent. Cutoff values for myocardial contrast replenishment discriminating abnormal myocardial perfusion, Echocardiography (Mount Kisco, N.Y.), 24, 638-648, 2007	Discussed with Topic Experts (validation of highly specific methods - not mainstream)
Mitsutake,Ryoko, Niimura,Hideya, Miura,Shin Ichiro, Zhang,Bo, Iwata,Atsushi, Nishikawa,Hiroaki, Kawamura,Akira, Kumagai,Koichiro, Shirai,Kazuyuki, Matsunaga,Akira, Saku,Keijiro, Clinical significance of the coronary calcification score by multidetector row computed tomography for the evaluation of coronary stenosis in Japanese patients, Circulation journal : official journal of the Japanese Circulation SocietyCirc J, 70, 1122-1127, 2006	Population (included asymptomatic patients)
Mollet,Nico R., Cademartiri,Filippo, Krestin,Gabriel P., McFadden,Eugene P., Arampatzis,Chourmouzios A., Serruys,Patrick W., de Feyter,Pim J., Improved diagnostic accuracy with 16-row multi-slice computed tomography coronary angiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 45, 128-132, 2005	16 slice scanner (minimum 64 slice)
Montz,R., Perez-Castejon,M.J., Jurado,J.A., Martin-Comin,J., Esplugues,E., Salgado,L., Ventosa,A., Cantinho,G., Sa,E.P., Fonseca,A.T., Vieira,M.R., Technetium-99m tetrofosmin rest/stress myocardial SPET with a same-day 2-hour protocol: comparison with coronary angiography. A Spanish-Portuguese multicentre clinical trial, European Journal of Nuclear MedicineEUR.J.NUCL.MED., 23, 639-647, 1996	Population (included patients with known or suspected CAD)
Moon,Jae Youn, Chung,Namsik, Choi,Byoung Wook, Choe,Kyu Ok, Seo,Hye Sun, Ko,Young Guk, Kang,Seok Min, Ha,Jong Won, Rim,Se Joong, Jang,Yangsoo, Shim,Won Heum, Cho,Seung Yun, The utility of multi-detector row spiral CT for detection of coronary artery stenoses, Yonsei Medical JournalYonsei Med.J., 46, 86-94, 2005	16 slice scanner (minimum 64 slice)
Moon,Jun Sung, Yoon,Ji Sung, Won,Kyu Chang, Cho,Ihn Ho, Lee,Hyoung Woo, Diagnostic Accuracy of 64-Slice MDCT Coronary Angiography for the Assessment of Coronary Artery Disease in Korean Patients with Type 2 Diabetes, Diabetes & metabolism journalDiabetes Metab J, 37, 54-62, 2013	Population (included patients with Type 2 Diabetes)
Mordini,Federico E., Haddad,Tariq, Hsu,Li Yueh, Kellman,Peter, Lowrey,Tracy B., Aletras,Anthony H., Bandettini,W.Patricia, Arai,Andrew E., Diagnostic accuracy of stress perfusion CMR in comparison with quantitative coronary angiography: fully quantitative, semiquantitative, and qualitative assessment, JACC.Cardiovascular imagingJACC Cardiovasc Imaging, 7, 14-22, 2014	Population (included patients with known CAD
Morgan-Hughes,G.J., Marshall,A.J., Roobottom,C.A., Multislice computed tomographic coronary angiography: Experience in a UK Centre, Clinical RadiologyClin.Radiol., 58, 378-383, 2003	Population (unclear - emailed author - not replied)

Author	Reason for exclusion
Morgan-Hughes,G.J., Roobottom,C.A., Owens,P.E., Marshall,A.J., Highly accurate coronary angiography with submillimetre, 16 slice computed tomography, Heart (British Cardiac Society), 91, 308-313, 2005	16 slice scanner (minimum 64 slice)
Morise,A.P., An incremental evaluation of the diagnostic value of thallium single-photon emission computed tomographic imaging and lung/heart ratio concerning both the presence and extent of coronary artery disease, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 2, 238-245, 1995	Design (correlation study not DTA study)
Morton,Geraint, Chiribiri,Amedeo, Ishida,Masaki, Hussain,Shazia T., Schuster,Andreas, Indermuehle,Andreas, Perera,Divaka, Knuuti,Juhani, Baker,Stacey, Hedstrom,Erik, Schleyer,Paul, O'Doherty,Michael, Barrington,Sally, Nagel,Eike, Quantification of absolute myocardial perfusion in patients with coronary artery disease: comparison between cardiovascular magnetic resonance and positron emission tomography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 60, 1546-1555, 2012	Population (included patients with known CAD)
Morton,K.A., Alazraki,N.P., Taylor,A.T., Datz,F.L., SPECT thallium-201 scintigraphy for the detection of left-ventricular aneurysm, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 28, 168-172, 1987	Not relevant
Mosalla,S.M.-M., Tavakoli,H., Gholamrezanezhad,A., A study of demographic and clinical features of patients referred to the nuclear medicine department of a military hospital for myocardial perfusion scintigraphy, Iranian Journal of Nuclear MedicineIran.J.Nucl.Med., 17, 34-40, 2009	Not all participants received reference standard
Motwani,Manish, Fairbairn,Timothy A., Larghat,Abdulghani, Mather,Adam N., Biglands,John D., Radjenovic,Aleksandra, Greenwood,John P., Plein,Sven, Systolic versus diastolic acquisition in myocardial perfusion MR imaging, Radiology, 262, 816-823, 2012	Population (unclear - included patients with MI)
Motwani,Manish, Maredia,Neil, Fairbairn,Timothy A., Kozerke,Sebastian, Radjenovic,Aleksandra, Greenwood,John P., Plein,Sven, High-resolution versus standard-resolution cardiovascular MR myocardial perfusion imaging for the detection of coronary artery disease, Circulation.Cardiovascular imagingCirc Cardiovasc Imaging, 5, 306-313, 2012	Population (20% of patients had previous MI or PCI)
Mowatt,G., Cook,J.A., Hillis,G.S., Walker,S., Fraser,C., Jia,X., Waugh,N., 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis, Heart (British Cardiac Society), 94, 1386-1393, 2008	Population (included patients with known CAD)
Mowatt,G., Cummins,E., Waugh,N., Walker,S., Cook,J., Jia,X., Hillis,G.S., Fraser,C., Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease, Health technology assessment (Winchester, England)Health Technol Assess, 12, iii-143, 2008	Population (included patients with known CAD)
Mowatt,G., Vale,L., Brazzelli,M., Hernandez,R., Murray,A., Scott,N., Fraser,C., McKenzie,L., Gemmell,H., Hillis,G., Metcalfe,M., Systematic review of the effectiveness and cost-	Population (included patients with previous MI)

Author	Reason for exclusion
effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction, Health technology assessment (Winchester, England)Health Technol Assess, 8, iii-207, 2004	
Naganuma,Toru, Latib,Azeem, Costopoulos,Charis, Takagi,Kensuke, Naim,Charbel, Sato,Katsumasa, Miyazaki,Tadashi, Kawaguchi,Masanori, Panoulas,Vasileios F., Basavarajaiah,Sandeep, Figini,Filippo, Chieffo,Alaide, Montorfano,Matteo, Carlino,Mauro, Colombo,Antonio, The role of intravascular ultrasound and quantitative angiography in the functional assessment of intermediate coronary lesions: correlation with fractional flow reserve, Cardiovascular revascularization medicine : including molecular interventionsCardiovasc Revasc Med, 15, 3-7, 2014	Population (included patients with previous PCI or CABG)
Nakamura,Ayako, Momose,Mitsuru, Kondo,Chisato, Nakajima,Takatomo, Kusakabe,Kiyoko, Hagiwara,Nobuhisa, Ability of 201Tl and 123I-BMIPP mismatch to diagnose myocardial ischemia in patients with suspected coronary artery disease, Annals of Nuclear MedicineAnn.Nucl.Med., 23, 793-798, 2009	Design (retrospective)
Nakamura,M., Takeda,K., Ichihara,T., Motomura,N., Shimizu,H., Saito,Y., Nomura,Y., Isaka,N., Konishi,T., Nakano,T., Feasibility of simultaneous stress 99mTc-sestamibi/rest 201Tl dual-isotope myocardial perfusion SPECT in the detection of coronary artery disease, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 40, 895-903, 1999	Population (included patients with previous MI)
Nakazato,Ryo, Berman,Daniel S., Dey,Damini, Le Meunier,Ludovic, Hayes,Sean W., Fermin,Jimmy S., Cheng,Victor Y., Thomson,Louise E.J., Friedman,John D., Germano,Guido, Slomka,Piotr J., Automated quantitative Rb-82 3D PET/CT myocardial perfusion imaging: normal limits and correlation with invasive coronary angiography, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 19, 265-276, 2012	Time flow (too long between tests)
Nakazato,Ryo, Tamarappoo,Balaji K., Kang,Xingping, Wolak,Arik, Kite,Faith, Hayes,Sean W., Thomson,Louise E.J., Friedman,John D., Berman,Daniel S., Slomka,Piotr J., Quantitative upright-supine high-speed SPECT myocardial perfusion imaging for detection of coronary artery disease: correlation with invasive coronary angiography, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 51, 1724-1731, 2010	Analysis (missing data) Time flow (too long between tests)
Nallamothu,B.K., Saint,S., Bielak,L.F., Sonnad,S.S., Peyser,P.A., Rubenfire,M., Fendrick,A.M., Electron-beam computed tomography in the diagnosis of coronary artery disease: a meta-analysis, Archives of Internal MedicineArch.Intern.Med., 161, 833-838, 2001	EBCT non protocol index test
Nallamothu,N., Ghods,M., Heo,J., Iskandrian,A.S., Comparison of thallium-201 single-photon emission computed tomography and electrocardiographic response during exercise in patients with normal rest electrocardiographic results, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 25, 830-836, 1995	Design (retrospective)
Namdar,Mehdi, Hany,Thomas F., Koepfli,Pascal,	Population (included patients with

Author	Reason for exclusion
Siegrist,Patrick T., Burger,Cyrill, Wyss,Christophe A., Luscher,Thomas F., von Schulthess,Gustav K., Kaufmann,Philipp A., Integrated PET/CT for the assessment of coronary artery disease: a feasibility study, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 46, 930-935, 2005	known CAD)
Nandalur,Kiran R., Dwamena,Ben A., Choudhri,Asim F., Nandalur,Mohan R., Carlos,Ruth C., Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 50, 1343-1353, 2007	Population (included patients with known CAD)
Nandalur,Kiran R., Dwamena,Ben A., Choudhri,Asim F., Nandalur,Sirisha R., Reddy,Priya, Carlos,Ruth C., Diagnostic performance of positron emission tomography in the detection of coronary artery disease: a meta-analysis, Academic RadiologyAcad.Radiol., 15, 444-451, 2008	Population (included patients with known CAD)
Naser,Nabil, Buksa,Marko, Sokolovic,Sekib, Hodzic,Enisa, The role of dobutamine stress echocardiography in detecting coronary artery disease compared with coronary angiography, Medicinski arhivMed Arh, 65, 140-144, 2011	Design (retrospective)
Nasis,Arthur, Ko,Brian S., Leung,Michael C., Antonis,Paul R., Nandurkar,Dee, Wong,Dennis T., Kyi,Leo, Cameron,James D., Troupis,John M., Meredith,Ian T., Seneviratne,Sujith K., Diagnostic accuracy of combined coronary angiography and adenosine stress myocardial perfusion imaging using 320-detector computed tomography: pilot study, European RadiologyEur.Radiol., 23, 1812-1821, 2013	Index test overlaps with DG3 (New Generation Scanner)
Nasis,Arthur, Leung,Michael C., Antonis,Paul R., Cameron,James D., Lehman,Sam J., Hope,Sarah A., Crossett,Marcus P., Troupis,John M., Meredith,Ian T., Seneviratne,Sujith K., Diagnostic accuracy of noninvasive coronary angiography with 320-detector row computed tomography, The American journal of cardiologyAm J Cardiol, 106, 1429-1435, 2010	Design (retrospective) Index test overlaps with DG3 (New Generation Scanner)
Nau,G., Albertal,M., Cura,F., Padilla,L., Candiello,A., Torrent,F., Peralta,S., Belardi,J., Efficacy and safety of dual-axis rotational coronary angiography versus conventional angiography, Revista Argentina de CardiologiaRev.Argent.Cardiol., 80, 280-285, 2012	Includes known CAD
Naya,Masanao, Murthy,Venkatesh L., Taqueti,Viviany R., Foster,Court, Klein,Josh, Garber,Mariya, Dorbala,Sharmila, Hainer,Jon, Blankstein,Ron, Resnic,Frederick, Di Carli,Marcelo F., Preserved coronary flow reserve effectively excludes high-risk coronary artery disease on angiography, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 55, 248-255, 2014	Analysis (missing data)
Nedeljkovic,I., Ostojic,M., Beleslin,B., Djordjevic-Dikic,A., Stepanovic,J., Nedeljkovic,M., Stojkovic,S., Stankovic,G., Saponjski,J., Petrasinovic,Z., Giga,V., Mitrovic,P., Comparison of exercise, dobutamine-atropine and dipyridamole-atropine stress echocardiography in detecting coronary artery disease, Cardiovascular ultrasoundCardiovasc Ultrasound, 4, 22-, 2006	Population (included patients with known CAD)
Neefjes,L.A., Rossi,A., Genders,T.S., Nieman,K., Papadopoulou,S.L., Dharampal,A.S., Schultz,C.J., Weustink,A.C., Dijkshoorn,M.L., Kate,G.J., Dedic,A.,	Index test overlaps with DG3 (New Generation Scanner)

Author	Reason for exclusion
Straten,M., Cademartiri,F., Hunink,M.G., Krestin,G.P., Feyter,P.J., Mollet,N.R., Diagnostic accuracy of 128-slice dual-source CT coronary angiography: a randomized comparison of different acquisition protocols, European RadiologyEur.Radiol., 23, 614-622, 2013	
Neglia,Danilo, Rovai,Daniele, Caselli,Chiara, Pietila,Mikko, Teresinska,Anna, Aguade-Bruix,Santiago, Pizzi,Maria Nazarena, Todiere,Giancarlo, Gimelli,Alessia, Schroeder,Stephen, Drosch,Tanja, Poddighe,Rosa, Casolo,Giancarlo, Anagnostopoulos,Constantinos, Pugliese,Francesca, Rouzet,Francois, Le Guludec,Dominique, Cappelli,Francesco, Valente,Serafina, Gensini,Gian Franco, Zawaideh,Camilla, Capitanio,Selene, Sambuceti,Gianmario, Marsico,Fabio, Perrone Filardi,Pasquale, Fernandez-Golfin,Covadonga, Rincon,Luis M., Graner,Frank P., de Graaf,Michiel A., Fiechter,Michael, Stehli,Julia, Gaemperli,Oliver, Reyes,Eliana, Nkomo,Sandy, Maki,Maija, Lorenzoni,Valentina, Turchetti,Giuseppe, Carpeggiani,Clara, Marinelli,Martina, Puzzuoli,Stefano, Mangione,Maurizio, Marcheschi,Paolo, Mariani,Fabio, Giannessi,Daniela, Nekolla,Stephan, Lombardi,Massimo, Sicari,Rosa, Scholte,Arthur J.H.A., Zamorano,Jose L., Kaufmann,Philipp A., Underwood,S Richard, Knuuti,Juhani, EVINCI,Study,I, Detection of significant coronary artery disease by noninvasive anatomical and functional imaging, Circulation.Cardiovascular imagingCirc Cardiovasc Imaging, 8, -, 2015	Design (population was people who had abnormal primary test)
Ng,Arnold C.T., Sitges,Marta, Pham,Phuong N., Tran,Da T., Delgado,Victoria, Bertini,Matteo, Nucifora,Gaetano, Vidaic,Jane, Allman,Christine, Holman,Eduard R., Bax,Jeroen J., Leung,Dominic Y., Incremental value of 2-dimensional speckle tracking strain imaging to wall motion analysis for detection of coronary artery disease in patients undergoing dobutamine stress echocardiography, American Heart JournalAm.Heart J., 158, 836-844, 2009	Design (retrospective) Time flow (too long between tests)
Nguyen,T., Heo,J., Ogilby,J.D., Iskandrian,A.S., Single photon emission computed tomography with Thallium-201 during adenosine-induced coronary hyperemia: Correlation with coronary arteriography, exercise thallium imaging and two-dimensional echocardiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 16, 1375-1383, 1990	Population (included patients with known CAD)
Nieman,Koen, Cademartiri,Filippo, Lemos,Pedro A., Raaijmakers,Rolf, Pattynama,Peter M.T., de Feyter,Pim J., Reliable noninvasive coronary angiography with fast submillimeter multislice spiral computed tomography, Circulation, 106, 2051-2054, 2002	16 slice scanner (minimum 64 slice)
Nieman,Koen, Rensing,Benno J., van Geuns,Robert Jan, Munne,Arie, Ligthart,Jurgen M.R., Pattynama,Peter M.T., Krestin,Gabriel P., Serruys,Patrick W., de Feyter,Pim J., Usefulness of multislice computed tomography for detecting obstructive coronary artery disease, The American journal of cardiologyAm J Cardiol, 89, 913-918, 2002	Insufficient CT scanner specification (4 slice)
Nikolaou,Konstantin, Rist,Carsten, Wintersperger,Bernd J., Jakobs,Tobias F., van Gessel,Roland, Kirchin,Miles A., Knez,Andreas, von Ziegler,Franz, Reiser,Maximilian F., Becker,Christoph R., Clinical value of MDCT in the diagnosis of coronary artery disease in patients with a low pretest	Population (included unknown patients with CAD and non cardiac CIP)

Author	Reason for exclusion
likelihood of significant disease, AJR.American journal of roentgenologyAJR Am J Roentgenol, 186, 1659-1668, 2006	
Nishida,Chikako, Okajima,Kaoru, Kudo,Takashi, Yamamoto,Takashi, Hattori,Ryuichi, Nishimura,Yasumasa, The relationship between coronary artery calcification detected by non-gated multi-detector CT in patients with suspected ischemic heart disease and myocardial ischemia detected by thallium exercise stress testing, Annals of Nuclear MedicineAnn.Nucl.Med., 19, 647-653, 2005	Population (included patients with suspected lung disease)
Norgaard,Bjarne L., Leipsic,Jonathon, Gaur,Sara, Seneviratne,Sujith, Ko,Brian S., Ito,Hiroshi, Jensen,Jesper M., Mauri,Laura, De Bruyne,Bernard, Bezerra,Hiram, Osawa,Kazuhiro, Marwan,Mohamed, Naber,Christoph, Erglis,Andrejs, Park,Seung Jung, Christiansen,Evald H., Kaltoft,Anne, Lassen,Jens F., Botker,Hans Erik, Achenbach,Stephan, NXT Trial Study Group, Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps), Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 63, 1145-1155, 2014	Reference standard (non protocol)
Norris,L.P., Stewart,R.E., Jain,A., Hibner,C.S., Chaudhuri,T.K., Zabalgoitia,M., Biplane transesophageal pacing echocardiography compared with dipyridamole thallium-201 single-photon emission computed tomography in detecting coronary artery disease, American Heart JournalAm.Heart J., 126, 676-685, 1993	Population (included patients with previous MI)
Ogilby,J.D., Iskandrian,A.S., Untereker,W.J., Heo,J., Nguyen,T.N., Mercuro,J., Effect of intravenous adenosine infusion on myocardial perfusion and function. Hemodynamic/angiographic and scintigraphic study, Circulation, 86, 887-895, 1992	Design (non consecutive)
O'Hara,M.J., Lahiri,A., Whittington,J.R., Detection of high-risk coronary artery disease by thallium imaging, British Heart JournalBR.HEART J., 53, 616-623, 1985	Population (included patients with known CAD)
Ollendorf,Daniel A., Kuba,Michelle, Pearson,Steven D., The diagnostic performance of multi-slice coronary computed tomographic angiography: a systematic review, Journal of General Internal MedicineJ.Gen.Intern.Med., 26, 307-316, 2011	Population (included patients with acute chest pain
Olszowska,Maria, Kostkiewicz,Magdalena, Tracz,Wieslawa, Przewlocki,Tadeusz, Assessment of myocardial perfusion in patients with coronary artery disease. Comparison of myocardial contrast echocardiography and 99mTc MIBI single photon emission computed tomography, International journal of cardiologyInt.J.Cardiol., 90, 49-55, 2003	Analysis (missing data)
Oncel,Dilek, Oncel,Guray, Turkoglu,Ipek, Accuracy of MR coronary angiography in the evaluation of coronary artery stenosis, Diagnostic and interventional radiology (Ankara, Turkey)Diagn Interv Radiol, 14, 153-158, 2008	Reference standard (non protocol)
Ong,Tiong Kiam, Chin,Sze Piaw, Liew,Chee Khoon, Chan,Wei Ling, Seyfarth,M.Tobias, Liew,Houng Bang, Rapaee,Annuar, Fong,Yean Yip Alan, Ang,Choon Kiat, Sim,Kui Hian, Accuracy of 64-row multidetector computed tomography in detecting coronary artery disease in 134 symptomatic patients: influence of calcification, American	Population (included patients with IHD already)

Author	Reason for exclusion
Heart JournalAm.Heart J., 151, 1323-1326, 2006	
O'Rourke,R.A., Brundage,B.H., Froelicher,V.F., Greenland,P., Grundy,S.M., Hachamovitch,R., Pohost,G.M., Shaw,L.J., Weintraub,W.S., Winters,W.L.J., American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 36, 326-340, 2000	Non protocol index test
Osawa,Kazuhiro, Miyoshi,Toru, Koyama,Yasushi, Hashimoto,Katsushi, Sato,Shuhei, Nakamura,Kazufumi, Nishii,Nobuhiro, Kohno,Kunihisa, Morita,Hiroshi, Kanazawa,Susumu, Ito,Hiroshi, Additional diagnostic value of first-pass myocardial perfusion imaging without stress when combined with 64-row detector coronary CT angiography in patients with coronary artery disease, Heart (British Cardiac Society), 100, 1008-1015, 2014	Index test overlaps with DG3 (New Generation Scanner)
Ostojic,M., Picano,E., Beleslin,B., Dordjevic-Dikic,A., Distante,A., Stepanovic,J., Reisenhofer,B., Babic,R., Stojkovic,S., Nedeljkovic,M., Dipyridamole-dobutamine echocardiography: a novel test for the detection of milder forms of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 23, 1115-1122, 1994	Population (included patients with previous MI)
Ozdemir,K., Kisacik,H.L., Oguzhan,A., Durmaz,T., Altunkeser,B.B., Altinyay,E., Kir,M., Korkmaz,S., Kutuk,E., Goksel,S., Comparison of exercise stress testing with dobutamine stress echocardiography and radionuclide ventriculography for diagnosis of coronary artery disease, Japanese Heart JournalJpn.Heart J., 40, 715-727, 1999	Population (included patients with previous MI)
Paech,Daniel C., Weston,Adele R., A systematic review of the clinical effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of suspected coronary artery disease, BMC cardiovascular disordersBMC Cardiovasc Disord, 11, 32-, 2011	Design (2 studies were retrospective, not all recruitment was consecutive) Index test overlaps with DG3 (New Generation Scanner)
Paijitprapaporn,Patcharee, Jongjirasiri,Sutipong, Tangpagasit,Laorporn, Laothamatas,Jiraporn, Reungratanaamporn,Ongkarn, Mahanonda,Nithi, Accuracy of sixteen-slice CT scanners in detected coronary artery disease, Journal of the Medical Association of Thailand = Chotmaihet thangphaetJ Med Assoc Thai, 89, 72-80, 2006	16 slice scanner (64 slice minimum)
Palmas,W., Friedman,J.D., Diamond,G.A., Silber,H., Kiat,H., Berman,D.S., Incremental value of simultaneous assessment of myocardial function and perfusion with technetium-99m sestamibi for prediction of extent of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 25, 1024-1031, 1995	Population (included patients with previous MI)
Palmieri,Vittorio, Pezzullo,Salvatore, Arezzi,Emma, D'Andrea,Claudia, Cassese,Salvatore, Martino,Stefania, Celentano,Aldo, Cycle-ergometry stress testing and use of chronotropic reserve adjustment of ST depression for identification of significant coronary artery disease in clinical practice, International journal of cardiologyInt.J.Cardiol., 127, 390-392, 2008	Reference standard (non protocol)
Palumbo,Anselmo Alessandro, Maffei,Erica, Martini,Chiara, Tarantini,Giuseppe, Di Tanna,Gian Luca, Berti,Elena,	Population (included patients with unstable angina

Author	Reason for exclusion
Grilli,Roberto, Casolo,Giancarlo, Brambilla,Valerio, Cerrato,Marcella, Rotondo,Antonio, Weustink,Annick C., Mollet,Nico R.A., Cademartiri,Filippo, Coronary calcium score as gatekeeper for 64-slice computed tomography coronary angiography in patients with chest pain: per-segment and per-patient analysis, European RadiologyEur.Radiol., 19, 2127-2135, 2009	
Pan,C.J., Qian,N., Wang,T., Tang,X.Q., Xue,Y.J., Adaptive prospective ECG-triggered sequence coronary angiography in dual-source CT without heart rate control: Image quality and diagnostic performance, Exp Ther Med, 5, 636-642, 2013	Population (included patients with known CAD)
Panmethis,Melissa, Wangsuphachart,Somjai, Rerkpattanapipat,Pairoj, Srimahachota,Suphot, Buddhari,Wacin, Kitsukjit,Weeranuch, Detection of coronary stenoses in chronic stable angina by multi-detector CT coronary angiography, Journal of the Medical Association of Thailand = Chotmaihet thangphaetJ Med Assoc Thai, 90, 1573-1580, 2007	Population (included patients with chronic angina) Reference standard unclear)
Park,J.W., Leithauser,B., Vrsansky,M., Jung,F., Dobutamine stress magnetocardiography for the detection of significant coronary artery stenoses - a prospective study in comparison with simultaneous 12-lead electrocardiography, Clinical Hemorheology and MicrocirculationClin.Hemorheol.Microcirc., 39, 21-32, 2008	Reference standard (non protocol)
Park,Jai Wun, Shin,Eun Seok, Ann,Soe Hee, Godde,Martin, Park,Lea Song, Brachmann,Johannes, Vidal-Lopez,Silvia, Wierzbinski,Jan, Lam,Yat Yin, Jung,Friedrich, Validation of magnetocardiography versus fractional flow reserve for detection of coronary artery disease, Clinical Hemorheology and MicrocirculationClin.Hemorheol.Microcirc., 59, 267-281, 2015	Reference standard (non protocol)
Parodi,O., Marcassa,C., Casucci,R., et al. (1991) Accuracy and safety of technetium-99m hexakis 2-methoxy-2-isobutyl isonitrile (Sestamibi) myocardial scintigraphy with high dose dipyridamole test in patients with effort angina pectoris: a multicenter study. Italian Group of Nuclear Cardiology. Journal of the American College of CardiologyJ.Am.Coll.Cardiol. 18 p.1439-1444	Non-protocol index test (planar imaging)
Patsilinakos,S.P., Kranidis,A.I., Antonelis,I.P., Filippatos,G., Houssianakou,I.K., Zamanis,N.I., Sioras,E., Tsiotika,T., Kardaras,F., Anthopoulos,L.P., Detection of coronary artery disease in patients with severe aortic stenosis with noninvasive methods, Angiology, 50, 309-317, 1999	non protocol population
Pauliks,Linda B., Vogel,Michael, Madler,Christoph F., Williams,R.Ian, Payne,Nicola, Redington,Andrew N., Fraser,Alan G., Regional response of myocardial acceleration during isovolumic contraction during dobutamine stress echocardiography: a color tissue Doppler study and comparison with angiocardiographic findings, Echocardiography (Mount Kisco, N.Y.), 22, 797-808, 2005	Analysis (missing data)
Pazhenkottil,Aju P., Herzog,Bernhard A., Husmann,Lars, Buechel,Ronny R., Burger,Irene A., Valenta,Ines, Landmesser,Ulf, Wyss,Christophe A., Kaufmann,Philipp A., Non-invasive assessment of coronary artery disease with CT coronary angiography and SPECT: a novel dose-saving fast-track algorithm, European Journal of Nuclear Medicine and Molecular ImagingEur.J.Nucl.Med.Mol.Imaging, 37, 522-527,	Not all patients received the reference standard

Author	Reason for exclusion
2010	
Peace,R.A., Staff,R.T., Gemmell,H.G., Mckiddie,F.I., Metcalfe,M.J., Automatic detection of coronary artery disease in myocardial perfusion SPECT using image registration and voxel to voxel statistical comparisons, Nuclear Medicine CommunicationsNUCL.MED.COMMUN., 23, 785-794, 2002	Population (included patients with known or suspected CAD)
Pelgrim,G.J., Dorrius,M., Xie,X., den Dekker,M.A., Schoepf,U.J., Henzler,T., Oudkerk,M., Vliegenthart,R., The dream of a one-stop-shop: Meta-analysis on myocardial perfusion CT, Eur J Radiol, -, 2015	Included non protocol reference test
Pelliccia,F., Pasceri,V., Evangelista,A., Pergolini,A., Barilla,F., Viceconte,N., Tanzilli,G., Schiariti,M., Greco,C., Gaudio,C., Diagnostic accuracy of 320-row computed tomography as compared with invasive coronary angiography in unselected, consecutive patients with suspected coronary artery disease, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 29, 443-452, 2013	Article retracted
Pennell,D.J., Underwood,S.R., Swanton,R.H., Walker,J.M., Ell,P.J., Dobutamine thallium myocardial perfusion tomography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 18, 1471-1479, 1991	Population (included patients with known or suspected CAD)
Pereira,Eulalia, Bettencourt,Nuno, Ferreira,Nuno, Schuster,Andreas, Chiribiri,Amedeo, Primo,Joao, Teixeira,Madalena, Simoes,Lino, Leite-Moreira,Adelino, Silva-Cardoso,Jose, Gama,Vasco, Nagel,Eike, Incremental value of adenosine stress cardiac magnetic resonance in coronary artery disease detection, International journal of cardiologyInt.J.Cardiol., 168, 4160-4167, 2013	Reference standard (different)
Petcherski,Oleg, Gaspar,Tamar, Halon,David A., Peled,Nathan, Jaffe,Ronen, Molnar,Ron, Lewis,Basil S., Rubinshtein,Ronen, Diagnostic accuracy of 256-row computed tomographic angiography for detection of obstructive coronary artery disease using invasive quantitative coronary angiography as reference standard, The American journal of cardiologyAm J Cardiol, 111, 510-515, 2013	Design (retrospective)
Peteiro,J., Monserrat,L., Perez,R., Vazquez,E., Vazquez,J.M., Castro-Beiras,A., Accuracy of peak treadmill exercise echocardiography to detect multivessel coronary artery disease: comparison with post-exercise echocardiography, European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of CardiologyEur J Echocardiogr, 4, 182-190, 2003	Design (retrospective)
Peteiro,Jesus, Bouzas-Mosquera,Alberto, Estevez,Rodrigo, Pazos,Pablo, Pineiro,Miriam, Castro-Beiras,Alfonso, Head-to-head comparison of peak supine bicycle exercise echocardiography and treadmill exercise echocardiography at peak and at post-exercise for the detection of coronary artery disease, Journal of the American Society of Echocardiography : official publication of the American Society of EchocardiographyJ Am Soc Echocardiogr, 25, 319-326, 2012	includes known CAD
Picano,E., Parodi,O., Lattanzi,F., Sambuceti,G., Andrade,M.J., Marzullo,P., Giorgetti,A., Salvadori,P., Marzilli,M., Distante,A., Assessment of anatomic and physiological severity of single-vessel coronary artery lesions	Population (included hospital inpatients with no details on reason for admission)

Author	Reason for exclusion
by dipyridamole echocardiography. Comparison with positron emission tomography and quantitative arteriography, Circulation, 89, 753-761, 1994	
Picano,E., Parodi,O., Lattanzi,F., Sambucetti,G., Masini,M., Marzullo,P., Distante,A., L'Abbate,A., Comparison of dipyridamole-echocardiography test and exercise thallium-201 scanning for diagnosis of coronary artery disease, American Journal of Noninvasive CardiologyAM.J.NONINVASIVE CARDIOL., 3, 85-92, 1989	Population (included patients with previous MI)
Picano,E., Pingitore,A., Conti,U., Kozakova,M., Boem,A., Cabani,E., Ciuti,M., Distante,A., L'Abbate,A., Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dipyridamole echocardiography, European Heart JournalEur.Heart J., 14, 1216-1222, 1993	Population (insufficient population characteristics)
Pijls,N.H., De Bruyne,B., Peels,K., Van Der Voort,P.H., Bonnier,H.J., Bartunek,J.Koolen, Koolen,J.J., Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses, The New England journal of medicineN Engl J Med, 334, 1703-1708, 1996	Reference standard (non protocol)
Pilz,Guenter, Eierle,Susanne, Heer,Tobias, Klos,Markus, Ali,Eman, Scheck,Roland, Wild,Michael, Bernhardt,Peter, Hoefling,Berthold, Negative predictive value of normal adenosine-stress cardiac MRI in the assessment of coronary artery disease and correlation with semiquantitative perfusion analysis, Journal of magnetic resonance imaging : JMRIJ Magn Reson Imaging, 32, 615-621, 2010	Population (included patients with known or suspected CAD)
Pirelli,S., Massa,D., Faletra,F., Piccalo,G., De,Vita C., Danzi,G.B., Campolo,L., Exercise electrocardiography versus dipyridamole echocardiography testing in coronary angioplasty. Early functional evaluation and prediction of angina recurrence, Circulation, 83, III-42, 1991	Population (recruited patients after angioplasty)
Pizzuto,Francesco, Voci,Paolo, Bartolomucci,Francesco, Puddu,Paolo Emilio, Strippoli,Giovanni, Broglia,Laura, Rossi,Plinio, Usefulness of coronary flow reserve measured by echocardiography to improve the identification of significant left anterior descending coronary artery stenosis assessed by multidetector computed tomography, The American journal of cardiologyAm J Cardiol, 104, 657-664, 2009	Non protocol index test
Plank,Fabian, Friedrich,Guy, Dichtl,Wolfgang, Klauser,Andrea, Jaschke,Werner, Franz,Wolfgang Michael, Feuchtner,Gudrun, The diagnostic and prognostic value of coronary CT angiography in asymptomatic high-risk patients: a cohort study, Open heart, 1, e000096-, 2014	Population (included asymptomatic patients)
Plass,Andre, Azemaj,Naim, Scheffel,Hans, Desbiolles,Lotus, Alkadhi,Hatem, Genoni,Michele, Falk,Volkmar, Grunenfelder,Jurg, Accuracy of dual-source computed tomography coronary angiography: evaluation with a standardised protocol for cardiac surgeons, European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 36, 1011-1017, 2009	Includes known CAD
Plass,Andre, Grunenfelder,Jurg, Leschka,Sebastian, Alkadhi,Hatem, Eberli,Franz R., Wildermuth,Simon, Zund,Gregor, Genoni,Michele, Coronary artery imaging with 64-slice computed tomography from cardiac surgical perspective, European journal of cardio-thoracic surgery :	Design (case/control)

Author	Reason for exclusion
official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 30, 109-116, 2006	
Plein,Sven, Kozerke,Sebastian, Suerder,Daniel, Luescher,Thomas F., Greenwood,John P., Boesiger,Peter, Schwitter,Juerg, High spatial resolution myocardial perfusion cardiac magnetic resonance for the detection of coronary artery disease, European Heart JournalEur.Heart J., 29, 2148-2155, 2008	Population (included patients with known or suspected CAD)
Ponte,Marta, Bettencourt,Nuno, Pereira,Eulalia, Ferreira,Nuno Dias, Chiribiri,Amedeo, Schuster,Andreas, Albuquerque,Anibal, Gama,Vasco, Nagel,Eike, Anatomical versus functional assessment of coronary artery disease: direct comparison of computed tomography coronary angiography and magnetic resonance myocardial perfusion imaging in patients with intermediate pre-test probability, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 30, 1589-1597, 2014	Reference standard (non protocol)
Pontone,G., Andreini,D., Quaglia,C., Ballerini,G., Nobili,E., Pepi,M., Accuracy of multidetector spiral computed tomography in detecting significant coronary stenosis in patient populations with differing pre-test probabilities of disease, Clinical RadiologyClin.Radiol., 62, 978-985, 2007	Population (included patients with known CAD)
Pontone,Gianluca, Andreini,Daniele, Ballerini,Giovanni, Nobili,Enrica, Pepi,Mauro, Diagnostic work-up of unselected patients with suspected coronary artery disease: complementary role of multidetector computed tomography, symptoms and electrocardiogram stress test, Coronary Artery DiseaseCoron.Artery Dis., 18, 265-274, 2007	Population (included patients with known CAD)
Pontone,Gianluca, Andreini,Daniele, Bartorelli,Antonio L., Bertella,Erika, Mushtaq,Saima, Annoni,Andrea, Formenti,Alberto, Chiappa,Luisa, Cortinovis,Sarah, Baggiano,Andrea, Conte,Edoardo, Bovis,Francesca, Veglia,Fabrizio, Foti,Claudia, Ballerini,Giovanni, Fiorentini,Cesare, Pepi,Mauro, Radiation dose and diagnostic accuracy of multidetector computed tomography for the detection of significant coronary artery stenoses: a meta-analysis, International journal of cardiologyInt.J.Cardiol., 160, 155-164, 2012	Design (retrospective) Population (described as patients with history of coronary revascularisation)
Post,J.C., Van Rossum,A.C., Hofman,M.B., Valk,J., Visser,C.A., Three-dimensional respiratory-gated MR angiography of coronary arteries: comparison with conventional coronary angiography, AJR.American journal of roentgenologyAJR Am J Roentgenol, 166, 1399-1404, 1996	Reference standard (non protocol)
Postel,Thomas, Frick,Matthias, Feuchtner,Gudrun, Alber,Hannes, Zwick,Ralf, Suessenbacher,Alois, Mallouhi,Ammar, Friedrich,Guy, Pachinger,Otmar, Nedden,Dieter Zur, Weidinger,Franz, Role of 16-multidetector computed tomography in the assessment of coronary artery stenoses: A prospective study of consecutive patients, Experimental and Clinical CardiologyExp.Clin.Cardiol., 12, 149-152, 2007	16 slice scanner (minimum 64 slices)
Pozzoli,M.M., Fioretti,P.M., Salustri,A., Reijs,A.E., Roelandt,J.R., Exercise echocardiography and technetium-99m MIBI single-photon emission computed tomography in the detection of coronary artery disease, American Journal of CardiologyAm.J.Cardiol., 67, 350-355, 1991	Population (included patients with previous MI)
Prakash,A., Ahlawat,K., Kaul,U.A., Tyagi,S., Aggarwal,B.,	No patient level analysis provided

Author	Reason for exclusion
Rajan,S., Kathuria,S., Accuracy of 64-slice CT coronary angiography: Our initial experience, Indian Heart JournalIndian Heart J., 60, 287-295, 2008	
Pundziute,Gabija, Schuijf,Joanne D., Jukema,J.Wouter, Lamb,Hildo J., de Roos,Albert, van der Wall,Ernst E., Bax,Jeroen J., Impact of coronary calcium score on diagnostic accuracy of multislice computed tomography coronary angiography for detection of coronary artery disease, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 14, 36-43, 2007	Population (included patients with known CAD)
Qian,Zhen, Anderson,Hunt, Marvasty,Idean, Akram,Kamran, Vazquez,Gustavo, Rinehart,Sarah, Voros,Szilard, Lesion- and vessel-specific coronary artery calcium scores are superior to whole-heart Agatston and volume scores in the diagnosis of obstructive coronary artery disease, Journal of Cardiovascular Computed TomographyJ.Cardiovasc.Comput.Tomogr., 4, 391-399, 2010	Design (retrospective)
Quinones,M.A., Verani,M.S., Haichin,R.M., Mahmarian,J.J., Suarez,J., Zoghbi,W.A., Exercise echocardiography versus 201Tl single-photon emission computed tomography in evaluation of coronary artery disease. Analysis of 292 patients, Circulation, 85, 1026-1031, 1992	Population (included patients with known or suspected CAD)
Rambaldi,R., Poldermans,D., Fioretti,P.M., Ten Cate,F.J., Vletter,W.B., Bax,J.J., Roelandt,J.R., Usefulness of pulse-wave Doppler tissue sampling and dobutamine stress echocardiography for the diagnosis of right coronary artery narrowing, The American journal of cardiologyAm J Cardiol, 81, 1411-1415, 1998	Population (included patients with previous MI)
Ramos,Vitor, Bettencourt,Nuno, Silva,Jennifer, Ferreira,Nuno, Chiribiri,Amedeo, Schuster,Andreas, Leite-Moreira,Adelino, Silva-Cardoso,Jose, Nagel,Eike, Gama,Vasco, Noninvasive anatomical and functional assessment of coronary artery disease, Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of CardiologyRev Port Cardiol, 34, 223-232, 2015	Reference standard (non protocol)
Ravipati,Gautham, Aronow,Wilbert S., Lai,Hoang, Shao,John, DeLuca,Albert J., Weiss,Melvin B., Pucillo,Anthony L., Kalapatapu,Kumar, Monsen,Craig E., Belkin,Robert N., Comparison of sensitivity, specificity, positive predictive value, and negative predictive value of stress testing versus 64-multislice coronary computed tomography angiography in predicting obstructive coronary artery disease diagnosed by coronary angiography, The American journal of cardiologyAm J Cardiol, 101, 774-775, 2008	Population (included patients with known CAD)
Redberg,R.F., Sobol,Y., Chou,T.M., Malloy,M., Kumar,S., Botvinick,E., Kane,J., Adenosine-induced coronary vasodilation during transesophageal Doppler echocardiography. Rapid and safe measurement of coronary flow reserve ratio can predict significant left anterior descending coronary stenosis, Circulation, 92, 190-196, 1995	Population (unclear) Part of separate treatment study
Regenfus,M., Ropers,D., Achenbach,S., Kessler,W., Laub,G., Daniel,W.G., Moshage,W., Noninvasive detection of coronary artery stenosis using contrast-enhanced three-	Non protocol index test

Author	Reason for exclusion
dimensional breath-hold magnetic resonance coronary angiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 36, 44-50, 2000	
Regenfus,Matthias, Ropers,Dieter, Achenbach,Stephan, Schlundt,Christian, Kessler,Winfried, Laub,Gerhard, Moshage,Werner, Daniel,Werner G., Comparison of contrast-enhanced breath-hold and free-breathing respiratory-gated imaging in three-dimensional magnetic resonance coronary angiography, The American journal of cardiologyAm J Cardiol, 90, 725-730, 2002	Non protocol index test
Renker,Matthias, Schoepf,U.Joseph, Wang,Rui, Meinel,Felix G., Rier,Jeremy D., Bayer,Richard R., Mollmann,Helge, Hamm,Christian W., Steinberg,Daniel H., Baumann,Stefan, Comparison of diagnostic value of a novel noninvasive coronary computed tomography angiography method versus standard coronary angiography for assessing fractional flow reserve, The American journal of cardiologyAm J Cardiol, 114, 1303-1308, 2014	Non protocol reference standard
Rensing,B.J., Bongaerts,A., van Geuns,R.J., van Ooijen,P., Oudkerk,M., De Feyter,P.J., Intravenous coronary angiography by electron beam computed tomography: a clinical evaluation, Circulation, 98, 2509-2512, 1998	Reference standard (non protocol)
Rief,M., Stenzel,F., Kranz,A., Schlattmann,P., Dewey,M., Time efficiency and diagnostic accuracy of new automated myocardial perfusion analysis software in 320-row CT cardiac imaging, Korean Journal of RadiologyKor.J.Radiol., 14, 21-29, 2013	Population (included patients with known CAD) Index test overlaps with DG3 (New Generation Scanner)
Rief,Matthias, Kranz,Anisha, Hartmann,Lisa, Roehle,Robert, Laule,Michael, Dewey,Marc, Computer-aided CT coronary artery stenosis detection: comparison with human reading and quantitative coronary angiography, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 30, 1621-1627, 2014	Population (included patients with known and suspected CAD)
Rigo,Fausto, Richieri,Margherita, Pasanisi,Emilio, Cutaia,Valeria, Zanella,Carlo, Della Valentina,Patrizia, Di Pede,Francesco, Raviele,Antonio, Picano,Eugenio, Usefulness of coronary flow reserve over regional wall motion when added to dual-imaging dipyridamole echocardiography, The American journal of cardiologyAm J Cardiol, 91, 269-273, 2003	Analysis (raw data did not add up)
Rijlaarsdam-Hermsen,D., Kuijpers,D., van Dijkman,P.R.M., Diagnostic and prognostic value of absence of coronary artery calcification in patients with stable chest symptoms, Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart FoundationNeth Heart J, 19, 223-228, 2011	Not relevant - prognostic study
Ripsweden,Jonaz, Brismar,Torkel B., Holm,Jon, Melinder,Annika, Mir-Akbari,Habib, Nilsson,Tage, Nyman,Ulf, Rasmussen,Elsbeth, Ruck,Andreas, Cederlund,Kerstin, Impact on image quality and radiation exposure in coronary CT angiography: 100 kVp versus 120 kVp, Acta radiologica (Stockholm, Sweden : 1987), 51, 903-909, 2010	Population (included patients with known or suspected CAD)
Rispler,Shmuel, Keidar,Zohar, Ghersin,Eduard, Roguin,Ariel, Soil,Adrian, Dragu,Robert, Litmanovich,Diana, Frenkel,Alex, Aronson,Doron, Engel,Ahuva, Beyar,Rafael, Israel,Ora, Integrated single-photon emission computed tomography and computed tomography coronary angiography for the	Population (included patients with previous MI)

Author	Reason for exclusion
assessment of hemodynamically significant coronary artery lesions, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 49, 1059-1067, 2007	
Ritchie,J.L., Trobaugh,G.B., Hamilton,G.W., Gould,K.L., Narahara,K.A., Murray,J.A., Williams,D.L., Myocardial imaging with thallium-201 at rest and during exercise. Comparison with coronary arteriography and resting and stress electrocardiography, Circulation, 56, 66-71, 1977	Population (included patients with known CAD)
Rocha-Filho,Jose A., Blankstein,Ron, Shturman,Leonid D., Bezerra,Hiram G., Okada,David R., Rogers,Ian S., Ghoshhajra,Brian, Hoffmann,Udo, Feuchtner,Gudrun, Mamuya,Wilfred S., Brady,Thomas J., Cury,Ricardo C., Incremental value of adenosine-induced stress myocardial perfusion imaging with dual-source CT at cardiac CT angiography, Radiology, 254, 410-419, 2010	Population (included patients with prior MI)
Rochitte,Carlos E., George,Richard T., Chen,Marcus Y., Arbab-Zadeh,Armin, Dewey,Marc, Miller,Julie M., Niinuma,Hiroyuki, Yoshioka,Kunihiro, Kitagawa,Kakuya, Nakamori,Shiro, Laham,Roger, Vavere,Andrea L., Cerci,Rodrigo J., Mehra,Vishal C., Nomura,Cesar, Kofoed,Klaus F., Jinzaki,Masahiro, Kuribayashi,Sachio, de Roos,Albert, Laule,Michael, Tan,Swee Yaw, Hoe,John, Paul,Narinder, Rybicki,Frank J., Brinker,Jeffery A., Arai,Andrew E., Cox,Christopher, Clouse,Melvin E., Di Carli,Marcelo F., Lima,Joao A.C., Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: the CORE320 study, European Heart JournalEur.Heart J., 35, 1120-1130, 2014	Population (included patients with known CAD)
Rodevand,Olaf, Hogalmen,Geir, Gudim,Lars Petter, Indrebo,Tor, Molstad,Per, Vandvik,Per Olav, Limited usefulness of non-invasive coronary angiography with 16-detector multislice computer tomography at a community hospital, Scandinavian cardiovascular journal : SCJScand Cardiovasc J, 40, 76-82, 2006	16 slice scanner (64 slice minimum)
Rossi,Alexia, Dharampal,Anoeshka, Wragg,Andrew, Davies,L.Ceri, van Geuns,Robert Jan, Anagnostopoulos,Costantinos, Klotz,Ernst, Kitslaar,Pieter, Broersen,Alexander, Mathur,Anthony, Nieman,Koen, Hunink,M.G.M., de Feyter,Pim J., Petersen,Steffen E., Pugliese,Francesca, Diagnostic performance of hyperaemic myocardial blood flow index obtained by dynamic computed tomography: does it predict functionally significant coronary lesions?, European Heart Journal Cardiovascular ImagingEur.Heart J.Cardiovasc.Imaging, 15, 85-94, 2014	Index test overlaps with DG3 (New Generation Scanner)
Rubinshtein,Ronen, Halon,David A., Gaspar,Tamar, Schliamser,Jorge E., Yaniv,Nisan, Ammar,Ronny, Flugelman,Moshe Y., Peled,Nathan, Lewis,Basil S., Usefulness of 64-slice multidetector computed tomography in diagnostic triage of patients with chest pain and negative or nondiagnostic exercise treadmill test result, The American journal of cardiologyAm J Cardiol, 99, 925-929, 2007	Design (retrospective)
Rumberger,J.A., Sheedy,P.F., Breen,J.F., Schwartz,R.S., Electron beam computed tomographic coronary calcium score cutpoints and severity of associated angiographic lumen stenosis, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 29, 1542-1548, 1997	EBCT non protocol index test

Author	Reason for exclusion
Ryan,T., Armstrong,W.F., Feigenbaum,H., Prospective evaluation of the left main coronary artery using digital two-dimensional echocardiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 7, 807-812, 1986	Non protocol index test
Sait Dogan,Mehmet, Yilmaz,Erkan, Dogan,Sumeyra, Akdeniz,Bahri, Baris,Nezihi, Eomete,Uygar, Iyilikci,Leyla, Evaluation of myocardial ischemia in coronary artery disease with cardiac MR perfusion method: comparison with the results of catheter or CT angiography, Medicinski glasnik : official publication of the Medical Association of Zenica-Doboj Canton, Bosnia and HerzegovinaMed.glas.Ljek.komore Zenicko-doboj.kantona, 10, 63-69, 2013	Non protocol reference test
Sajjadieh,Amirreza, Hekmatnia,Ali, Keivani,Maryam, Asoodeh,Abdollah, Pourmoghaddas,Masoud, Sanei,Hamid, Diagnostic performance of 64-row coronary CT angiography in detecting significant stenosis as compared with conventional invasive coronary angiography, ARYA AtherosclerosisArya Atheroscler., 9, 157-163, 2013	Design (non consecutive)
Sakuma,Hajime, Ichikawa,Yasutaka, Chino,Shuji, Hirano,Tadanori, Makino,Katsutoshi, Takeda,Kan, Detection of coronary artery stenosis with whole-heart coronary magnetic resonance angiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 48, 1946-1950, 2006	Reference standard (non protocol)
Sakuma,Hajime, Ichikawa,Yasutaka, Suzawa,Naohisa, Hirano,Tadanori, Makino,Katsutoshi, Koyama,Nozomu, Van Cauteren,Marc, Takeda,Kan, Assessment of coronary arteries with total study time of less than 30 minutes by using whole-heart coronary MR angiography, Radiology, 237, 316-321, 2005	Reference standard (non protocol)
Sakuma,Hajime, Suzawa,Naohisa, Ichikawa,Yasutaka, Makino,Katsutoshi, Hirano,Tadanori, Kitagawa,Kakuya, Takeda,Kan, Diagnostic accuracy of stress first-pass contrast-enhanced myocardial perfusion MRI compared with stress myocardial perfusion scintigraphy, AJR.American journal of roentgenologyAJR Am J Roentgenol, 185, 95-102, 2005	Design (retrospective)
Salerno,Michael, Taylor,Angela, Yang,Yang, Kuruvilla,Sujith, Ragosta,Michael, Meyer,Craig H., Kramer,Christopher M., Adenosine stress cardiovascular magnetic resonance with variable-density spiral pulse sequences accurately detects coronary artery disease: initial clinical evaluation, Circulation.Cardiovascular imagingCirc Cardiovasc Imaging, 7, 639-646, 2014	Population (included patients with known CAD)
Salustri,A., Fioretti,P.M., McNeill,A.J., Pozzoli,M.M., Roelandt,J.R., Pharmacological stress echocardiography in the diagnosis of coronary artery disease and myocardial ischaemia: a comparison between dobutamine and dipyridamole, European Heart JournalEur.Heart J., 13, 1356-1362, 1992	Population (included patients with known or suspected CAD and patients with pervious MI)
Salustri,A., Fioretti,P.M., Pozzoli,M.M., McNeill,A.J., Roelandt,J.R., Dobutamine stress echocardiography: its role in the diagnosis of coronary artery disease, European Heart JournalEur.Heart J., 13, 70-77, 1992	Population (included patients with previous MI)
Saner,H.E., Olson,J., Daniel,J.A., Jorgensen,C.R., Homans,D.C., Lange,H.W., Cook,A.A., Gobel,F.L., Exercise two-dimensional echocardiography in patients with ischemic	Population (can't tease out those with previous MI)

Author	Reason for exclusion
heart disease, Journal of Cardiovascular UltrasonographyJ.CARDIOVASC.ULTRASONOGRAPHY, 6, 193-201, 1987	
Santana,Cesar A., Garcia,Ernest V., Faber,Tracy L., Sirineni,Gopi K.R., Esteves,Fabio P., Sanyal,Rupan, Halkar,Raghuveer, Ornelas,Mario, Verdes,Liudmila, Lerakis,Stamatios, Ramos,Julie J., Aguade-Bruix,Santiago, Cuellar,Hugo, Candell-Riera,Jaume, Raggi,Paolo, Diagnostic performance of fusion of myocardial perfusion imaging (MPI) and computed tomography coronary angiography, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 16, 201-211, 2009	Population (included patients with prior MI and PCI)
Santana-Boado,C., Candell-Riera,J., Castell-Conesa,J., Aguade-Bruix,S., Garcia-Burillo,A., Canela,T., Gonzalez,J.M., Cortadellas,J., Ortega,D., Soler-Soler,J., Diagnostic accuracy of technetium-99m-MIBI myocardial SPECT in women and men, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 39, 751-755, 1998	Population (included patients with proven CAD)
Sarwar,Ammar, Shaw,Leslee J., Shapiro,Michael D., Blankstein,Ron, Hoffmann,Udo, Hoffman,Udo, Cury,Ricardo C., Abbara,Suhny, Brady,Thomas J., Budoff,Matthew J., Blumenthal,Roger S., Nasir,Khurram, Diagnostic and prognostic value of absence of coronary artery calcification, JACC.Cardiovascular imagingJACC Cardiovasc Imaging, 2, 675-688, 2009	Mixed populations in included studies (including self referral)
Sato,Akira, Nozato,Toshihiro, Hikita,Hiroyuki, Miyazaki,Shinsuke, Takahashi,Yoshihide, Kuwahara,Taishi, Takahashi,Atsushi, Hiroe,Michiaki, Aonuma,Kazutaka, Incremental value of combining 64-slice computed tomography angiography with stress nuclear myocardial perfusion imaging to improve noninvasive detection of coronary artery disease, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 17, 19-26, 2010	Includes only people with negative pre-study stress tests.
Sato,Yuichi, Matsumoto,Naoya, Kato,Masahiko, Inoue,Fumio, Horie,Toshiyuki, Kusama,Junji, Yoshimura,Akihiro, Imazeki,Takako, Fukui,Takahiro, Furuhashi,Satoru, Takahashi,Motoichiro, Kanmatsuse,Katsuo, Noninvasive assessment of coronary artery disease by multislice spiral computed tomography using a new retrospectively ECG-gated image reconstruction technique, Circulation journal : official journal of the Japanese Circulation SocietyCirc J, 67, 401-405, 2003	Mixed population: included acute phase
Sawada,S.G., Segar,D.S., Ryan,T., Brown,S.E., Dohan,A.M., Williams,R., Fineberg,N.S., Armstrong,W.F., Feigenbaum,H., Echocardiographic detection of coronary artery disease during dobutamine infusion, Circulation, 83, 1605-1614, 1991	Design (retrospective)
Schaap,Jeroen, de Groot,Joris A.H., Nieman,Koen, Meijboom,W.Bob, Boekholdt,S Matthijs, Kauling,Robert M., Post,Martijn C., Van der Heyden,Jan A., de Kroon,Thom L., Rensing,Benno J.W.M., Moons,Karel G.M., Verzijlbergen,J.Fred, Added value of hybrid myocardial perfusion SPECT and CT coronary angiography in the diagnosis of coronary artery disease, European Heart Journal Cardiovascular ImagingEur.Heart J.Cardiovasc.Imaging, 15, 1281-1288, 2014	Non protocol reference test

Author	Reason for exclusion
Schaap,Jeroen, Kauling,Robert M., Boekholdt,S Matthijs, Nieman,Koen, Meijboom,W.Bob, Post,Martijn C., Van der Heyden,Jan A., de Kroon,Thom L., van Es,H.Wouter, Rensing,Benno J., Verzijlbergen,J.Fred, Incremental diagnostic accuracy of hybrid SPECT/CT coronary angiography in a population with an intermediate to high pre-test likelihood of coronary artery disease, European Heart Journal Cardiovascular ImagingEur.Heart J.Cardiovasc.Imaging, 14, 642-649, 2013	Non protocol reference standard
Schaap,Jeroen, Kauling,Robert M., Boekholdt,S Matthijs, Post,Martijn C., Van der Heyden,Jan A., de Kroon,Thom L., van Es,H.Wouter, Rensing,Benno J.W.M., Verzijlbergen,J.Fred, Usefulness of coronary calcium scoring to myocardial perfusion SPECT in the diagnosis of coronary artery disease in a predominantly high risk population, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 29, 677-684, 2013	Reference standard (non protocol)
Scherhag,A., Pfleger,S., Haase,K.K., Sueselbeck,T., Borggrefe,M., Diagnostic value of stress echocardiography for the detection of restenosis after PTCA, International journal of cardiologyInt.J.Cardiol., 98, 191-197, 2005	Not relevant
Schlattmann,Peter, Schuetz,Georg M., Dewey,Marc, Influence of coronary artery disease prevalence on predictive values of coronary CT angiography: a meta-regression analysis, European RadiologyEur.Radiol., 21, 1904-1913, 2011	Population (inadequate detail on study population)
Schlosser,T., Mohrs,O.K., Magedanz,A., Nowak,B., Voigtlander,T., Barkhausen,J., Schmermund,A., Noninvasive coronary angiography using 64-detector-row computed tomography in patients with a low to moderate pretest probability of significant coronary artery disease, Acta radiologica (Stockholm, Sweden : 1987), 48, 300-307, 2007	Population (included patients with known hypertensive heart disease)
Schmermund,A., Bailey,K.R., Rumberger,J.A., Reed,J.E., Sheedy,P.F., Schwartz,R.S., An algorithm for noninvasive identification of angiographic three-vessel and/or left main coronary artery disease in symptomatic patients on the basis of cardiac risk and electron-beam computed tomographic calcium scores, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 33, 444-452, 1999	EBCT not protocol index test
Schmermund,A., Baumgart,D., Sack,S., Mohlenkamp,S., Gronemeyer,D., Seibel,R., Erbel,R., Assessment of coronary calcification by electron-beam computed tomography in symptomatic patients with normal, abnormal or equivocal exercise stress test, European Heart JournalEur.Heart J., 21, 1674-1682, 2000	EBCT not protocol index test
Schnapauff,D., Teige,F., Hamm,B., Dewey,M., Comparison between the image quality of multisegment and halfscan reconstructions of non-invasive CT coronary angiography, The British journal of radiologyBr J Radiol, 82, 969-975, 2009	16 slice CT (minimum 64 slice)
Schnapauff,Dirk, Dubel,Hans Peter, Scholze,Jurgen, Baumann,Gert, Hamm,Bernd, Dewey,Marc, Multislice computed tomography: angiographic emulation versus standard assessment for detection of coronary stenoses, European RadiologyEur.Radiol., 17, 1858-1864, 2007	16 slice scanner (minimum 64 slice)
Schuetz,G.M., Schlattmann,P., Dewey,M., Use of 3x2 tables with an intention to diagnose approach to assess clinical performance of diagnostic tests: meta-analytical evaluation of	Study design: not a diagnostic study.

Author	Reason for exclusion
coronary CT angiography studies, BMJBMJ (Online), 345, -, 2012	
Schuijf,Joanne D., Bax,Jeroen J., Shaw,Leslee J., de Roos,Albert, Lamb,Hildo J., van der Wall,Ernst E., Wijns,William, Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and multislice computed tomography for noninvasive coronary angiography, American Heart JournalAm.Heart J., 151, 404-411, 2006	Population (included patients with known or suspected CAD)
Schuijf,Joanne D., Pundziute,Gabija, Jukema,J.Wouter, Lamb,Hildo J., van der Hoeven,Bas L., de Roos,Albert, van der Wall,Ernst E., Bax,Jeroen J., Diagnostic accuracy of 64-slice multislice computed tomography in the noninvasive evaluation of significant coronary artery disease, The American journal of cardiologyAm J Cardiol, 98, 145-148, 2006	Population (included patients with previous MI)
Schwartz,Leonard, Overgaard,Christopher B., The accuracy of noninvasive stress myocardial imaging for detecting coronary artery disease in clinical practice, Hospital practice (1995), 38, 14-18, 2010	Not available via British Library or Royal Society of Medicine
Schwitter,J., Wacker,C.M., Rossum,A.C., Lombardi,M., Al-Saadi,N., Ahlstrom,H., Dill,T., Larsson,H.B., Flamm,S.D., Marquardt,M., Johansson,L., MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial, European Heart JournalEur.Heart J., 29, 480-489, 2008	Population (unclear inclusion criteria, included patients with history of MI
Schwitter,J., Wacker,C.M., Wilke,N., Al-Saadi,N., Sauer,E., Huettle,K., Schönberg,S.O., Debl,K., Strohm,O., Ahlstrom,H., Dill,T., Hoebel,N., Simor,T., Superior diagnostic performance of perfusion-cardiovascular magnetic resonance versus SPECT to detect coronary artery disease: The secondary endpoints of the multicenter multivendor MR-IMPACT II (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease Trial), Journal of Cardiovascular Magnetic ResonanceJ.Cardiovasc.Magn.Reson., 14, 61-, 2012	Reference standard (non protocol)
Schwitter,Juerg, Wacker,Christian M., Wilke,Norbert, Al-Saadi,Nidal, Sauer,Ekkehart, Huettle,Kalman, Schonberg,Stefan O., Luchner,Andreas, Strohm,Oliver, Ahlstrom,Hakan, Dill,Thorsten, Hoebel,Nadja, Simor,Tamas, MR-IMPACT,Investigators, MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial, European Heart JournalEur.Heart J., 34, 775-781, 2013	Includes mixed population
Sciagra,R., Zoccarato,O., Bisi,G., Pupi,A., Decreased [99mTc]Sestamibi uptake with dobutamine versus dipyridamole stress, The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the Society of RadiopharmaceuticaQ J Nucl Med Mol Imaging, 53, 671-677, 2009	Analysis: cannot calculate 2x2 table for per patient analysis (no specificity reported).
Seese,B., Moshage,W., Achenbach,S., Bachmann,K., Kirchgeorg,M., Possibilities of electron beam tomography in noninvasive diagnosis of coronary artery disease: A	Reference standard (non protocol)

Author	Reason for exclusion
comparison between quantity of coronary calcification and angiographic findings, International Journal of AngiologyInt.J.Angiol., 6, 124-129, 1997	
Segar,D.S., Brown,S.E., Sawada,S.G., Ryan,T., Feigenbaum,H., Dobutamine stress echocardiography: correlation with coronary lesion severity as determined by quantitative angiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 19, 1197-1202, 1992	Non protocol population
Sehovic,S., Diagnostic capabilities of 64 slice CT coronography compared to classic in coronary disease detection, Acta Informatica MedicaActa Inform.Med., 21, 208-210, 2013	Analysis : insufficient data to back calculate 2x2 table
Senior,Roxy, Monaghan,Mark, Main,Michael L., Zamorano,Jose L., Tiemann,Klaus, Agati,Luciano, Weissman,Neil J., Klein,Allan L., Marwick,Thomas H., Ahmad,Masood, DeMaria,Anthony N., Zabalgoitia,Miguel, Becher,Harald, Kaul,Sanjiv, Udelson,James E., Wackers,Frans J., Walovitch,Richard C., Picard,Michael H., and,R.A.M.P., Detection of coronary artery disease with perfusion stress echocardiography using a novel ultrasound imaging agent: two Phase 3 international trials in comparison with radionuclide perfusion imaging, European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of CardiologyEur J Echocardiogr, 10, 26-35, 2009	Mixed population (known CAD). Non protocol study design.
Senior,Roxy, Moreo,Antonella, Gaibazzi,Nicola, Agati,Luciano, Tiemann,Klaus, Shivalkar,Bharati, von Bardeleben,Stephan, Galiuto,Leonarda, Lardoux,Herve, Trocino,Giuseppe, Carrio,Ignasi, Le Guludec,Dominique, Sambuceti,Gianmario, Becher,Harald, Colonna,Paolo, Ten Cate,Folkert, Bramucci,Ezio, Cohen,Ariel, Bezante,Gianpaolo, Aggeli,Costantina, Kasprzak,Jaroslaw D., Comparison of sulfur hexafluoride microbubble (SonoVue)-enhanced myocardial contrast echocardiography with gated single-photon emission computed tomography for detection of significant coronary artery disease: a large European multicenter study, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 62, 1353-1361, 2013	Mixed population (includes known disease)
Shahzad,Rahil, Kirisli,Hortense, Metz,Coert, Tang,Hui, Schaap,Michiel, van Vliet,Lucas, Niessen,Wiro, van Walsum,Theo, Automatic segmentation, detection and quantification of coronary artery stenoses on CTA, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 29, 1847-1859, 2013	Design (retrospective)
Shapiro,Michael D., Butler,Javed, Rieber,Johannes, Sheth,Tej N., Cury,Ricardo C., Ferencik,Maros, Nichols,John H., Goehler,Alexander, Abbara,Suhny, Pena,Antonio J., Brady,Thomas J., Hoffmann,Udo, Analytic approaches to establish the diagnostic accuracy of coronary computed tomography angiography as a tool for clinical decision making, The American journal of cardiologyAm J Cardiol, 99, 1122-1127, 2007	Population (included patients with a history of CAD)
Sharir,T., Bacher-Stier,C., Dhar,S., Lewin,H.C., Miranda,R., Friedman,J.D., Germano,G., Berman,D.S., Identification of severe and extensive coronary artery disease by postexercise regional wall motion abnormalities in Tc-99m sestamibi gated single-photon emission computed tomography, The American journal of cardiologyAm J	Population (unclear)

Author	Reason for exclusion
Cardiol, 86, 1171-1175, 2000	
Sharma,Punit, Patel,Chetan D., Karunanithi,Sellam, Maharjan,Sagar, Malhotra,Arun, Comparative accuracy of CT attenuation-corrected and non-attenuation-corrected SPECT myocardial perfusion imaging, Clinical Nuclear MedicineClin.Nucl.Med., 37, 332-338, 2012	Design (retrospective) Population (included patients with known/suspected CAD)
Shavelle,D.M., Budoff,M.J., LaMont,D.H., Shavelle,R.M., Kennedy,J.M., Brundage,B.H., Exercise testing and electron beam computed tomography in the evaluation of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 36, 32-38, 2000	Non protocol index test
Shelley,S., Indirani,M., Sathyamurthy,I., Subramanian,K., Priti,N., Harshad,K., Padma,D., Correlation of myocardial perfusion SPECT with invasive and computed tomography coronary angiogram, Indian Heart JournalIndian Heart J., 64, 43-49, 2012	Not all participants received the reference standard. Per artery analysis only.
Shelley,S., Sathyamurthy,I., Madhavan, Subramanyan,K., Najeeb,O.M., Ramachandran,P., Adenosine myocardial SPECT--its efficacy and safety and correlation with coronary angiogram, The Journal of the Association of Physicians of India, 51, 557-560, 2003	Population (included patients with previous MI. Not all patients had c.angio)
Sheth,Tej, Amlani,Shoaib, Ellins,Mary Lou, Mehta,Shamir, Velianou,James, Cappelli,Gail, Yang,Sean, Natarajan,Madhu, Computed tomographic coronary angiographic assessment of high-risk coronary anatomy in patients with suspected coronary artery disease and intermediate pretest probability, American Heart JournalAm.Heart J., 155, 918-923, 2008	Population (included patients with previous MI but no proportion reported)
Shi,Heshui, Aschoff,Andrik J., Brambs,Hans Juergen, Hoffmann,Martin H.K., Multislice CT imaging of anomalous coronary arteries, European RadiologyEur.Radiol., 14, 2172-2181, 2004	Population (included patients with suspected CAD or patients with PCI)
Shin,John H., Pokharna,Hemlata K., Williams,Kim A., Mehta,Rupa, Ward,R.Parker, SPECT myocardial perfusion imaging with prone-only acquisitions: correlation with coronary angiography, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 16, 590-596, 2009	Not all participants received reference standard
Shrivastava,Sameer, Agrawal,Vinayak, Kasliwal,Ravi R., Jangid,Dhanraj R., Sen,Ashok, Verma,Atul, Trehan,Naresh, Coronary calcium and coronary artery disease: an Indian perspective, Indian Heart JournalIndian Heart J., 55, 344-348, 2003	single slice scanner (minimum 64 slice)
Sicari,Rosa, Pingitore,Alessandro, Aquaro,Giovanni, Pasanisi,Emilio G., Lombardi,Massimo, Picano,Eugenio, Cardiac functional stress imaging: a sequential approach with stress echo and cardiovascular magnetic resonance, Cardiovascular ultrasoundCardiovasc Ultrasound, 5, 47-, 2007	Mixed population (includes known CAD)
Sirol,Marc, Sanz,Javier, Henry,Patrick, Rymer,Roland, Leber,Alexander, Evaluation of 64-slice MDCT in the real world of cardiology: a comparison with conventional coronary angiography, Archives of Cardiovascular DiseasesArch Cardiovasc Dis, 102, 433-439, 2009	Includes known CAD
Slavin,A., Meyer,T.E., A comparison of dipyridamole and exercise stress using technetium-99m sestamibi myocardial perfusion imaging, Cardiovascular Journal of Southern	Outcomes not diagnosis of CAD

Author	Reason for exclusion
AfricaCARDIOVASC.J.SOUTH.AFR., 5, 208-213, 1994	
Slomka,P.J., Diaz-Zamudio,M., Dey,D., Motwani,M., Brodov,Y., Choi,D., Hayes,S., Thomson,L., Friedman,J., Germano,G., Berman,D., Automatic registration of misaligned CT attenuation correction maps in Rb-82 PET/CT improves detection of angiographically significant coronary artery disease, J Nucl Cardiol, -, 2015	Design (retrospective)
Slomka,Piotr J., Cheng,Victor Y., Dey,Damini, Woo,Jonghye, Ramesh,Amit, Van Kriekinge,Serge, Suzuki,Yasuzuki, Elad,Yaron, Karlsberg,Ronald, Berman,Daniel S., Germano,Guido, Quantitative analysis of myocardial perfusion SPECT anatomically guided by coregistered 64-slice coronary CT angiography, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 50, 1621-1630, 2009	Design (retrospective)
Smart,S.C., Bhatia,A., Hellman,R., Stoiber,T., Krasnow,A., Collier,B.D., Sagar,K.B., Dobutamine-atropine stress echocardiography and dipyridamole sestamibi scintigraphy for the detection of coronary artery disease: limitations and concordance, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 36, 1265-1273, 2000	Population (included patients with known CAD)
Smedsrud,Marit Kristine, Sarvari,Sebastian, Haugaa,Kristina H., Gjesdal,Ola, Orn,Stein, Aaberge,Lars, Smiseth,Otto A., Edvardsen,Thor, Duration of myocardial early systolic lengthening predicts the presence of significant coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 60, 1086-1093, 2012	Non protocol index test (Echo without stress)
Soman,P., Khattar,R., Lahiri,A., Senior,R., Superiority of arbutamine over dipyridamole for the stress echocardiographic assessment of coronary artery disease and reversible ischaemia, Journal of Noninvasive CardiologyJ.Noninvasive Cardiol., 2, 24-30, 1998	Time flow (too long between tests)
Soman,P., Khattar,R., Senior,R., Lahiri,A., Inotropic stress with arbutamine is superior to vasodilator stress with dipyridamole for the detection of reversible ischemia with Tc-99m sestamibi single-photon emission computed tomography, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 4, 364-371, 1997	Mixed population (includes previous MI). >3months between index/reference tests.
Song,J.K., Lee,S.J., Kang,D.H., Cheong,S.S., Hong,M.K., Kim,J.J., Park,S.W., Park,S.J., Ergonovine echocardiography as a screening test for diagnosis of vasospastic angina before coronary angiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 27, 1156-1161, 1996	Not relevant
Soon,K.H., Chaitowitz,I., Cox,N., MacGregor,L., Eccleston,D., Bell,K.W., Kelly,A.M., Lim,Y.L., Diagnostic accuracy of 16-slice CT coronary angiography in the evaluation of coronary artery disease, Australasian RadiologyAustralas.Radiol., 51, 365-369, 2007	Design (retrospective)
Sozzi,F.B., Poldermans,D., Bax,J.J., Boersma,E., Vletter,W.B., Elhendy,A., Borghetti,A., Roelandt,J.R., Second harmonic imaging improves sensitivity of dobutamine stress echocardiography for the diagnosis of coronary artery disease, American Heart JournalAm.Heart J., 142, 153-159, 2001	Population (included patients with previous MI)
Stehli,Julia, Fuchs,Tobias A., Bull,Sacha, Clerc,Olivier F.,	Population (mixed)

Author	Reason for exclusion
Possner,Mathias, Buechel,Ronny R., Gaemperli,Oliver, Kaufmann,Philipp A., Accuracy of coronary CT angiography using a submillisievert fraction of radiation exposure: comparison with invasive coronary angiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 64, 772-780, 2014	
Stein,Paul D., Beemath,Afzal, Kayali,Fadi, Skaf,Elias, Sanchez,Julia, Olson,Ronald E., Multidetector computed tomography for the diagnosis of coronary artery disease: a systematic review, The American journal of medicineAm J Med, 119, 203-216, 2006	Population (some studies included patients with known CAD)
Stein,Paul D., Yaekoub,Abdo Y., Matta,Fadi, Sostman,H.Dirk, 64-slice CT for diagnosis of coronary artery disease: a systematic review, The American journal of medicineAm J Med, 121, 715-725, 2008	Population (included patients with known CAD)
Stoddard,M.F., Prince,C.R., Morris,G.T., Coronary flow reserve assessment by dobutamine transesophageal Doppler echocardiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 25, 325-332, 1995	Non protocol index tests
Stolzmann,Paul, Donati,Olivio F., Desbiolles,Lotus, Kozerke,Sebastian, Hoffmann,Udo, Alkadhi,Hatem, Scheffel,Hans, Coronary artery plaques and myocardial ischaemia, European RadiologyEur.Radiol., 21, 1628-1634, 2011	Index test overlaps with DG3 (New Generation Scanner)
Stolzmann,Paul, Goetti,Robert, Baumueller,Stephan, Plass,Andre, Falk,Volkmar, Scheffel,Hans, Feuchtner,Gudrun, Marincek,Borut, Alkadhi,Hatem, Leschka,Sebastian, Prospective and retrospective ECG-gating for CT coronary angiography perform similarly accurate at low heart rates, European Journal of RadiologyEur.J.Radiol., 79, 85-91, 2011	Design (prospective vs retrospective ECG gating)
Stolzmann,Paul, Scheffel,Hans, Leschka,Sebastian, Plass,Andre, Baumuller,Stephan, Marincek,Borut, Alkadhi,Hatem, Influence of calcifications on diagnostic accuracy of coronary CT angiography using prospective ECG triggering, AJR.American journal of roentgenologyAJR Am J Roentgenol, 191, 1684-1689, 2008	Population (mixed - included patients having routine (pre surgical) procedure (known CAD)
Stuijfzand,W.J., Uusitalo,V., Kero,T., Danad,I., Rijnierse,M.T., Saraste,A., Raijmakers,P.G., Lammertsma,A.A., Harms,H.J., Heymans,M.W., Huisman,M.C., Marques,K.M., Kajander,S.A., Pietila,M., Sorensen,J., Van,Royen N., Knuuti,J., Knaapen,P., Relative flow reserve derived from quantitative perfusion imaging may not outperform stress myocardial blood flow for identification of hemodynamically significant coronary artery disease, Circulation: Cardiovascular ImagingCirc.Cardiovasc.Imaging, 8, -, 2014	Non protocol reference standards
Stuijfzand,Wijnand J., Uusitalo,Valtteri, Kero,Tanja, Danad,Ibrahim, Rijnierse,Mischa T., Saraste,Antti, Raijmakers,Pieter G., Lammertsma,Adriaan A., Harms,Hans J., Heymans,Martijn W., Huisman,Marc C., Marques,Koen M., Kajander,Sami A., Pietila,Mikko, Sorensen,Jens, van Royen,Niels, Knuuti,Juhani, Knaapen,Paul, Relative flow reserve derived from quantitative perfusion imaging may not outperform stress myocardial blood flow for identification of hemodynamically significant coronary artery disease, Circulation.Cardiovascular imagingCirc Cardiovasc Imaging, 8, -, 2015	Design (retrospective)

Author	Reason for exclusion
Sun,Ming Li, Lu,Bin, Wu,Run Ze, Johnson,Laura, Han,Lei, Liu,Gang, Yu,Fang Fang, Hou,Zhi Hui, Gao,Yang, Wang,Hong Yu, Jiang,Shiliang, Yang,Yue Jin, Qiao,Shu bin, Diagnostic accuracy of dual-source CT coronary angiography with prospective ECG-triggering on different heart rate patients, European RadiologyEur.Radiol., 21, 1635-1642, 2011	Design (retrospective)
Sun,Z., Lin,C., Diagnostic value of 320-slice coronary CT angiography in coronary artery disease: A systematic review and meta-analysis, Current Medical Imaging ReviewsCurr.Med.Imaging Rev., 10, 272-280, 2014	Index test overlaps with DG3 (New Generation Scanner)
Sun,Zhonghua, Jiang,Wen, Diagnostic value of multislice computed tomography angiography in coronary artery disease: a meta-analysis, European Journal of RadiologyEur.J.Radiol., 60, 279-286, 2006	Population (unclear) Design (retrospective)
Sun,Zhonghua, Lin,Chenghsun, Davidson,Robert, Dong,Chiauhuei, Liao,Yunchan, Diagnostic value of 64-slice CT angiography in coronary artery disease: a systematic review, European Journal of RadiologyEur.J.Radiol., 67, 78-84, 2008	Design (retrospective) Population (included patients with known CAD)
Sundram,F.X., Lam,L.K., Ang,E.S., Goh,A.S., Johan,A., Tan,A.T., Chia,B.L., Tomographic thallium-201 stress scintigraphy in the evaluation of coronary artery disease, Annals of the Academy of Medicine, SingaporeAnn.Acad.Med.Singap., 15, 471-475, 1986	Population (included patients with angina pain, post CABG pain and post MI pain)
Sylven,C., Hagerman,I., Ylen,M., Nyquist,O., Nowak,J., Variance ECG detection of coronary artery disease--a comparison with exercise stress test and myocardial scintigraphy, Clinical CardiologyClin.Cardiol., 17, 132-140, 1994	Reference standard (non protocol)
Takahashi,N., Tamaki,N., Tadamura,E., Kawamoto,M., Torizuka,T., Yonekura,Y., Okuda,K., Nohara,R., Sasayama,S., Konishi,J., Combined assessment of regional perfusion and wall motion in patients with coronary artery disease with technetium 99m tetrofosmin, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 1, 29-38, 1994	Reference standard (non protocol)
Takeishi,Y., Takahashi,N., Fujiwara,S., Atsumi,H., Takahashi,K., Tomoike,H., Myocardial tomography with technetium-99m-tetrofosmin during intravenous infusion of adenosine triphosphate, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 39, 582-586, 1998	Population included prior MI
Takx,R.A.P., Blomberg,B.A., Aidi,H.E., Habets,J., De Jong,P.A., Nagel,E., Hoffmann,U., Leiner,T., Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis, Circulation: Cardiovascular ImagingCirc.Cardiovasc.Imaging, 8, -, 2014	Non protocol reference standard
Takx,Richard A.P., Blomberg,Bjorn A., El Aidi,Hamza, Habets,Jesse, de Jong,Pim A., Nagel,Eike, Hoffmann,Udo, Leiner,Tim, Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis, Circulation.Cardiovascular imagingCirc Cardiovasc Imaging, 8, -, 2015	Non protocol reference standard
Tamaki,N., Yonekura,Y., Mukai,T., Fujita,T., Nohara,R.,	Population (included patients with

Author	Reason for exclusion
Kadota,K., Kambara,H., Kawai,C., Torizuka,K., Ishii,Y., Segmental analysis of stress thallium myocardial emission tomography for localization of coronary artery disease, European Journal of Nuclear MedicineEUR.J.NUCL.MED., 9, 99-105, 1984	previous MI)
Teferici,D., Qirko,S., Petrela,E., Bara,P., Diagnostic value of 2D strain imaging in patients with suspected coronary artery disease, Macedonian Journal of Medical SciencesMaced.J.Med.Sci., 7, 46-50, 2014	Non protocol index test Population (included patients with suspected ACS)
Thiele,Holger, Plein,Sven, Breeuwer,Marcel, Ridgway,John P., Higgins,David, Thorley,Penelope J., Schuler,Gerhard, Sivananthan,Mohan U., Color-encoded semiautomatic analysis of multi-slice first-pass magnetic resonance perfusion: comparison to tetrofosmin single photon emission computed tomography perfusion and X-ray angiography, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 20, 371-377, 2004	Population (included patients with known CAD)
Thomas,D., Xie,F., Smith,L.M., O'Leary,E., Smith,K., Olson,J., Nalty,K., Hess,R., Graham,M., Therrien,S., Porter,T.R., Prospective randomized comparison of conventional stress echocardiography and real-time perfusion stress echocardiography in detecting significant coronary artery disease, Journal of the American Society of EchocardiographyJ.Am.Soc.Echocardiogr., 25, 1207-1214, 2012	Population (not everyone - only a small proportion with positive index test will get CA)
Tian,J., Zhang,G., Wang,X., Cui,J., Xiao,J., Exercise echocardiography: feasibility and value for detection of coronary artery disease, Chinese medical journalChin.Med.J., 109, 381-384, 1996	Population mixed. Includes known CAD.
Timins,M.E., Pinsk,R., Sider,L., Bear,G., The functional significance of calcification of coronary arteries as detected on CT, Journal of Thoracic ImagingJ.Thorac.Imaging, 7, 79-82, 1991	Design (retrospective)
Toledo,Eran, Jacobs,Lawrence D., Lodato,Joseph A., DeCara,Jeanne M., Coon,Patrick, Mor-Avi,Victor, Lang,Roberto M., Quantitative diagnosis of stress-induced myocardial ischemia using analysis of contrast echocardiographic parametric perfusion images, European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of CardiologyEur J Echocardiogr, 7, 217-225, 2006	Not relevant
Tolstrup,Kirsten, Madsen,Bo E., Ruiz,Jose A., Greenwood,Stephen D., Camacho,Judeen, Siegel,Robert J., Gertzen,H.Caroline, Park,Jai Wun, Smars,Peter A., Non-invasive resting magnetocardiographic imaging for the rapid detection of ischemia in subjects presenting with chest pain, Cardiology, 106, 270-276, 2006	Reference standard (non protocol)
Tonino,P.A., Fearon,W.F., Bruyne,B., Oldroyd,K.G., Leesar,M.A., Ver Lee,P.N., Maccarthy,P.A., Van't Veer,M., Pijls,N.H., Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 55, 2816-2821, 2010	Not relevant. Population includes known CAD
Treuth,M.G., Reyes,G.A., He,Z.X., Cwajg,E., Mahmarian,J.J., Verani,M.S., Tolerance and diagnostic accuracy of an abbreviated adenosine infusion for myocardial scintigraphy: a	Population (included patients with a history of CAD)

Author	Reason for exclusion
randomized, prospective study, Journal of Nuclear CardiologyJ.Nucl.Cardiol., 8, 548-554, 2001	
Trippi,J.A., Lee,K.S., Kopp,G., Nelson,D.R., Yee,K.G., Cordell,W.H., Dobutamine stress tele-echocardiography for evaluation of emergency department patients with chest pain, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 30, 627-632, 1997	Non protocol population.
Truong,Q.A., Knaapen,P., Pontone,G., Andreini,D., Leipsic,J., Carrascosa,P., Lu,B., Branch,K., Raman,S., Bloom,S., Min,J.K., Rationale and design of the dual-energy computed tomography for ischemia determination compared to "gold standard" non-invasive and invasive techniques (DECIDE-Gold): A multicenter international efficacy diagnostic study of rest-stress dual-energy computed tomography angiography with perfusion, J Nucl Cardiol, -, 2014	Non protocol reference test
Tsai,Jui Peng, Yun,Chun Ho, Wu,Tung Hsin, Yen,Chih Hsuan, Hou,Charles Jia-Yin, Kuo,Jen Yuan, Hung,Chung Lieh, A meta-analysis comparing SPECT with PET for the assessment of myocardial viability in patients with coronary artery disease, Nuclear Medicine CommunicationsNUCL.MED.COMMUN., 35, 947-954, 2014	Non protocol reference test
Turkvatan,A., Biyikoglu,S.F., Buyukbayraktar,F., Olcer,T., Cumhur,T., Duru,E., Clinical value of 16-slice multidetector computed tomography in symptomatic patients with suspected coronary artery disease, Acta radiologica (Stockholm, Sweden : 1987), 49, 400-408, 2008	16 slice scanner (64 slice minimum)
Uchiyama,T., Fujibayashi,Y., Sato,Y., Sakamaki,T., Kajiwara,N., Clinical application of echocardiographic imaging to diagnosis of coronary artery disease, Japanese Circulation JournalJPN.CIRC.J., 54, 309-315, 1990	Reference standard (unclear) Design (correlation study rather than DTA)
Ugolini,P., Pressacco,J., Lesperance,J., Berry,C., L'Allier,P.L., Ibrahim,R., Gregoire,J., Ouellet,R., Heinonen,T., Levesque,S., Guertin,Marie Claude, Tardif,Jean Claude, Evaluation of coronary atheroma by 64-slice multidetector computed tomography: Comparison with intravascular ultrasound and angiography, The Canadian journal of cardiologyCan J Cardiol, 25, 641-647, 2009	Includes known CAD
Utsunomiya,H., Hidaka,T., Masada,K., Shimonaga,T., Higaki,T., Iwasaki,T., Mitsuba,N., Ishibashi,K., Kurisu,S., Kihara,Y., Value of Resting Echocardiographic Findings and Dobutamine Stress Echocardiography for Diagnosing Myocardial Ischemia in Patients with Suspected Angina Pectoris, Echocardiography, -, 2015	Non protocol reference test
Vallejo,E., Acevedo,C., Varela,S., Alburez,J.C., Bialostozky,D., Assessment of myocardial perfusion tomography photon emission computed individual (SPECT) Cardiac usefulness of stress-only protocol, Gaceta Medica de MexicoGac.Med.Mex., 148, 6-13, 2012	Full article not in english
Van Lingen,R., Kakani,N., Veitch,A., Manghat,N.E., Roobottom,C.A., Morgan-Hughes,G.J., Prognostic and accuracy data of multidetector CT coronary angiography in an established clinical service, Clinical RadiologyClin.Radiol., 64, 601-607, 2009	Population (included patients with known CAD) Design (retrospective)
van Mieghem,Carlos A.G., Thury,Attila, Meijboom,Willem B., Cademartiri,Filippo, Mollet,Nico R., Weustink,Annick C., Sianos,Georgios, de Jaegere,Peter P.T., Serruys,Patrick W.,	Population (included patients with post CABG

Author	Reason for exclusion
de Feyter,Pim, Detection and characterization of coronary bifurcation lesions with 64-slice computed tomography coronary angiography, European Heart JournalEur.Heart J., 28, 1968-1976, 2007	
Van Rugge,F.P., Van Der Wall,E.E., de Roos,A., Bruschke,A.V., Dobutamine stress magnetic resonance imaging for detection of coronary artery disease, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 22, 431-439, 1993	Includes previous MI
Van Train,K.F., Garcia,E.V., Maddahi,J., Areeda,J., Cooke,C.D., Kiat,H., Silagan,G., Folks,R., Friedman,J., Matzer,L., Multicenter trial validation for quantitative analysis of same-day rest-stress technetium-99m-sestamibi myocardial tomograms, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 35, 609-618, 1994	Includes mixed population
Van Train,K.F., Maddahi,J., Berman,D.S., Kiat,H., Areeda,J., Prigent,F., Friedman,J., Quantitative analysis of tomographic stress thallium-201 myocardial scintigrams: a multicenter trial, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 31, 1168-1179, 1990	Includes prior MI
van Velzen,Joella E., Schuijf,Joanne D., de Graaf,Fleur R., Boersma,Eric, Pundziute,Gabija, Spano,Fabrizio, Boogers,Mark J., Schalij,Martin J., Kroft,Lucia J., de Roos,Albert, Jukema,J.Wouter, van der Wall,Ernst E., Bax,Jeroen J., Diagnostic performance of non-invasive multidetector computed tomography coronary angiography to detect coronary artery disease using different endpoints: detection of significant stenosis vs. detection of atherosclerosis, European Heart JournalEur.Heart J., 32, 637-645, 2011	New generation scanner (protocol exclusion)
Vanhoenacker,Piet K., Heijenbrok-Kal,Majanka H., Van Heste,Ruben, Decramer,Isabel, Van Hoe,Lieven R., Wijns,William, Hunink,M.G.M., Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis, Radiology, 244, 419-428, 2007	Population (included patients with known CAD)
Vavere,Andrea L., Arbab-Zadeh,Armin, Rochitte,Carlos E., Dewey,Marc, Niinuma,Hiroyuki, Gottlieb,Ilan, Clouse,Melvin E., Bush,David E., Hoe,John W.M., de Roos,Albert, Cox,Christopher, Lima,Joao A.C., Miller,Julie M., Coronary artery stenoses: accuracy of 64-detector row CT angiography in segments with mild, moderate, or severe calcification--a subanalysis of the CORE-64 trial, Radiology, 261, 100-108, 2011	Non standard method of calcium scoring (excluded on topic expert advice).
Verani,M.S., Mahmarian,J.J., Hixson,J.D., Boyce,T.M., Staudacher,R.A., Diagnosis of coronary artery disease by controlled coronary vasodilation with adenosine and thallium-201 scintigraphy in patients unable to exercise, Circulation, 82, 80-87, 1990	Population (included patients with MI and post CABG)
Verzijlbergen,J.F., Cramer,M.J., Niemeyer,M.G., Ascoop,C.A., Van Der Wall,E.E., Pauwels,E.K., 99Tcm-SESTAMIBI for planar myocardial perfusion imaging; not as ideal as the physical properties, Nuclear Medicine CommunicationsNUCL.MED.COMMUN., 12, 381-391, 1991	Population (included patients with previous MI)
Verzijlbergen,J.F., Zwinderman,A.H., Ascoop,C.A., Van Der Wall,E.E., Niemeyer,M.G., Pauwels,E.K., Comparison of technetium-99m sestamibi left ventricular wall motion and	Population (included patients with known disease/stenosis)

Author	Reason for exclusion
perfusion studies with thallium-201 perfusion imaging: in search of the combination of variables with the highest accuracy in predicting coronary artery disease, European Journal of Nuclear MedicineEUR.J.NUCL.MED., 23, 550-559, 1996	
Vidal,R., Buvat,I., Darcourt,J., Migneco,O., Desvignes,P., Baudouy,M., Bussiere,F., Impact of attenuation correction by simultaneous emission/transmission tomography on visual assessment of 201Tl myocardial perfusion images, Journal of nuclear medicine : official publication, Society of Nuclear MedicineJ Nucl Med, 40, 1301-1309, 1999	Study design : retrospective
Vincent,N.R., Denis,L., Exercise thallium stress testing compared with coronary angiography in patients without exclusions for suboptimal exercise or cardioactive medications, Clinical Nuclear MedicineClin.Nucl.Med., 11, 688-691, 1986	Population (not all participants could perform exercise testing)
Vogel,R., Indermuhle,A., Meier,P., Seiler,C., Quantitative stress echocardiography in coronary artery disease using contrast-based myocardial blood flow measurements: prospective comparison with coronary angiography, Heart (British Cardiac Society), 95, 377-384, 2009	Mixed population - includes previous angina
Vogler,N., Meyer,M., Fink,C., Schoepf,U.J., Schonberg,S.O., Henzler,T., Predictive value of zero calcium score and low-end percentiles for the presence of significant coronary artery stenosis in stable patients with suspected coronary artery disease, RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der NuklearmedizinROFO Fortschr Geb Rontgenstr Nuklearmed, 185, 726-732, 2013	Mixed population
von Ballmoos,Moritz Wyler, Haring,Bernhard, Juillerat,Pascal, Alkadhi,Hatem, Meta-analysis: diagnostic performance of low-radiation-dose coronary computed tomography angiography, Annals of Internal MedicineANN.INTERN.MED., 154, 413-420, 2011	Design (included retrospective studies)
von Ziegler,Franz, Schenzle,Jan, Schiessl,Stephan, Greif,Martin, Helbig,Susanne, Tittus,Janine, Becker,Christoph, Becker,Alexander, Use of multi-slice computed tomography in patients with chest-pain submitted to the emergency department, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 30, 145-153, 2014	Acute chest pain population
Voros,S., Rinehart,S., Vazquez-Figueroa,J.G., Kalynych,A., Karmpaliotis,D., Qian,Z., Joshi,P.H., Anderson,H., Murrieta,L., Wilmer,C., Carlson,H., Ballard,W., Brown,C., Prospective, head-to-head comparison of quantitative coronary angiography, quantitative computed tomography angiography, and intravascular ultrasound for the prediction of hemodynamic significance in intermediate and severe lesions, using fractional flow reserve as reference standard (from the ATLANTA i and II Study), American Journal of CardiologyAm.J.Cardiol., 113, 23-29, 2014	Non protocol reference standard
Wagner,Moritz, Rosler,Roberta, Lembcke,Alexander, Butler,Craig, Dewey,Marc, Laule,Michael, Huppertz,Alexander, Schwenke,Carsten, Warmuth,Carsten, Rief,Matthias, Hamm,Bernd, Taupitz,Matthias, Whole-heart coronary magnetic resonance angiography at 1.5 Tesla: does a blood-pool contrast agent improve diagnostic accuracy?, Investigative RadiologyInvest.Radiol., 46, 152-159, 2011	Non protocol index test

Author	Reason for exclusion
Walcher,Thomas, Ikuye,Katharina, Rottbauer,Wolfgang, Wohrle,Jochen, Bernhardt,Peter, Is contrast-enhanced cardiac magnetic resonance imaging at 3 T superior to 1.5 T for detection of coronary artery disease?, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 29, 355-361, 2013	Not possible to back calculate 2x2 table.
Walcher,Thomas, Manzke,Robert, Hombach,Vinzenz, Rottbauer,Wolfgang, Wohrle,Jochen, Bernhardt,Peter, Myocardial perfusion reserve assessed by T2-prepared steady-state free precession blood oxygen level-dependent magnetic resonance imaging in comparison to fractional flow reserve, Circulation.Cardiovascular imagingCirc Cardiovasc Imaging, 5, 580-586, 2012	Non protocol reference test
Wang,Rui, Yu,Wei, Wang,Yongmei, He,Yi, Yang,Lin, Bi,Tao, Jiao,Jian, Wang,Qian, Chi,Liquan, Yu,Yang, Zhang,Zhaoqi, Incremental value of dual-energy CT to coronary CT angiography for the detection of significant coronary stenosis: comparison with quantitative coronary angiography and single photon emission computed tomography, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 27, 647-656, 2011	Population (included patients with known CAD)
Warner,M.F., Pippin,J.J., DiSciascio,G., Paulsen,W.H., Arrowood,J.A., Tatum,J.L., Goudreau,E., Vetrovec,G.W., Assessment of thallium scintigraphy and echocardiography during dobutamine infusion for the detection of coronary artery disease, Catheterization and cardiovascular diagnosisCathet Cardiovasc Diagn, 29, 122-127, 1993	Population (included patients with known CAD)
Watanabe,N., Akasaka,T., Yamaura,Y., Akiyama,M., Koyama,Y., Kamiyama,N., Neishi,Y., Kaji,S., Saito,Y., Yoshida,K., Noninvasive detection of total occlusion of the left anterior descending coronary artery with transthoracic Doppler echocardiography, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 38, 1328-1332, 2001	Non protocol index test
Watanabe,S., Ajisaka,R., Masuoka,T., Iida,K., Sugishita,Y., Ito,I., Takeda,T., Toyama,H., Akisada,M., Isoproterenol stress thallium scintigraphy for detecting coronary artery disease, Journal of CardiologyJ.Cardiol., 19, 657-665, 1989	Design (retrospective)
Watkins,Matthew W., Hesse,Barbara, Green,Curtis E., Greenberg,Neil L., Manning,Michael, Chaudhry,Eram, Dauerman,Harold L., Garcia,Mario J., Detection of coronary artery stenosis using 40-channel computed tomography with multi-segment reconstruction, The American journal of cardiologyAm J Cardiol, 99, 175-181, 2007	Population (included patients with known or suspected CAD)
Watkins,Stuart, McGeoch,Ross, Lyne,Jonathan, Steedman,Tracey, Good,Richard, McLaughlin,Mairi Jean, Cunningham,Tony, Bezlyak,Vladimir, Ford,Ian, Dargie,Henry J., Oldroyd,Keith G., Validation of magnetic resonance myocardial perfusion imaging with fractional flow reserve for the detection of significant coronary heart disease, Circulation, 120, 2207-2213, 2009	Non protocol reference standard
Wehrschuetz,M., Wehrschuetz,E., Schuchlenz,H., Schaffler,G., Accuracy of MSCT Coronary Angiography with 64 Row CT Scanner-Facing the Facts, Clinical Medicine Insights.CardiologyClin Med Insights Cardiol, 4, 15-22, 2010	Retrospective study design
Weidemann,F., Jung,P., Hoyer,C., Broscheit,J., Voelker,W., Ertl,G., Stork,S., Angermann,C.E., Strotmann,J.M., Assessment of the contractile reserve in patients with	Not relevant

Author	Reason for exclusion
intermediate coronary lesions: A strain rate imaging study validated by invasive myocardial fractional flow reserve, European Heart JournalEur.Heart J., 28, 1425-1432, 2007	
Weustink,A.C., Neefjes,L.A., Rossi,A., Meijboom,W.B., Nieman,K., Capuano,E., Boersma,E., Mollet,N.R., Krestin,G.P., De Feyter,P.J., Diagnostic performance of exercise bicycle testing and single-photon emission computed tomography: comparison with 64-slice computed tomography coronary angiography, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 28, 675-684, 2012	Patients recruited on basis of results of initial stress test
Weustink,Annick C., Mollet,Nico R., Neefjes,Lisan A., Meijboom,W.Bob, Galema,Tjebbe W., van Mieghem,Carlos A., Kyrzopoulous,Stamatis, Eu,Rick Neoh, Nieman,Koen, Cademartiri,Filippo, van Geuns,Robert Jan, Boersma,Eric, Krestin,Gabriel P., de Feyter,Pim J., Diagnostic accuracy and clinical utility of noninvasive testing for coronary artery disease, Annals of Internal MedicineANN.INTERN.MED., 152, 630-639, 2010	Not all patients had reference standard
Weustink,Annick C., Mollet,Nico R., Neefjes,Lisan A., van Straten,Marcel, Neoh,Eurick, Kyrzopoulos,Stamatis, Meijboom,Bob Willem, Van Mieghem,Carlos, Cademartiri,Filippo, de Feyter,Pim J., Krestin,Gabriel P., Preserved diagnostic performance of dual-source CT coronary angiography with reduced radiation exposure and cancer risk, Radiology, 252, 53-60, 2009	Mixed population - includes patients with unstable chest pain
Wexler L, Brundage B, Crouse J et al (1996) Coronary Artery Calcification: pathophysiology epidemiology, imaging methods and clinical implications. Circulation: 94:1175-1192.	Study design. Review article.
Williams,K.A., Schuster,R.A., Williams,K.A., Schneider,C.M., Pokharna,H.K., Correct spatial normalization of myocardial perfusion SPECT improves detection of multivessel coronary artery disease, Journal of Nuclear CardiologyJ.Nucl.Cardiol., 10, 353-360, 2003	Population (included patients with known CAD) Design (retrospective)
Wittlinger,Thomas, Martinovic,Ivo, Moosdorf,Rainer, Moritz,Anton, Imaging of calcified coronary arteries with multislice computed tomography, Asian cardiovascular & thoracic annals, 14, 321-327, 2006	Population (only patients with inconclusive ECG at intermediate CAD risk)
Wittlinger,Thomas, Voigtlander,Thomas, Rohr,Martin, Meyer,Jurgen, Thelen,Martin, Kreitner,Karl Friedrich, Kalden,Peter, Magnetic resonance imaging of coronary artery occlusions in the navigator technique, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 18, 203-205, 2002	non protocol index test
Wolak,Arik, Slomka,Piotr J., Fish,Mathews B., Lorenzo,Santiago, Acampa,Wanda, Berman,Daniel S., Germano,Guido, Quantitative myocardial-perfusion SPECT: comparison of three state-of-the-art software packages, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 15, 27-34, 2008	Not all participants had reference standard
Wolff,S.D., Schwitter,J., Coulden,R., Friedrich,M.G., Bluemke,D.A., Biederman,R.W., Martin,E.T., Lansky,A.J., Kashanian,F., Foo,T.K., Licato,P.E., Comeau,C.R., Myocardial first-pass perfusion magnetic resonance imaging: a multicenter dose-ranging study, Circulation, 110, 732-737, 2004	Non protocol index test Population (included patients with known CAD)

Author	Reason for exclusion
Wong,Dennis T.L., Ko,Brian S., Cameron,James D., Nerlekar,Nitesh, Leung,Michael C.H., Malaiapan,Yuvaraj, Crossett,Marcus, Leong,Darryl P., Worthley,Stephen G., Troupis,John, Meredith,Ian T., Seneviratne,Sujith K., Transluminal attenuation gradient in coronary computed tomography angiography is a novel noninvasive approach to the identification of functionally significant coronary artery stenosis: a comparison with fractional flow reserve, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 61, 1271-1279, 2013	Non protocol reference standard
Wu,C.C., Ho,Y.L., Kao,S.L., Chen,W.J., Lee,C.M., Chen,M.F., Liau,C.S., Lee,Y.T., Dobutamine stress echocardiography for detecting coronary artery disease, Cardiology, 87, 244-249, 1996	Mixed population - includes people with previous MI
Wu,Ming Che, Chin,Kun Chou, Lin,Ku Hung, Chiu,Nan Tsing, Diagnostic efficacy of a low-dose 32-projection SPECT 99mTc-sestamibi myocardial perfusion imaging protocol in routine practice, Nuclear Medicine CommunicationsNUCL.MED.COMMUN., 30, 140-147, 2009	Population (not all patients had c.angio)
Wu,Y.-W., Lin,L.-C., Tseng,W.-K., Liu,Y.-B., Kao,H.-L., Lin,M.-S., Huang,H.-C., Wang,S.-Y., Horng,H.-E., Yang,H.-C., Wu,C.-C., QTcheterogeneity in rest magnetocardiography is sensitive to detect coronary artery disease: In comparison with stress myocardial perfusion imaging, Acta Cardiologica SinicaActa Cardiol.Sin., 30, 445-454, 2014	Includes known CAD
Xu,Lei, Sun,Zhonghua, Virtual intravascular endoscopy visualization of calcified coronary plaques: a novel approach of identifying plaque features for more accurate assessment of coronary lumen stenosis, MedicineMedicine (GBR), 94, e805-, 2015	Non protocol index test
Xu,Yi, Tang,Lijun, Zhu,Xiaomei, Xu,Hai, Tang,Jinhua, Yang,Zhijian, Wang,Liansheng, Wang,Dehang, Comparison of dual-source CT coronary angiography and conventional coronary angiography for detecting coronary artery disease, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 26 Suppl 1, 75-81, 2010	Index test overlaps with DG3 (New Generation Scanner)
Yamada,T., Sawada,T., Yamano,T., Azuma,A., Nakagawa,M., Evaluation of coronary arterial stenoses using 2D magnetic resonance coronary angiography, Minimally Invasive Therapy and Allied TechnologiesMinimally Invasive Ther.Allied Technol., 11, 7-15, 2002	Non protocol index test
Yang,Carina W., Carr,James C., Francois,Christopher J., Shea,Steven M., Deshpande,Vibhas S., Meyers,Sheridan N., Beohar,Nirat, Finn,J.Paul, Li,Debiao, Coronary magnetic resonance angiography using magnetization-prepared contrast-enhanced breath-hold volume-targeted imaging (MPCE-VCATS), Investigative RadiologyInvest.Radiol., 41, 639-644, 2006	Non protocol index test
Yang,D.H., Kim,Y.H., Roh,J.H., Kang,J.W., Han,D., Jung,J., Kim,N., Lee,J.B., Ahn,J.M., Lee,J.Y., Park,D.W., Kang,S.J., Lee,S.W., Lee,C.W., Park,S.W., Park,S.J., Lim,T.H., Stress Myocardial Perfusion CT in Patients Suspected of Having Coronary Artery Disease: Visual and Quantitative Analysis-Validation by Using Fractional Flow Reserve, Radiology, 141126-, 2015	Index test overlaps with DG3 (New Generation Scanner)
Yang,Linfeng, Zhou,Tao, Zhang,Ruijie, Xu,Lin, Peng,Zhaohui, Ding,Juan, Wang,Sen, Li,Min, Sun,Gang,	New generation scanners used in included studies. Populations not

Author	Reason for exclusion
Meta-analysis: diagnostic accuracy of coronary CT angiography with prospective ECG gating based on step-and-shoot, Flash and volume modes for detection of coronary artery disease, European RadiologyEur.Radiol., 24, 2345-2352, 2014	described.
Yang,Phillip C., Meyer,Craig H., Terashima,Masahiro, Kaji,Shuichiro, McConnell,Michael V., Macovski,A., Pauly,John M., Nishimura,Dwight G., Hu,Bob S., Spiral magnetic resonance coronary angiography with rapid real-time localization, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 41, 1134-1141, 2003	Non protocol index test
Yang,Qi, Li,Kuncheng, Liu,Xin, Bi,Xiaoming, Liu,Zhi, An,Jing, Zhang,Al, Jerecic,Renate, Li,Debiao, Contrast-enhanced whole-heart coronary magnetic resonance angiography at 3.0-T: a comparative study with X-ray angiography in a single center, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 54, 69-76, 2009	Non protocol index test
Yang,Qi, Li,Kuncheng, Liu,Xin, Du,Xiangying, Bi,Xiaoming, Huang,Feng, Jerecic,Renate, Liu,Zhi, An,Jing, Xu,Dong, Zheng,Hairong, Fan,Zhaoyang, Li,Debiao, 3.0T whole-heart coronary magnetic resonance angiography performed with 32-channel cardiac coils: a single-center experience, Circulation.Cardiovascular imagingCirc Cardiovasc Imaging, 5, 573-579, 2012	Non protocol index test
Yao,Z., Liu,X.J., Shi,R., Dai,R., Zhang,S., Liu,Y., Li,S., Tian,Y., Zhang,X., A comparison of 99mTc-MIBI myocardial SPET with electron beam computed tomography in the assessment of coronary artery disease, European Journal of Nuclear MedicineEUR.J.NUCL.MED., 24, 1115-1120, 1997	Population (included patients with history of chest pain
Yerramasu,Ajay, Lahiri,Avijit, Venuraju,Shreenidhi, Dumo,Alain, Lipkin,David, Underwood,S Richard, Rakhit,Roby D., Patel,Deven J., Diagnostic role of coronary calcium scoring in the rapid access chest pain clinic: prospective evaluation of NICE guidance, European Heart Journal Cardiovascular ImagingEur.Heart J.Cardiovasc.Imaging, 15, 886-892, 2014	Not all patients received reference standard
Yonezawa,Masato, Nagata,Motonori, Kitagawa,Kakuya, Kato,Shingo, Yoon,Yeonyee, Nakajima,Hiroshi, Nakamori,Shiro, Sakuma,Hajime, Hatakenaka,Masamitsu, Honda,Hiroshi, Quantitative analysis of 1.5-T whole-heart coronary MR angiograms obtained with 32-channel cardiac coils: a comparison with conventional quantitative coronary angiography, Radiology, 271, 356-364, 2014	Non protocol index test
Yoon,Yeonyee E., Choi,Jin Ho, Kim,Ji Hyun, Park,Kyung Woo, Doh,Joon Hyung, Kim,Yong Jin, Koo,Bon Kwon, Min,James K., Erglis,Andrejs, Gwon,Hyeon Cheol, Choe,Yeon Hyeon, Choi,Dong Ju, Kim,Hyo Soo, Oh,Byung Hee, Park,Young Bae, Noninvasive diagnosis of ischemia-causing coronary stenosis using CT angiography: diagnostic value of transluminal attenuation gradient and fractional flow reserve computed from coronary CT angiography compared to invasively measured fractional flow reserve, JACC.Cardiovascular imagingJACC Cardiovasc Imaging, 5, 1088-1096, 2012	Population (included patients with known CAD) Non protocol reference test
Yoshitani,Hidetoshi, Takeuchi,Masaaki, Mor-Avi,Victor, Otsuji,Yutaka, Hozumi,Takeshi, Yoshiyama,Minoru, Comparative diagnostic accuracy of multiplane and multislice three-dimensional dobutamine stress echocardiography in	Population (included patients with known or suspected CAD)

Author	Reason for exclusion
the diagnosis of coronary artery disease, Journal of the American Society of Echocardiography : official publication of the American Society of EchocardiographyJ Am Soc Echocardiogr, 22, 437-442, 2009	
Yun,Hong, Jin,Hang, Yang,Shan, Huang,Dong, Chen,Zhang Wei, Zeng,Meng su, Coronary artery angiography and myocardial viability imaging: a 3.0-T contrast-enhanced magnetic resonance coronary artery angiography with Gd-BOPTA, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 30, 99-108, 2014	Population (included patients with previous MI)
Zaag-Loonen,H.J., Dikkers,R., de Bock,G.H., Oudkerk,M., The clinical value of a negative multi-detector computed tomographic angiography in patients suspected of coronary artery disease: A meta-analysis, European RadiologyEur.Radiol., 16, 2748-2756, 2006	Insufficient scanner slices (all studies <64 slice)
Zhang,Long Jiang, Wu,Sheng Yong, Wang,Jing, Lu,Ying, Zhang,Zhuo Li, Jiang,Shi Sen, Zhou,Chang sheng, Lu,Guang ming, Diagnostic accuracy of dual-source CT coronary angiography: The effect of average heart rate, heart rate variability, and calcium score in a clinical perspective, Acta radiologica (Stockholm, Sweden : 1987), 51, 727-740, 2010	Mixed population - includes people with unstable CAD.
Zhang,T., Luo,Z., Wang,D., Han,D., Bai,J., Meng,X., Shen,B., Radiation dose in coronary artery angiography with 320-detector row CT and its diagnostic accuracy: comparison with 64-detector row CT, Minerva medicaMinerva Med, 102, 249-259, 2011	Mixed population includes people with decompensated heart failure.
Zhao,R.P., Hao,Z.R., Song,Z.J., Diagnostic value of Flash dual-source CT coronary artery imaging combined with dual-energy myocardial perfusion imaging for coronary heart disease, Exp Ther Med, 7, 865-868, 2014	Population known CAD and New generation scanner used
Zheng,Xiao Zhi, Yang,Bin, Wu,Jing, Comparison of the efficacy of conventional echocardiographic parameters in the diagnosis of significant coronary artery stenosis, Iranian journal of radiology : a quarterly journal published by the Iranian Radiological SocietyIran.j.radiol., 12, e11405-, 2015	Non protocol index test Population (included patients with known CAD)
Zhou,Tao, Yang,Lin Feng, Zhai,Ji Liang, Li,Jiang, Wang,Qi Meng, Zhang,Rui Jie, Wang,Sen, Peng,Zhao Hui, Li,Min, Sun,Gang, SPECT myocardial perfusion versus fractional flow reserve for evaluation of functional ischemia: a meta analysis, European Journal of RadiologyEur.J.Radiol., 83, 951-956, 2014	Reference standard (non protocol)

F.2 Review question 1 – supplementary test and treat randomised controlled trials review

Study	Reason for Exclusion
Cury,R.C., Kitt,T.M., Feaheny,K., Blankstein,R., Ghoshhajra,B.B., Budoff,M.J., Leipsic,J., Min,J.K., Akin,J., George,R.T., A randomized, multicenter, multivendor study of myocardial perfusion imaging with regadenoson CT perfusion vs single photon emission CT, Journal of cardiovascular computed tomography, 9, 103-112, 2015	Incorrect population: part of the population had known coronary artery disease on trial entry. Also did not report effectiveness outcomes.
Douglas,P.S., Hoffmann,U., Lee,K.L., Mark,D.B., Al-Khalidi,H.R., Anstrom,K., Dolor,R.J.,	Trial protocol only.

Study	Reason for Exclusion
Kosinski,A., Krucoff,M.W., Mudrick,D.W., Patel,M.R., Picard,M.H., Udelson,J.E., Velazquez,E.J., Cooper,L., PROMISE,Investigators, PROspective Multicenter Imaging Study for Evaluation of chest pain: rationale and design of the PROMISE trial, American Heart Journal, 167, 796-803, 2014	
McKavanagh,P., Lusk,L., Ball,P.A., Trinick,T., Duly,E., Walls,G., Verghis,R., Agus,A., Harbinson,M., Donnelly,P.M., The 1 year clinical results of the CAPP study, European Heart Journal.Conference: European Society of Cardiology, ESC Congress 2013 Amsterdam Netherlands.Conference Start: 20130831 Conference End: 20130904.Conference Publication: (var.pagings).34 (pp 320-321), 2013.Date of Publication: August 201, 320-321, 2013	Conference abstract
McKavanagh,P., Lusk,L.I.S.A., Ball,P.A., Trinick,T.R., Duly,E., Walls,G., Orr,C., Harbinson,M.T., Donnelly,P.M., Cardiac ct for the assessment of pain and plaque: The 90 day results of a randomised control trial, European Heart Journal Cardiovascular Imaging.Conference: 16th Annual Meeting of the European Association of Echocardiography, EUROECHO 2012 Athens Greece.Conference Start: 20121205 Conference End: 20121208.Conference Publication: (var.pagings).13 (pp, i114-, 2012	Conference abstract
Sabharwal,N.K., Stoykova,B., Taneja,A.K., Lahiri,A., A randomized trial of exercise treadmill ECG versus stress SPECT myocardial perfusion imaging as an initial diagnostic strategy in stable patients with chest pain and suspected CAD: cost analysis.[Erratum appears in J Nucl Cardiol. 2007 May-Jun;14(3):414], Journal of Nuclear Cardiology, 14, 174-186, 2007	Does not report effectiveness outcomes (test and treat RCT, but only reports costs for each strategy)
Schwitter,J., Wacker,C.M., Wilke,N., Al-Saadi,N., Sauer,E., Huettle,K., Schonberg,S.O., Debl,K., Strohm,O., Ahlstrom,H., Dill,T., Hoebel,N., Simor,T., MR-IMPACT,investigators, Superior diagnostic performance of perfusion-cardiovascular magnetic resonance versus SPECT to detect coronary artery disease: The secondary endpoints of the multicenter multivendor MR-IMPACT II (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease Trial), Journal of Cardiovascular Magnetic Resonance, 14, 61-, 2012	Not a test and treat RCT: participants were not randomised to diagnostic strategy
Thom,H., West,N.E., Hughes,V., Dyer,M., Buxton,M., Sharples,L.D., Jackson,C.H., Crean,A.M., CECaT study group, Cost-effectiveness of initial stress cardiovascular MR, stress SPECT or stress echocardiography as a gate-keeper test, compared with upfront invasive coronary angiography in the investigation and	Participants had to have a positive exercise stress test (indicative of CAD) for inclusion.

Study	Reason for Exclusion
management of patients with stable chest pain: mid-term outcomes from the CECaT randomised controlled trial, BMJ Open, 4, e003419-, 2014	
Zacharias,K., Shah,B., Pabla,J., Ahmed,A., Gurunathan,S., Senior,R., Exercise echo has superior cost efficacy compared to exercise ECG for the diagnosis of coronary artery disease in patients with new suspected angina: A randomised prospective study, European Heart Journal, 35, 117-118, 2014	Conference abstract.

F.31 Review question 2

Reference	Reason for exclusion
de Araujo Goncalves P, Garcia-Garcia H.M, Dores H, Carvalho M.S, Jeronimo Sousa P, et al. (2013) Coronary computed tomography angiography-adapted Leaman score as a tool to noninvasively quantify total coronary atherosclerotic burden, The International Journal of Cardiovascular Imaging, 29, 1575-1584.	Incorrect population (prior stress or CT testing, or pre-operative CAD assessment).
Dores H, de Araujo Goncalves P, Ferreira A.M, Carvalho M, Sousa P, et al. (2015) Performance of traditional risk factors in identifying a higher than expected coronary atherosclerotic burden, Revista Portuguesa de Cardiologia, 34, 247-253.	Incorrect population - majority of patients had failed prior stress test.
Doukky R, Shih M.J, Rahaby M, Alyousef T, Abusin S, et al. (2013) A simple validated clinical tool to predict the absence of coronary artery disease in patients with systolic heart failure of unclear etiology, American Journal of Cardiology, 112, 1165-1170.	Incorrect population – systolic heart failure.
Gencer B, Vaucher P, Herzig L, Verdon F, Ruffieux C et al. (2010) Ruling out coronary heart disease in primary care patients with chest pain: a clinical prediction score, BMC Medicine, 8, 9-,	Incorrect population - not limited to stable / suspected CAD-related chest pain.
George J, Jack D, Mackle G, Callaghan T.S, Wei L, et al. (2012) High sensitivity troponin T provides useful prognostic information in non-acute chest pain. QJM, 105, 159-166.	Incorrect population - patients pre-selected as intermediate/high probability using Diamond & Forrester.
Haasenritter J, Bosner S, Vaucher P, Herzig L, Heinzel-Gutenbrunner M, et al. (2012). Ruling out coronary heart disease in primary care: external validation of a clinical prediction rule. British Journal of General Practice, 62, e415-e421.	Incorrect study type and reference standard - prognostic study using 6 month delayed-type reference (only some patients underwent standard diagnostic testing).
Haybar H, Assareh A, Ghotbi Y, Torabizadeh M, Bozorgmanesh M. (2013) Incremental diagnostic value of circulating pentraxin in patients with intermediate risk of coronary artery disease. Heart, 99: 640-648.	Incorrect population - all patients were 'intermediate risk' as determined by prior stress testing.
Johnson K, Dowe D (2010) The detection of any coronary calcium outperforms Framingham risk score as a first step in screening for	Incorrect population - patients were previously

Reference	Reason for exclusion
coronary atherosclerosis. AJR American Journal of Roentgenology, 194, 1235-1243.	screened, underwent diagnostic testing or had non-chest pain symptoms.
Kreatsoulas C, Natarajan M, Khatun R, Velianou J, Anand S. (2010) Identifying women with severe angiographic coronary disease, Journal of Internal Medicine, 268, 66-74.	Incorrect population (30% had no angina-type symptoms) and outcomes (odds ratios only).
Lappe J, Grodin J, Wu Y, Bott-Silverman C, Cho L. (2015) Prevalence and prediction of obstructive coronary artery disease in patients referred for valvular heart surgery, American Journal of Cardiology, 116, 280-285.	Incorrect population (pre-operative valvular heart surgery).
Leem J, Koh E, Jang J, Woo C, Oh J, et al. (2015) Serum total bilirubin levels provide additive risk information over the Framingham Risk Score for identifying asymptomatic diabetic patients at higher risk for coronary artery stenosis. Diabetes & Metabolism Journal, 39, 414-423.	Incorrect population - asymptomatic patients with diabetes (chest pain / angina were exclusion criteria).
Lo M, Bonthala N, Holper E, Banks K, Murphy S, et al. (2013) A risk score for predicting coronary artery disease in women with angina pectoris and abnormal stress test finding. American Journal of Cardiology, 111, 781-785.	Incorrect population - females who had failed prior stress testing.
Mair J, Jaffe A (2014) Biomarker tests for risk assessment in coronary artery disease: will they change clinical practice? Molecular Diagnosis & Therapy, 18, 5-15.	Study type - general overview of clinical area (biomarkers for CAD risk assessment).
Munakata R, Otsuka T, Uchiyama S, Shimura T, Kurihara O, (2015) Volume elastic modulus of the brachial artery and coronary artery stenosis in patients with suspected stable coronary artery disease. Heart Vessels [ePub ahead of print].	Incorrect population - majority had prior stress testing.
Nucifora G, Schuijf J, van Werkhoven J, Jukema J, Djaberi R (2009) Prevalence of coronary artery disease across the Framingham risk categories: coronary artery calcium scoring and MSCT coronary angiography. Journal of Nuclear Cardiology, 16, 368-375.	Incorrect population - only patients who were asymptomatic / atypical angina / non-cardiac chest pain.
Okwuosa T, Mallikethi-Reddy S, Lloyd Jones D. (2014) Strategies for treating lipids for prevention: Risk stratification models with and without imaging. Best Practice and Research: Clinical Endocrinology and Metabolism 28, 295-307.	Incorrect study type – overview of clinical area.
Paredes S, Rocha T, de Carvalho P, Henriques J, Morais J, Ferreira J. (2015) Integration of different risk assessment tools to improve stratification of patients with coronary artery disease. Medical and Biological Engineering and Computing, 53, 1069-1083.	Incorrect study type - theoretical modelling applied to incorrect population data (patients with ACS).
Pietka I, Sakowicz A , Pietrucha T, Cichocka-Radwan A, Lelonek M. (2014) Usefulness of Reynolds Risk Score in men with stable angina, Central European Journal of Medicine, 9, 21-27.	Incorrect outcome data (odds ratios only).

Reference	Reason for exclusion
Rovai D, Neglia D, Lorenzoni V, Caselli C, Knuuti J, Underwood S (2015) EVINCI,Study,I. Limitations of chest pain categorization models to predict coronary artery disease. American Journal of Cardiology, 116, 504-507.	Incorrect outcome data (global chi-square only).
Sayin M, Cetiner M, Karabag T, Akpinar I, Sayin E, Kurcer, M, Dogan S, Aydin M (2014) Framingham risk score and severity of coronary artery disease, Herz, 39, 638-643.	Incorrect population - patients had undergone prior testing.
Van der Meer M, Backus B, van der Graaf Y, Cramer M, Appelman Y, et al. (2015) The diagnostic value of clinical symptoms in women and men presenting with chest pain at the emergency department, a prospective cohort study. PLos ONE, 10, e0116431-	Incorrect population – patients with non-stable chest pain presenting to emergency department.
Wessler B, Yh L, Kramer W, Cangelosi M, Raman G, Lutz J, Kent D. (2015) Clinical prediction models for cardiovascular disease: Tufts predictive analytics and comparative effectiveness clinical prediction model database, Circulation: Cardiovascular Quality and Outcomes.8 368-375.	Incorrect study type - describes a database of different types of clinical predication model for cardiovascular disease, but no data on accuracy of individual models is given.
Yayan J (2014) Weak prediction power of the Framingham Risk Score for coronary artery disease in nonagenarians, PLoS ONE, 9: e113044.	Incorrect population and study type - retrospective case-control study of patients over 90yrs.
Yeh J-S, Lin F-Y, Kao Y-T, Tsao N-W, Hsieh M-H, et al. (2013) Diagnostic value of coronary artery plaque detected on computed tomography coronary artery angiography in healthy adults with zero to low calcium scores. Journal of Experimental and Clinical Medicine, 5: 222-226.	Incorrect population - asymptomatic healthy adults who had undergone prior calcium testing and were having CTCA as part of general screening.

Appendix G: Evidence tables

G.1 Review question 1

G.1.1 Computer tomography cardiac angiography (CTCA)

Table 19 Budoff 2008

Bibliographic reference	**Author: Budoff et al** **Diagnostic Performance of 64-Multidetector Row Coronary Computed Tomographic Angiography for Evaluation of Coronary Artery Stenosis in Individuals Without Known Coronary Artery Disease. Results from the prospective multicentre ACCURACY (assessment by Coronary Computed Tomographic angiography of Individuals Undergoing Invasive Coronary Angiography) Trial.** **Year: 2008**
Study type	Cross-sectional
Aim	To evaluate the diagnostic accuracy of electrocardiographically gated 64-multidetector row coronary computed tomography angiography (CCTA) in individuals without known coronary artery disease (CAD).
Patient characteristics	Prospectively evaluated patients with chest pain being clinically referred for non-emergent invasive coronary invasive coronary angiography, screened for below criteria. **Inclusion** ≥18 years Typical or atypical chest pain Being referred for non-emergent ICA **Exclusion** Known allergy to contract Baseline renal insufficiency Irregular heart rhythm Resting hear rate >100bpm Resting systolic BP <100mmHG Contraindication to beta-blocker, calcium-channel blocker or nitroglycerin

	Pregnancy Known history of CAD (prior MI, percutaneous transluminal coronary angioplasty or intracoronary stent or coronary artery bypass surgery). **Patient Characteristics, mean (SD) or n (%)** Age 57 (10) Male 136 (59%) BMI 31.4kg/m^2 (6.2) Diabetes 55 (24%) Hypertension 154 (67%) Hyperlipidaemia 157 (68.3%) Family history CAD 169 (74%) Smoker 128 (56%) Obesity 90 (39%) Sedentary lifestyle 78 (34%)
Number of patients	230 (245 originally enrolled but 15 either did not complete or opted out of either CCTA or ICA and were excluded)
Index test	**CTCA** All scans were 64-multidetector scanners and patients were in sinus rhythm at the time of the scan. Those with HR>65bmp were given oral beta-blockers. All patients were scanned regardless of whether target HR was achieved. 10-20ml contrast was administered after 0.4mg nitro-glycerine sublingually. 80ml iodinated contrast was injected during CCTA acquisition. Retrospective ECG gated helical contrast enhanced CCTA was performed with scan initiation 20mm above level of the left main artery to 20mm below the inferior myocardial apex. Radiation reduction algorithms using ECG modulation were used which reduce radiation exposure (mA) during systole and end-systole. Once complete, multiphasic reconstruction of the CCTA scan was performed. Images were interpreted separately by 3 separate readers blinded to patient data and other test results, using a 3-D image analysis workstation. Readers were permitted to use any or all of the reconstruction algorithms, including 2-D and 3-D maximal intensity projection, multi-planar reform, cross-sectional analysis and volume-rendered technique. Arteries were scored using a 15-segment AHA coronary artery classification. For each segment, visual estimations of luminal stenosis were recorded as: No stenosis, 1-29%, 30-49%, 50-69%, 70-99% and 100% stenosis.

	For artery segments considered to be non-evaluable, stenosis severity was assigned based on the outcome of the most adjacent proximal and identifiable segment. Degree of coronary artery stenosis identified by CCTA was assigned based on consensus identified narrowing of the artery lumen at thresholds of 50% or 70% stenosis.
Reference standard (or Gold standard)	**Coronary angiography** Performed using standard trans-femoral arterial catherisation. Minimum 8 projections were obtained. All images were interpreted by an independent reader blinded to all patient data and test results. AHA tree model was used and were judged at having significant stenosis at 2 levels (≥50% and ≥70% luminal narrowing).
Time between testing & treatment	Not specified
Length of follow-up	Not specified
Location	16 centres in the US.
Diagnostic accuracy measures (2 x 2 table)	**TP FP FN TN SENS% SPEC%** CTCA 50% 54 29 3 144* 95.0 83.0 CTCA 70% 30 34 2 164* 94.0 83.0 *Back calculations done by reviewer Side Effects/Adverse Events: 1 patient had a coronary artery dissection during ICA.
Source of funding	Not mentioned
Comments	**Study Limitations** 1A – Prospective but does not specify consecutive enrolment UNCLEAR 1B – HIGH – patients were recruited on the basis of referral for coronary angiography (higher prevalence population) 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – UNCLEAR the time between tests and the study duration were not specified.

Table 20 Cademartiri 2007

Bibliographic reference	**Author: Cademartiri et al** **Diagnostic accuracy of 64-slice computed tomography coronary angiography in patients with low-to-intermediate risk** **Year: 2007**
Study type	Cross-sectional
Aim	To evaluate the diagnostic accuracy of 64-slice computed tomography coronary angiography (MSCT-CA) for detecting significant stenosis (≥50% lumen reduction) in a population of patients at low to intermediate risk.
Patient characteristics	Patients scheduled for coronary angiography were recruited with a low-to intermediate cardiovascular risk, atypical (26/72) or typical (exertional angina) (46/72) chest pain and positive, doubtful or inconclusive stress ECG. **Inclusion** Sinus rhythm No history of percutaneous angioplasty or surgical bypass grafting Able to hold breath for at least 12s **Exclusions** Absolute contraindications to IV contrast material (known allergy, thyroid disorders or renal insufficiency). **Patient Characteristics** Men/women 38/34 Age (mean(SD)) 53.9 (8.0) **n(%)** Hypertension 4 (5.6) Hypercholesterolaemia 18 (25.0) Diabetes 0 Smoking 9 (12.5) Family history of ACS 12 (16.7) Obesity (BMI ≥30kg/m^2) 22 (30.6) Distribution of atherosclerosis **n(%)** No stenosis 51 (71) Single-vessel disease 13 (18) Two-vessel disease 6(8)

	Three-vessel disease 1(1) Multi-vessel disease 7 (10)
Number of patients	72
Index test	**64 slice CT (MSCTA)** Patients with HR >65bpm were given 100mg of metoprolol tartrate 45 mins prior. 32x2 slices per rotation. Slice thickness 3mm. 100ml iodinated contrast material at 5ml/s via an automatic injector in an antecubital vein. Bolus tracking technique was used to optimise opacification of the arteries and data acquired at a single acquisition. ECG based reconstructions were performed. All scans were independently analysed by two observers blinded to coronary angiography results. All visualised segments were considered assessable for the presence of significant stenosis. Image quality was assessed as good, adequate or poor.
Reference standard (or Gold standard)	**Coronary angiography** A single observer blinded to MSCTA results identified coronary segments using 17 segment classification modified from AHA classifications. All segments were included. <50%, normal or with wall irregularities were classed as non-significantly stenotic. ≥50% lumen reduction was classed as significantly stenotic.
Time between testing & treatment	Within 2 weeks
Length of follow-up	Duration March 2005 and March 2006
Location	Italy
Diagnostic accuracy measures (2 x 2 table)	Per patient analysis: **TP FP FN TN SENS% SPEC%** 64slice CT 20 1 0 51 100.0 98.1 No scans were excluded due to scan failure or inadequate image quality. No segment was excluded from analysis due to size. No procedural problems or adverse events reported.
Source of funding	Not mentioned
	Study Limitations

Comments	1A – LOW 1B – HIGH only included people with low-intermediate cardiovascular risk. Unclear if inclusion was based on referral for coronary angiography. 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – LOW

Table 21 Cademartiri 2008

Bibliographic reference	**Author: Cardemartiri et al** **64-Slice computed tomography coronary angiography: diagnostic accuracy in the real world** **Year: 2008**
Study type	Cross sectional
Aim	To evaluate the diagnostic accuracy of 64-slice CTCA compared to conventional coronary angiography for the detection of significant coronary artery stenosis in the real clinical world.
Patient characteristics	**Inclusion** - Suspected coronary artery disease (atypical chest pain and stable angina pectoris) - In sinus rhythm without history of percutaneous angioplasty or bypass surgery who were able to breath hold for at least 12 seconds. **Exclusion** - Acute coronary syndrome - Absolute contraindications for IV administration of iodine containing contrast (known allergy, kidney failure, or thyroid disorder). **Other characteristics** Age in years, mean (SD): 63.4+/- 10.2years. Gender: 92 men, 52 women. Symptoms: Stable angina 32 (22%) Atypical chest pain 85 (59%) Silent ischaemia 28 (19%) Cardiovascular risk factors: Hypertension 76 (52%)

Bibliographic reference	**Author: Cardemartiri et al** **64-Slice computed tomography coronary angiography: diagnostic accuracy in the real world** **Year: 2008**
	Hypercholesterolemia 58 (33%) Diabetes 56 (39%) Cigarette smoking 19 (13%) Family history 61 (42%) Obesity (BMI≥30kg/m^2) 5 (3%) Calcium score (Agatston Score): mean ±SD (range) 235.3±392.8 (0-2,265) 75 patients had an ECG stress test. Positive results in 21 patients, negative in 54. Tests was equivocal or the test could not be performed in the remaining 59.
Number of patients	145
Index test	Patient preparation – those with HR >65bpm without specific contraindications received 5mg IV dose of beta-blockers (atenolol). In addition in the absence of contraindications, patients received 5mg sublingual dose of nitrate. **64-slice computed tomography coronary angiography (CTCA)** – corresponds to test 2a in review protocol - CT scanner: Sensation 64, Siemens - Prior to the angiography scan a preliminary scan was performed in all patients without the IV administration of iodinated contrast material with the aim of quantifying coronary calcification - Scan data obtained during a single breath hold of 10-12s - Scans analysed by an observer with 5yrs experience and UNAWARE of CA findings. - Coronary segments analysed using AHA modified 17-segment classification - Classification of segments were **(i) not significantly stenotic (normal or with wall irregularities or noncritical stenosis <50%) or (ii) significantly stenotic (stenosis ≥50%).**
Reference standard (or Gold standard)	**Conventional coronary angiography (CCA)** - CCA was performed 2 weeks after the CTCA with a conventional technique. - Operator was not blinded to the data and images from the CTCA scan. - Coronary segments were identified by the operator using visual evaluation according to the AHA modified 17-segment classification. All segments without diameter limits were included. - Classification of segments were **(i) not significantly stenotic (normal or with wall irregularities or noncritical stenosis <70%) or (ii) significantly stenotic (stenosis ≥70%) using conventional classifications and guidelines.**

<table>
<tr><td>Bibliographic reference</td><td>Author: Cardemartiri et al
64-Slice computed tomography coronary angiography: diagnostic accuracy in the real world
Year: 2008</td></tr>
<tr><td></td><td>-</td></tr>
<tr><td>Time between testing & treatment</td><td>2 weeks after index test.</td></tr>
<tr><td>Length of follow-up</td><td>Study dates January – June 2005</td></tr>
<tr><td>Location</td><td>Italy</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Accuracy of CTCA to detect significant stenosis defined as ≥50% for CTCA and ≥70% for CA. (patient based analysis reported only)

Analysis based on all 134 patients (11 patients results were excluded due to poor scan quality).

TP 82; TN:29; FP: 21; FN: 2*
<table><tr><td>Sensitivity % (95%CI):</td><td>97.6 (91-99)</td></tr><tr><td>Specificity % (95%CI):</td><td>79.6 (70-86)</td></tr><tr><td>PPV % (95%CI):</td><td>58.0 (43-71)</td></tr><tr><td>NPV % (95%CI):</td><td>93.5 (78-99)</td></tr><tr><td>LR+ (95%CI):</td><td>2.32 (1.67-3.22)</td></tr><tr><td>LR- (95%CI):</td><td>0.041 (0.01-0.16)</td></tr></table>
Analysis based on HR<70bm (107 patients)
TP69; TN 19; FP:18; FN:1*
<table><tr><td>Sensitivity % (95%CI):</td><td>98.6 (92-99)</td></tr><tr><td>Specificity % (95%CI):</td><td>79.3 (69-87)</td></tr><tr><td>PPV % (95%CI):</td><td>51.4 (34-68)</td></tr><tr><td>NPV % (95%CI):</td><td>95.0 (75-99)</td></tr><tr><td>LR+ (95%CI):</td><td>2.02 (1.45-2.82)</td></tr><tr><td>LR- (95%CI):</td><td>0.027 (0.003-0.19)</td></tr></table>
Analysis based on HR<65bmp (89 patients)
TP 59; TN:14; FP: 15; FN: 1*</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Author: Cardemartiri et al
64-Slice computed tomography coronary angiography: diagnostic accuracy in the real world
Year: 2008</td></tr>
<tr><td></td><td>
<table>
<tr><td>Sensitivity % (95%CI):</td><td>98.3 (91-99)</td></tr>
<tr><td>Specificity % (95%CI):</td><td>79.7 (68-99)</td></tr>
<tr><td>PPV % (95%CI):</td><td>48.3 (29-67)</td></tr>
<tr><td>NPV % (95%CI):</td><td>93.3 (68-99)</td></tr>
<tr><td>LR+ (95%CI):</td><td>1.9 (1.33-2.7)</td></tr>
<tr><td>LR- (95%CI):</td><td>0.034 (0.004-0.24)</td></tr>
</table>

Analysis based on HR>70bpm Ca score ≤10 (41 patients)
TP 29; TN:8; FP:4; FN:0*
<table>
<tr><td>Sensitivity % (95%CI):</td><td>100 (88-100)</td></tr>
<tr><td>Specificity % (95%CI):</td><td>87.9 (71-96)</td></tr>
<tr><td>PPV % (95%CI):</td><td>66.7 (34-90)</td></tr>
<tr><td>NPV % (95%CI):</td><td>100 (63-100)</td></tr>
<tr><td>LR+ (95%CI):</td><td>2.99 (1.34-6.67)</td></tr>
<tr><td>LR- (95%CI):</td><td>0 (0-NaN)</td></tr>
</table>

No mention of any adverse events.</td></tr>
<tr><td>Source of funding</td><td>Supported by the National Centre for Competence in Research, Computer Aided and Image Guided Medical interventions of the Swiss National Science Foundation</td></tr>
<tr><td>Comments</td><td>Statistical methods
- Statistics for diagnostic accuracy of CTCA on a segment-based, a vessel-based and on a patient-based analysis were calculated. For the latter, of the total patients (n=134), 84 (62.2%) displayed at least one at least one significant stenosis
- Values were calculated for entire population for each analysis level
- CIs calculated with binomial expansion.

Study limitations (as assessed using QUADAS-2 checklist)
1A. No evidence of consecutive enrolment. UNCLEAR</td></tr>
</table>

Bibliographic reference	**Author: Cardemartiri et al** **64-Slice computed tomography coronary angiography: diagnostic accuracy in the real world** **Year: 2008**
	1B. Suspected CAD with breakdown of numbers with chest pain. Unclear if patients recruited on basis of referral for coronary angiography or not. UNCLEAR 2A. Unclear why significant stenosis levels were different according to index and reference test. 2B. LOW 3A. Reference standard results interpreted with knowledge of CTCA results. HIGH 3B. LOW 4. LOW

Table 22 Carrascosa 2010

Bibliographic reference	**Author: Carrascosa et al** **Accuracy of low-dose prospectively gated axial coronary CT angiography for the assessment of coronary artery stenosis in patients with stable heart rate** **Year: 2010**
Study type	Cross-sectional
Aim	To assess diagnostic accuracy of a low dose, prospectively gated axial cardiac CT angiography protocol for the evaluation of patients with suspected coronary artery disease (CAD).
Patient characteristics	50 consecutive patients (out of an initially screened 59) referred for diagnostic invasive coronary angiography (ICA) with a stable HR <60BPM after beta blocker administration were prospectively enrolled in a single centre study. **Exclusion criteria** <18yrs old Weight >100kg Pregnancy Pacemaker Allergy to contrast dye Unstable angina or presence of congestive heart failure. 9 patients were excluded due to previous coronary bypass surgery (n=3), PCI within 3 months (n=2) or elevated serum creatinine (n=2).

	Patient Characteristics Age (y) mean (SD), (range). 62.4 (12.5) (34-88) Female/male, n 17/33 BMI kg/m^2 mean (SD), (range). 27.7 (3.4) (21.1-40.1) *Reasons for CCTA n(%)* Chest pain 41 (82) Suspected CAD 9 (18) *Coronary risk factors n(%)* Hypertension 33 (66) Dyslipidaemia 27 (54) Smoker 7 (14) Diabetes mellitus 4 (8) Obese (BMI >30kg/m^2) 11 (22) Family history of CAD 12 (24) *Pre-test probability of significant CAD n(%)* High (>70%) 31 (62) Intermediate (30-70%) 13 (26) Low (<30%) 6 (12) Pre-scan hr/BPM mean (SD) 0.84 (0.2)
Number of patients	50
Index test	**64-row multi-detector CT scanner (Brilliance, Philips Healthcare).** Pre-scan HR>60bpm given 50-100mg metoprolol orally (night before and 1hr before). Propranolol was also given if still >60bpm at time of examination. All patients received 2.5mg isosorbide dinitrate sublingually 2 mins prior to scan. Similar contrast injection (iobitridol 350mg/mL IV at 5-6mL/s followed by saline flush into antecubital vein) protocol used for axial and helical CT acquisitions, adjusted for body weight. Prospectively gated axial scanning mode triggered at 75% of cardiac cycle. If this was determined to be non diagnostic due to poor image quality a standard retrospectively gated helical examination without ECG gated tube current modulation was performed immediately after the axial scan. Dedicated cardiac adaptive multicycle algorithms were used. Both axial and helical CT data were reconstructed with standard convolution Kernel and overlapping slice thickness of 0.9mm. A modified 17-segment AHA model was used. All segments with diameter of ≥1.5mm at origin were included. Two observers independently assessed the image quality with a 4-point scale. Evaluable segments were

	assessed by both readers for presence or absence of significant coronary stenosis, determined as diameter narrowing >50%. Non evaluable segments were considered as positive findings for diagnostic purposes.
Reference standard (or Gold standard)	**Coronary angiography** Conventional CA performed using standard technique. The minimum lumen diameter and both a proximal and distal normal reference diameters were determined for each segment to assess the amount of luminal narrowing. This value was reported percentage of diameter stenosis. Once the two view results were averaged a diameter stenosis of >50% was defined as significant coronary stenosis.
Time between testing & treatment	Mean (SD) 14 (4) days (range, 7-22 days).
Length of follow-up	Duration of study July to December 2008.
Location	Buenos Aires, Argentina.
Diagnostic accuracy measures (2 x 2 table)	Prospectively gated was successfully performed in 46/50 patients. Patient based analysis **TP FP FN TN SENS% SPEC%** Evaluable segments (n=47) 26 3 0 18 100 86 All segments* (n=50) 26 6 0 18 100 75 *(censoring non-evaluable segments as positive) No adverse reactions to contrast or premeds was observed.
Source of funding	One of the authors is an employee of Philips Healthcare. Funding is not mentioned.
Comments	**Study Limitations** 1A – LOW 1B – HIGH – patients recruited on basis of referral for coronary angiography (high prevalence population) 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – LOW

Table 23 Chen 2011

Bibliographic reference	**Author: Chen et al** **The effect of calcium score on the diagnostic accuracy of coronary computed tomography angiography** **Year: 2011**
Study type	Cross sectional
Aim	To assess the effect of coronary calcium score (CS) on the diagnostic accuracy of detecting coronary artery disease using multi-detector CT angiography (MDCTA) (64-slice) compared to coronary angiography.
Patient characteristics	**Inclusion** 119 consecutive, symptomatic patients with chest pain or chest discomfort referred for cardiac CT including CS and coronary angiography. **Exclusion** Contraindications to CTA (allergy to iodinated contrast material or beta-blockers, renal insufficiency, HR >100bpm, AF or arrhythmia and haemodynamic instability. 6 patients were excluded to prolonged time interval (>90 days) between MDCTA and CA. **Other** Age (y) mean 62.3 (range 37-87) Males 92/113 BMI mean 25.5kg/m^2 (range 17.6-35.4) Calcium Scores (n) 0 = 18 1 to 100 = 18 101-400 = 27 >400 = 50.
Number of patients	113
Index test	**Preparation** Oral dose of 10-40mg propranolol was administered 30-60mins prior to the scan if HR ≥65bpm. Alternatively 500µg/kg esmolol was administered under ECG monitoring. 5mins prior, sublingual nitro-glycerine (0.3mg) was administered to optimize visualization of small coronary vessels. **MDCTA** All patients underwent 64-row MDCT scanner (Aquilion 64, Toshiba).

Bibliographic reference	**Author: Chen et al** **The effect of calcium score on the diagnostic accuracy of coronary computed tomography angiography** **Year: 2011**
	Retrospective ECG gating and timing bolus were used to determine scan start times. Weight/gender radiation dose of 12-15mSv were given with a maximum dose of 20mSv for the combination of calcium scoring and coronary CTA exam. For vascular enhancement, a bolus of contrast (80-100mls at 4-5ml/s) was administered IV via antecubital vein followed by saline chasing. Multiple temporal phases of the cardiac cycle were set for ECG gated retrospective reconstructions. Datasets with least residual motion were selected for evaluation. **Calcium scoring** was performed with the use of prospective ECG gating. Assessment involved use of Vitrea software/workstation. Agatston scoring system was used (see above). Two radiologists blinded to reference standard results independently evaluated all calcium scoring and CTA images. Arteries were divided into segments per AHA classification. All coronary arteries greater than 2mm in diameter were evaluated for presence of significant (≥50%) diameter reduction/stenosis.
Reference standard (or Gold standard)	**Coronary Angiography** 2 experienced cardiologists scored all coronary segments using quantitative CCA algorithm (Integris BH3000). Severity of stenosis was quantified in two orthogonal views. Significant stenosis was defined as luminal diameter reduction ≥50%.
Time between testing & treatment	Within 90 days (mean 9.6 days)
Length of follow-up	Duration of study - 2 years and 9 months.
Location	Taiwan
Diagnostic accuracy measures (2 x 2 table)	**Results are reported for overall CTCA only as calcium scoring was not evaluated as a diagnostic test.** **CTCA Overall (Index test 2)** **TP FN FP TP * Sens% Spec%** CTCA Overall 76 7 4 26* 95.0 78.8 No mention of any adverse events.

Bibliographic reference	**Author: Chen et al** **The effect of calcium score on the diagnostic accuracy of coronary computed tomography angiography** **Year: 2011**
Source of funding	Supported by a grant from the National Science Council
Comments	**Study limitations:** 1a. LOW 1b. All patients had chest pain however patients recruited on basis of referral for coronary angiography. HIGH 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

*= calculated by reviewer

Table 24 Donati 2011

Bibliographic reference	**Author: Donati et al** **Coronary artery disease: Which degree of coronary artery stenosis is indicative of ischemia?** **Year: 2011**
Study type	Cross sectional
Aim	To prospectively determine the best cut-off value of stenosis degree for low-dose computed tomography coronary angiography (CTCA) to predict the hemodynamic significance of coronary artery stenoses compared to catheter angiography (CA) using a cardiac magnetic resonance based approach as standard of reference.
Patient characteristics	**Inclusion** Patients with suspected CAD undergoing elective CA (all patients had stable angina or atypical chest pain). **Exclusion** Previous percutaneous coronary intervention or coronary artery bypass surgery. *Exclusion for low dose CTCA* Impaired renal function, known hypersensitivity to contrast medium and arrhythmia. Scanning with prospective ECG triggering was not performed in patients with heart rates >70bpm. *Excluded from CMR* if presented with any contraindications to adenosine (second or third degree AV block, sick sinus syndrome, symptomatic bradycardia, severe asthma or obstructive pulmonary disease) or to MR (implanted electronic devices, metallic foreign bodies in the eye, severe claustrophobia and others according to

Bibliographic reference	Author: Donati et al Coronary artery disease: Which degree of coronary artery stenosis is indicative of ischemia? Year: 2011
	manufacturer's recommendations. **Other n (%)** Men 46 (88), Age, years (mean, SD) 64 ±10 (range 41-77) BMI kg/m^2 (mean, SD) 24 ±8 BMI >25 kg/m^2 32 (62) **Cardiovascular risk factors** Hypertension 37 (71) Nicotine abuse 16 (31) Hyperlipidaemia 36 (69) Diabetes 10 (19) Family history 8 (15) **Symptoms** Atypical angina 9 (17) Typical angina 24 (46) **Pre-test probability of CAD (as determined by Diamond and Forrester 1979 criteria based on age, gender and symptomatic status. Cut offs <13.4% = low, >87.2% = High. All those between these values = intermediate probability)** Low 20 (39) Intermediate 10 (19) High 22 (42)
Number of patients	70 patients screened. After exclusions 52 patients were included.
Index test	**CTCA with 64-Slice dual source CT scanner (Somatom Definition, Siemens)** Performed using prospective ECG triggering. 2.5mg dose of sublingual isosorbide dinitrate was given to all patients. Iopromide contrast used (1mL/kg body weight) (dual head power injector) controlled by bolus-tracking. Images were reconstructed with a slice thickness of 0.6mm and all were transferred to an external workstation. Low-dose CTCA analysis was performed by two independent radiologists blinded to all patient data. All segments with diameter ≥1mm at origin were included. Vessel segments distal to occlusions were excluded from analysis. Segments were defined according to AHA scheme. First each segment was rated for image quality

Bibliographic reference	**Author: Donati et al** **Coronary artery disease: Which degree of coronary artery stenosis is indicative of ischemia?** **Year: 2011**
	as diagnostic or non-diagnostic. Grading of stenosis was made quantitatively using an electronic calliper tool and categorized into a decimal scale in 10% steps from 0-100% diameter stenosis. **NB Data for CMR is not reported here as it was not compared to coronary angiography as the reference standard.**
Reference standard (or Gold standard)	**Coronary angiography** Evaluated by an experienced observer blinded to patient data. Artery division as above. Automated edge-detection system was used. Significant coronary stenosis was defined as narrowing of the artery of >50%.
Time between testing & treatment	Unclear (CMR and CTCA were performed on same day).
Length of follow-up	Study duration not specified
Location	Unclear Switzerland or USA
Diagnostic accuracy measures (2 x 2 table)	**Low dose CTCA vs CA** TP 32, FP 2, FN 0, TN 18* Sensitivity %(95%CI) 100 (89-100) Specificity %(95%CI) 90 (68-99) *calculated by reviewer Of a total of 832 coronary segments in 156 main coronary arteries were analysed. Of these, 812 (98%) segments were included into the analysis. Image quality was diagnostic in 50/52 patients. Analysis was complete on all 52 patients (unclear how treated). No mention of any adverse events.
Source of funding	Not mentioned
Comments	**Study limitations:** 1A – Prospective but does not specifically state consecutive enrolment. UNCLEAR 1B – Suspected CAD population with typical angina or atypical chest pain. Patients recruited based on referral for coronary angiography. HIGH. 2A – LOW 2B – LOW 3A – LOW 3B – LOW

Bibliographic reference	**Author: Donati et al** **Coronary artery disease: Which degree of coronary artery stenosis is indicative of ischemia?** **Year: 2011**
	4 – Unclear interval between tests. Unclear how the 2 non diagnostic image quality results were classified. Overall UNCLEAR

Table 25 Herzog 2007

Bibliographic reference	**Author: Herzog et al** **Does Two-Segment Image Reconstruction at 64-Section CT Coronary Angiography Improve Image Quality and Diagnostic Accuracy?** **Year: 2007**
Study type	Cross-sectional
Aim	To evaluate the effect of single-versus two segment image reconstruction on image quality and diagnostic accuracy at 64-Section multi-detector CT coronary angiography by using conventional coronary angiography as the reference standard.
Patient characteristics	**Inclusion** Referred to department of Cardiology between time period below for evaluation of suspected CAD. Stable condition (stable symptoms, vital signs and results of monitored ECG). Patients with contraindications to β-blockers were eligible for participation in the study but no β-blockers were used in such individuals. **Exclusion** Unstable symptoms, vital signs or ECG results Creatinine level of >2.0mg/dL Potential pregnancy Known allergy to iodinated contrast material. **Other characteristics** Men 22, Women 18. Age, mean (SD) 61 (8). Range 49-73).
Number of patients	40 consecutive
Index test	**CTCA (protocol index test 2a) performed with 64-section scanner, Somatom Sensation 64.** Patients with average heart rates (>65bpm) (n=32) received up to two IV injections of 5mg of metoprolol

	immediately before the exam. Scans were acquired with simultaneous recording of patient's ECG signal to allow image reconstruction (on basis of retrospective ECG gating). Performed by one author. Each data set was reconstructed twice – once using a single-segment and once using a two-segment adaptive cardiac volume reconstruction algorithm (provided within the standard cardiac software package of CT scanner). Both data sets were independently analysed by two experienced cardiovascular radiologists who were unaware of patient data including coronary angiography results. Coronary artery stenosis was measured using a semi-automated stenosis measuring tool classified as No stenosis 49% or less Stenosis 50-69%, Stenosis 70-99%, or total occlusion
Reference standard (or Gold standard)	**Coronary Angiography** Results obtained using Judkin technique and three experienced cardiologists reached consensus on findings. Quantitative grading of stenosis was performed using a stenosis grading tool with automatic distance and scale calibration.
Time between testing & treatment	Not reported
Length of follow-up	Study period October 2004 and July 2005
Location	USA
Diagnostic accuracy measures (2 x 2 table)	64-Section CT Angiography for grading stenosis (Protocol test 2a). Per patient analysis only reported. **Per-patient basis** **61–87 beats per minute (n= 40) (TP 16, TN 21, FP 0, FN 3)*** **Single segment reconstruction** / **Two-segment reconstruction** Accuracy 92.5 (79.6, 98.4) [37/40] / 97.5 (86.8, 99.9) [39/40] Sensitivity 100 (79.4, 100) [16/16] / 100 (79.4, 100) [16/16] Specificity 87.5 (67.6, 97.3) [21/24] / 95.8 (78.9, 99.9) [23/24] Positive predictive value 84.2 (60.2, 96.6) [16/19] / 94.1 (71.3, 99.8) [16/17] Negative predictive value 100 (83.9, 100) [21/21] / 100 (85.2, 100) [23/23] **80–82 beats per minute* (n= 6) (TP 4, TN 2, FP 0, FN 0)*** Accuracy 100 (54.1, 100) [6/6] / 100 (54.1, 100) [6/6] Sensitivity 100 (39.8, 100) [4/4] / 100 (39.8, 100) [4/4]

	Specificity	100 (15.8, 100) [2/2]	100 (15.8, 100) [2/2]
	Positive predictive value	100 (39.8, 100) [4/4]	100 (39.8, 100) [4/4]
	Negative predictive value	100 (15.8, 100) [2/2]	100 (15.8, 100) [2/2]
	No mention of any adverse events.		
Source of funding	Study supported by research grants provided by Siemens Medical Solutions, Bracco Diagnostics and Medrad.. One author is a medical consultant to Siemens and Bracco, one is a medical consultant to Bracco and another is an employee of Siemens. The authors who are not employees or consultants for either company providing support had control of the data and information submitted for publication.		
Comments	**Statistical evaluation** Accuracy, sensitivity, specificity and positive and negative predictive values were calculated for detection of stenosis of >50%. **Study Limitations** 1A – LOW 1B – UNCLEAR (suspected CAD population – no reports of chest pain numbers). Unclear if patients recruited on basis of referral for coronary angiography. 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – UNCLEAR interval between tests. Overall LOW		

Table 26 Herzog 2008

Bibliographic reference	**Author: Herzog et al** **Accuracy of low-dose computed tomography coronary angiography using prospective electrocardiogram-triggering: first clinical experience** **Year: 2008**
Study type	Cross-sectional
Aim	To evaluate the accuracy of low-dose computed tomography coronary angiography (CTCA) using prospective ECG-triggering for the assessment of coronary artery disease (CAD).
Patient characteristics	Of 112 consecutive patients referred for coronary angiography , 70 patients were deemed to ineligible due to known significant CAD. 4 of the remaining 42 patients refused to give consent and 8 were excluded due to allergy to iodinated contrast (n=1), nephropathy (n=4), non-sinus rhythm (n=3).

Number of patients	30 patients referred for coronary angiography for Dyspnoea (n=3) typical angina pectoris (n=9) atypical chest pain (n=10) pathological exercise test or ECG (n=11). **Patient characteristics** Mean age (SD) 59 (10) Female/male 11/19 Mean BMI kg/m^2 (SD) 27.0 (2.9)
Index test	**MSCTA (64 slice Lightspeed CT scanner)** All patients received 2.5mg isosorbide dintrate sublingually 2 mins prior to scan. IV metoprolol was given to achieve HR <65bpm. 80mL iodixanol was administered at 5mL/s followed by 50mL saline injected into antecubital vein. Bolus tracking was performed with a region of interest placed in the ascending aorta and image acquisition was started 4s after signal density reached ~120 Hounsfield units. Prospective ECG triggering was performed. Images were reconstructed with slice thickness of 0.6mm. Coronary arteries were segmented as suggested by the AHA. (16-segments). Two readers assessed overall image quality on a four point scale (scores 1-3 were considered diagnostic, score 4 non diagnostic) and assessed all arteries for presence of haemodynamically significant stenoses, defined as narrowing of the luminal diameter ≥50%.
Reference standard (or Gold standard)	**Coronary angiography** Performed using standard techniques by an experienced observer blinded to CTCA results. Images were assessed using the same segment model and were assessed with automated edge-detection system. Coronary arteries with diameter of at least 1.5mm were included and those vessels distal to complete occlusions. Each vessel was scored as being normal or significantly stenosed (defined as diameter reduction of ≥50%).
Time between testing & treatment	Not specified
Length of follow-up	Study duration not specified
Location	Zurich, Switzerland
Diagnostic accuracy measures (2 x 2 table)	Patient based analysis **TP FP FN TN SENS% SPEC%** MSCTA 18 2 0 10 100.0 83.3

	16 segments in 4/30 patients were non diagnostic and considered false positive. 2/4 patients were re-categorised as true positives as they had correctly identified lesions in other segments. No mention of any adverse events.
Source of funding	Supported by a grant from the Swiss National Science Foundation and by the Zurich Centre for Integrative Human Physiology.
Comments	**Study Limitations** 1A – LOW 1B – Population suspected CAD with breakdown including numbers with typical and atypical angina. Patients recruited on basis of referral for coronary angiography HIGH. 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – Timing between tests not specified. UNCLEAR.

Table 27 Herzog 2009

Bibliographic reference	**Author: Herzog et al** **First head-to-head comparison of effective radiation dose from low-dose 64-slice CT with prospective ECG-triggering versus invasive coronary angiography.** **Year: 2009**
Study type	Cross-sectional
Aim	To compare effective radiation dose of low-dose 64-slice CTCA using prospective ECG-triggering versus diagnostic invasive coronary angiography (CA).
Patient characteristics	74 patients were consecutively screened for known CAD. 9 refused to consent. Of the 65 enrolled patients 14 were deemed ineligible due to renal insufficiency (n=8), allergy to iodinated contrast (n=3), non-sinus rhythm (n=12) Pre-test probabilities were estimated using the Duke clinical score. All patients were referred for elective invasive CA because of suspected CAD with the following symptoms: Dyspnoea (n=9) Typical angina pectoris (n=7)

	Atypical chest pain (n=19) Pathological exercise test or ECG (n=14) **Other patient characteristics** Age, y (mean (SD) 62 (8.4) (range 42-82) Male/Female 29/13. On beta blockers n=13 BMI (mean (SD)) kg/m^2 26.9 (4.4) (RANGE 18.6-44.9)
Number of patients	42 (different to patients included in previously reported studies including Herzog et al 2008)
Index test	**CTCA with prospective ECG triggering using Lightspeed 64 slice CT scanner.** All patients received 2.5mg isosorbide dinitrate sublingually 2 mins prior to scan. IV metoprolol was given if necessary to achieve HR <65bpm. For CTCA 80mls of iodixanol was given at 5/ml/s followed by 50ml saline via antecubital vein. Bolus tracking performed with region of interest in ascending aorta. Image acquisition 4 seconds after signal density reached threshold of ~120 Hounsfield units. Images were reconstructed with a slice thickness of 0.6mm and transferred to an external workstation. Coronary arteries were segmented as per AHA 16 segment suggestion. All segments with diameter of min 1.5mm at their origin were included. All non-evaluable segments classified the whole vessel as not evaluative which was censored as positive and included in the final analysis. Two experienced readers assessed all coronary vessels for presence of haemodynamically significant stenoses, defined as narrowing of the coronary luminal diameter ≥50%.
Reference standard (or Gold standard)	**Coronary Angiography** Performed via femoral artery using routine procedure. An experienced observer blinded to results from CTCA evaluated the angiograms. Each vessel was scored as being normal or significantly stenosed (defined as diameter reduction of ≥50%) .
Time between testing & treatment	Same day
Length of follow-up	Study duration not specified
Location	Zurich, Switzerland.
Diagnostic accuracy measures (2 x 2 table)	Patient based analysis **TP FP FN TN SENS% SPEC%** CTCA Per patient (overall) 23 2 0 17 100.0 89.5 low pre-test probability 3 1 0 3 100.0 75.0 Intermediate pre-test probability 13 0 0 9 100.0 100.0

	High pre-test probability	7	1	0	5	100.0	83.3
	551/567 segments were considered diagnostic, thus 16 segments (2.8%) were considered non-diagnostic and considered as positive. No mention of any adverse events.						
Source of funding	Supported by a grant from the Swiss National Science Foundation and by the Zurich Centre for Integrative Human Physiology.						
Comments	**Study Limitations** 1A – LOW 1B – Patients recruited on basis of referral for coronary angiography (high prevalence population) HIGH 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – Study duration not specified. Authors note that population is different to previously reported studies. LOW.						

Table 28 Meng 2009

Bibliographic reference	**Author: Meng et al** **Effect of Heart Rate and coronary calcification on the diagnostic accuracy of the dual source CT coronary angiography in patients with suspected coronary artery disease** **Year: 2009**
Study type	Cross-sectional
Aim	To evaluate the diagnostic accuracy of dual-source computed tomography (DSCT) coronary angiography, with a particular focus on the effect of heart rate and calcifications.
Patient characteristics	**Inclusion** Patients with suspected CAD were enrolled between dates stated below. **Exclusion** Allergy to iodine-containing contrast medium, thyroid disorder, renal insufficiency, pregnancy, hemodynamic instability and previous stent deployment or bypass surgery. People with high heart rates were included into this

	study. **Patient characteristics** Age (y) mean (SD) 63(9) Gender (M/F) 68/41 N(%) Diabetes 15 (14) 75 (69) Smoking 46 (42) Dyslipidaemia 86 (79) Mean BMI (kg/m^2) 26.9 (3.3)
Number of patients	109
Index test	**Dual Source CT (Somatom Definition, Siemens) – 64 slice.** No beta blockers will administered irrespective of individual heart rate. ECG monitoring was performed. A contrast enhanced DSCT for a coronary angiography was performed and controlled by bolus tracking. A continuous injection of iohexol 80ml was administered continuously antecutibtally followed by saline flush. Region of interest was placed in the aortic root and imagine acquisition began 5 seconds after the predetermined threshold of 80 Hounsfield units was attained. A mono-segment reconstruction algorithm was used for image reconstruction. Slice thickness 0.75mm. Datasets were transferred to an offsite workstation with Syngo cardiac processing software. Maximum intensity projections and 3D volume rendering technique reconstructions were created for visualisation and analysis of the data. All data sets were independently analysed by 2 blinded observers.
Reference standard (or Gold standard)	**Coronary angiography** Performed according to Judkin's technique. Coronary segments were classified according to AHA guidelines. Stenosis severity was evaluated using quantitative analysis software. A reduction in minimal lumen diameter >50% compared to proximal reference was defined as significant stenosis. All vessels >1.5mm were analysed. Angiograms were judged by one experienced cardiologist not involved in data read-out of DSCT.
Time between testing & treatment	1-30 days (mean (SD)) 10 (8)
Length of follow-up	Duration November 2006 and November 2007
Location	China
Diagnostic accuracy measures (2 x 2 table)	Both tests successfully administered in all patients with no complications. Average heart rate during scanning 71.8 (13.2), range 50-115bpm. 1558 segments were imaged by ICA. Of these 25 were not evaluated by DSCT due to poor image quality.

	Overall per patient analysis **TP FP FN TN SENS% SPEC%** 64slice DSCT 83 5 2 19 98 79
Source of funding	Not mentioned
Comments	**Study Limitations** 1A – Enrolment not specified as consecutive UNCLEAR 1B – suspected CAD population with no breakdown. Unclear if patients were recruited on basis of referral for coronary angiography. UNCLEAR 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – LOW

Table 29 Muhlenbrusch 2007

Bibliographic reference	**Author: Muhlenbrusch et al** **Diagnostic value of 64-slice multi-detector row cardiac CTA in symptomatic patients** **Year: 2007**
Study type	Cross-sectional
Aim	To determine the value of 64 slice cardiac CTA for detection of significant coronary artery disease in a population of symptomatic patients.
Patient characteristics	51 consecutive patients with symptoms of coronary artery disease already scheduled for conventional coronary angiography. Screening medical examination Exercise stress tests, Framingham risk assessment and blood profile. Decision on further work up was made based on their profile and history with e.g. a positive stress tests or typical symptoms of CAD combined with a high risk profile being indications for invasive coronary angiography. 18 patients were excluded for fulfilling one of the below

	Exclusion criteria Previous coronary stent placement (n=9) Bypass graft surgery (n=5) Presence of tachyarrhythmias, AF and other irregular heart rhythms (n=4) Documented renal insufficiency (n=3) Inability to hold breath for at least 15 seconds (n=2) Known allergy to iodine contrast material. (n=1) **Patient Characteristics** Male/Female 39/12 Mean age (y) 58.5 (7.9)
Number of patients	51
Index test	**64-slice MDCT scanner (Somatom Sensation 64)** All patients with resting HR>70bpm received 50-100mg of metoprolol 1-2hrs prior to test. ECG monitoring was performed. Contrast material was administered via the right cubital vein. Scan delay was determined using bolus tracking. When a threshold of 120 Hounsfield units was reached in the ascending aorta at the level of the origin of the coronary arteries, a delay of 5 seconds was applied before the scan was initiated. 80ml of non-ionic contrast material at 4mls/s was injected followed by a saline chaser bolus of 50ml. Patient dose was calculated using CT-Expo. Version 1.4. Images were reconstructed from the raw data with slice thickness of 0.75mm. All images were analysed by an experienced radiologist, blinded to the CCA findings. 15 segments were identified based on established AHA criteria. Each segment was classified as 0=smoothly delineated vessel wall, 1=vessel wall abnormalities but no stenosis ≥70% and 2=significant lumen narrowing of ≥70% compared to pre and post stenotic vessel lumen by visual estimation. Segments that were absent, not opacified or poor image quality or heavily calcified were excluded from further analysis.
Reference standard (or Gold standard)	**Coronary angiography** Performed using digital flat panel fluoroscopy via femoral artery. 80ml of non-ionic contrast administered. Minimum 6 orthogonal views obtained. Images interpreted by experienced, blinded cardiologists. Assessment of diameter stenosis was by visual estimation with lumen narrowing of ≥70% being considered as significant.
Time between testing & treatment	Mean (SD) 2.4 (3.2) days
Length of follow-up	Duration not specified
Location	Germany
Diagnostic accuracy measures (2 x 2 table)	CTA was performed without complications in all 51 patients. Mean HR (SD) 61 (7.7)bpm. Effective radiation dose was 13.6(13.2)mSv and 17.3(2.6)mSV for male/female patients.

	Of 765 segments, 39 were excluded from further analysis due to heavy calcification, non-opacification, true absence of vessel, segment not visible. **TP FP FN TN SENS% SPEC%** 64slice CT 44 3 1 3 97.8 50.0
Source of funding	Not mentioned
Comments	**Study Limitations** 1A – LOW (missing segments, does this indicate previous surgery?) 1B – Symptoms of CAD not specified (no breakdown of numbers with chest pain). High risk population. HIGH 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – LOW

Table 30 Nazeri 2009

Bibliographic reference	**Author: Nazeri et al** **Impact of calcification on diagnostic accuracy of 64-slice spiral computed tomography for detecting coronary artery disease: a single centre experience** **Year: 2009**
Study type	Cross sectional
Aim	To investigate the influence of calcification on the accuracy of 64-slice computed tomography for identification of significant coronary artery disease
Patient characteristics	**Inclusion** - Patient scheduled for conventional coronary angiography because of suspected CAD **Exclusion** - Previous allergic reaction to iodine contrast media - Renal insufficiency (serum creatinine level >1.5mg/dl) - Inability to comply with breath-hold commands - Contraindication to administration of beta-blocker drugs - Atrial fibrillation

Bibliographic reference	**Author: Nazeri et al** **Impact of calcification on diagnostic accuracy of 64-slice spiral computed tomography for detecting coronary artery disease: a single centre experience** **Year: 2009**
	- Hemodynamic instability - History of previous stenting or coronary artery bypass surgery **Other characteristics** Age in years, mean (SD): 58 (11) Male, n (%) 126 (75) Body mass index, kg/m^2, mean (SD) 25.7 (4.2) Family history of CAD, n (%) 118 (70) Smoker, n (%) 114 (68) Hypertension, n (%) 98 (58) Hyperlipidaemia, n (%) 142 (84.5) Diabetes, n (%) 61 (36) Heart rate during scanning in beats per minute, mean (SD) 62 (11)
Number of patients	186 referred, 168 met inclusion criteria
Index test	**1. 64-slice CT (MSCT) – corresponds to test 2b in review protocol** - Somatom Sensation 64, Siemens **2. Calcium scoring – corresponds to test 3 in review protocol** - Patients were ranked by total calcium score which was expressed in Agatston units Both above tests were analysed by 2 investigators who were blinded to both the clinical and angiographic results
Reference standard (or Gold standard)	**Conventional invasive angiography** - Performed according to standard techniques - Angiograms evaluated by cardiologist blinded to the MSCT findings - Significant stenosis defined as diameter ≥50%
Time between testing & treatment	Index test and reference standard performed within a 3 day interval.

<table>
<tr><td>Bibliographic reference</td><td>Author: Nazeri et al
Impact of calcification on diagnostic accuracy of 64-slice spiral computed tomography for detecting coronary artery disease: a single centre experience
Year: 2009</td></tr>
<tr><td>Length of follow-up</td><td>Study dates September 2006 to May 2007</td></tr>
<tr><td>Location</td><td>Iran</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Accuracy of 64-slice CT coronary angiography for detecting significant stenosis defined as lumen narrowing of >50% (patient based analysis)
TP: 120; TN: 41; FP: 5; FN: 2
<table><tr><td>Sensitivity (95%CI):</td><td>98.4% (93.6 to 99.7)</td></tr><tr><td>Specificity (95%CI):</td><td>89.1% (75.6 to 95.9)</td></tr></table>*Confidence intervals calculated by analyst based on data reported in the article

The following data are extracted but not used in analysis since it does not treat calcium score as a diagnostic test.

Accuracy of 64-slice CT for detecting significant stenosis according to calcium score
a) calcium score 0 to 100 (n=99)
TP: 72; TN: 25; FP: 2; FN:0
<table><tr><td>Sensitivity (95%CI)*:</td><td>100% (94.9 to 100)</td></tr><tr><td>Specificity (95%CI)*:</td><td>92.6% (76.6 to 97.9)</td></tr></table>
b) calcium score 101 to 418 (n=45)
TP: 31; TN: 13; FP: 1; FN: 0
<table><tr><td>Sensitivity (95%CI)*:</td><td>100% (89.0 to 100.0)</td></tr><tr><td>Specificity (95%CI)*:</td><td>92.9% (68.5 to 98.7)</td></tr></table>
a) calcium score 419 to 8420 (n=24)
TP: 17; TN: 3; FP: 2; FN: 2
<table><tr><td>Sensitivity (95%CI)*:</td><td>89.5% (68.6 to 97.1)</td></tr><tr><td>Specificity (95%CI)*:</td><td>60.0% (23.1 to 88.2)</td></tr></table>*Confidence intervals calculated by analyst based on data reported in the article.</td></tr>
</table>

Bibliographic reference	**Author: Nazeri et al** **Impact of calcification on diagnostic accuracy of 64-slice spiral computed tomography for detecting coronary artery disease: a single centre experience** **Year: 2009**
	CTA was performed without complications.
Source of funding	Not reported
Comments	**Statistical methods** Diagnostic accuracy of 64-slice CT in the detecting of significant stenosis was expressed as sensitivity, specificity, positive predictive value and negative predictive values along with 95% CIs. **Study limitations (as assessed using QUADAS-2 checklist)** 1a. LOW 1b. HIGH – suspected CAD, no other details given. Patients recruited based on referral for coronary angiography. 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

Table 31 Nieman 2009

Bibliographic reference	**Author: Nieman et al** **Computed tomography versus exercise electrocardiography in patients with stable chest complaints: real-world experiences from a fast-track chest pain clinic** **Year: 2009**
Study type	Cross-sectional
Aim	To compare the diagnostic performance of CT angiography and exercise electrocardiography in a symptomatic population with a low intermediate prevalence of coronary artery disease (CAD).
Patient characteristics	471 consecutive ambulatory patients with stable chest pain complaints and no history of CAD were evaluated at the 1 day chest pain clinic. Patients had a low-intermediate prevalence of coronary artery disease (CAD) (>5% probability) **Exclusions** Contraindications to CTA (pregnancy, known allergy to iodine contrast media, impaired kidney function). Patient characteristics are only reported on the 471 patients, not the 98 included in the diagnostic test accuracy

	evaluation. **Patient Characteristics** Age (y) mean (SD) 56 (10) Female/Male 227/244 Risk profile n(%) Nicotine abuse 138 (29) Hypertension 233 (49) Diabetes 68 (14) Dyslipidaemia 280 (59) Family history of CVD 214 (45) History of vascular disease 31 (7) Chest Pain profile Typical angina 146 (31) Atypical angina 251 (53) Non-anginal chest pain 74 (16) Pre-test probability % (mean, SD) 52 (28)
Number of patients	98 patients (of the 471, whereby invasive coronary angiography was clinically driven)
Index test	**CT angiography (Siemens 64 slice dual-source scanner).** Prospective ECG triggering was used. 70-100ml bolus was injected at 5.0-5.5ml/s through a peripheral vein in the arm followed by 40ml saline. Bolus tracking was performed to synchronise data acquisition with contrast enhancement. A dose of sublingual nitroglycerin was given just before the scan. No additional beta blockers were administered. Retrospective ECG gated image reconstruction was performed using a slice thickness of 0.75mm. Vessels were quantitatively scored as significantly stenosed (>50% diameter narrowing), less than significantly stenosed (<50%) or normal.
Reference standard (or Gold standard)	**Coronary angiography** Standard technique used. Semiautomatic quantification of luminal obstruction was performed by an independent, blinded observer. Maximum lumen diameter stenosis ≥50 was considered moderate and ≥70% was considered severely stenosed.
Time between testing & treatment	Not reported
Length of follow-up	Duration September 2006-December 2008

Location	Tertiary hospital, Holland
Diagnostic accuracy measures (2 x 2 table)	**64 Slice CTCA** CTA could not be performed on 16/471 patients but data not provided for eventual 98 included patients. Patient based analysis **TP FP FN TN SENS% SPEC%** CTCA 53 26 2 15 96.4 36.6 Data are not reported for exercise ECG as this was not a protocol index test. No mention of any adverse events.
Source of funding	Not mentioned
Comments	**Study Limitations** 1A – 98 patients out of initial sample of 471 had the reference standard as it was "clinically driven". Discussion states the test was not available to the majority of patients "without non-invasive evidence of severe CAD". Inappropriate exclusion. HIGH 1B –Low and intermediate risk included only HIGH. 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – timing between tests was not specified. UNCLEAR.

Table 32 Overhus 2010

Bibliographic reference	**Author: Overhus et al** **Comparison of Usefulness of Exercise Testing Versus Coronary Computed Tomographic Angiography for Evaluation of Patients Suspected of Having Coronary Artery Disease** **Year: 2010**
Study type	Cross sectional
Aim	To investigate the diagnostic performance of exercise testing using a diagnostic definition according to the ST-segment changes or the development of angina pectoris, ST-segment changes, and hemodynamic variables

Bibliographic reference	**Author: Overhus et al** **Comparison of Usefulness of Exercise Testing Versus Coronary Computed Tomographic Angiography for Evaluation of Patients Suspected of Having Coronary Artery Disease** **Year: 2010**
	compared to CTCA.
Patient characteristics	**Inclusion** - Patients referred for invasive coronary angiography (CAG) because of suspected CAD **Exclusion** - Known allergy to iodine contrast media - Renal insufficiency - Clinical instability (Canadian Cardiovascular society class IV, New York Heart Assoc. class IV, or systolic BP <95mmHg) - Inadequate scanner capacity - Pregnancy For patients scheduled for CTA with 64 slice scanner - Atrial fibrillation - Irregular heart rate or baseline HR ≥65BPM and - Contraindication to administration of beta-blocker drugs - Hemodynamic instability - History of previous stenting or coronary artery bypass surgery **Other baseline characteristics** Age in years, mean (SD): 61 (9) Male, n (%) 50 (50) Body mass index, mean (SD) 27kg/m^2, (4) Family history of premature CAD, n (%) 53 (53 Hypertension n(%) 50 (50) Hypercholesterolaemia n(%) 69(69) Smoker n(%) 52 (52) Diabetes mellitus 3 (3) Non-angina pectoris n(%) 35(35) Atypical angina pectoris n(%) 26(26) Typical angina pectoris n(%) 39(39)

Bibliographic reference	**Author: Overhus et al** **Comparison of Usefulness of Exercise Testing Versus Coronary Computed Tomographic Angiography for Evaluation of Patients Suspected of Having Coronary Artery Disease** **Year: 2010**
	(Typical angina pectoris was defined as substernal discomfort or chest pain provoked by physical exercise or emotional stress and relieved by rest or nitroglycerin. The presence of 2 of these characteristics defined atypical angina and the presence of 1 defined non-anginal chest pain).
Number of patients	100
Index test	64-slice CTA or dual -source CTA – corresponds to test 2a in review protocol All patients received 0.25mg nitroglycerin 5 mins prior to CTA. An initial non enhanced scan was performed for calcium scoring. (Quantified using Agatston Score). **64 slice CTA (Siemens Sensation)** Performed on first 51 patients. Before 64-slice CTA patients with a resting HR OF ≥65bpm received 50mg metoprolol orally and if necessary additional IV preparation was given to lower HR further. CTA was performed regardless of achieved HR. **Dual-source CTA (Siemens Definition) (No further technical information provided)** Performed on next 49 patients β-Blockers were not routinely administered before CTA using dual-source CTA.
Reference standard (or Gold standard)	**Coronary angiography** - Performed according to standard techniques - Standardized projections were acquired and intracoronary nitroglycerin was administered if coronary lumen reduction was detected. - Angiograms evaluated by 2 experienced observers blinded to the MSCT findings. Consensus readings were performed in the event of any discrepancies. - Coronary segments were identified using modified 16-segment classification model. - Significant stenosis defined as diameter ≥50%
Time between testing & treatment	Reference standard performed followed by Index test within 1 week and before any interventional treatment.

<table>
<tr><td>Bibliographic reference</td><td>Author: Overhus et al
Comparison of Usefulness of Exercise Testing Versus Coronary Computed Tomographic Angiography for Evaluation of Patients Suspected of Having Coronary Artery Disease
Year: 2010</td></tr>
<tr><td>Length of follow-up</td><td>Study dates August 2006 – November 2007</td></tr>
<tr><td>Location</td><td>Denmark</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Only the results of the diagnostic accuracy for CTCA were relevant to the protocol thus these results only are reported.

Accuracy CTCA (both scanner types combined) for detecting significant stenosis defined as lumen narrowing of ≥50% (intention to diagnose results reported) N= 100 (5 patients with inconclusive tests included)
TP:28 TN:57; FP: 14; FN: 1
<table><tr><td>Sensitivity %(95%CI):</td><td>97 (82-100)</td></tr><tr><td>Specificity% (95%CI):</td><td>80 (69-89)</td></tr><tr><td>PPV %(95%CI):</td><td>67 (51-80)</td></tr><tr><td>NPV %(95%CI):</td><td>98 (91-100)</td></tr></table>
Coronary artery calcium score, median (IQR) 23 (0-189).
26 patients had a calcium score of zero.

Pre-test probabilities of significant CAD
LOW – 10 (10%)
INTERMEDIATE – 55 (55%)
HIGH – 35 (35%)

No mention of any adverse events.</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Statistical methods
Diagnostic accuracy of 64-slice CT in the detecting of significant stenosis was expressed as sensitivity, specificity, positive predictive value and negative predictive values along with 95% CIs.

Study limitations (as assessed using QUADAS-2 checklist)</td></tr>
</table>

Bibliographic reference	Author: Overhus et al Comparison of Usefulness of Exercise Testing Versus Coronary Computed Tomographic Angiography for Evaluation of Patients Suspected of Having Coronary Artery Disease Year: 2010
	1A. Of a consecutively enrolled sample (211), only those that could complete exercising testing (ECG) were included in the final study (n=100). UNCLEAR 1B. Patients recruited on basis of referral for coronary angiography. HIGH 2A. 2 different scanners used for index test. LOW 2B. LOW 3A. LOW 3B. LOW 4. LOW

[1] *<Insert Note here>*

Table 33 Piers 2009

Bibliographic reference	Author: Piers et al Computed tomographic angiography or conventional coronary angiography in therapeutic decision-making Year: 2009
Study type	Cross-sectional
Aim	To evaluate non-invasive angiography using dual-source computed tomography (CT) for the determination of the most appropriate therapeutic strategy in patients with suspected coronary artery disease (CAD).
Patient characteristics	60 consecutive patients scheduled for elective coronary angiography. **Inclusion** Over 50 years of age, selected for elective coronary angiography. **Exclusion** Acute coronary syndrome (i.e. ST-segment elevation and non ST-segment evaluation myocardial infarction) were not included. Known iodine allergy, severe renal insufficiency, hyperthyroidism, arrhythmias, unstable clinical condition, inability to follow breath-hold commands, previous PCI or CABG.

	Characteristics Age (mean, range) 64 (57-70) Male 51 (85% Risk Factors n (%) Hypertension 45 (75%) Hypercholesterolaemia 46 (77%) Smoker 28 (47%) Diabetes mellitus 15 (25%) Family history of CAD 34 (57%) Obesity 11 (18%) 10 year risk of CVD (%) 10 (6-13)
Number of patients	60
Index test	**Dual source computed tomography** Retrospective ECG triggered DSCT angiogram was performed with contrast enhancement. Iomeprol was administered via antecubital vein (followed by saline bolus). Bolus triggering was used. Sublingual nitroglycerin (0.4mg) was given just before scan. Mean effective radiation dose was 7.3mSv. Images were reconstructed with 0.6mm slice thickness. 16 segments of the coronary artery were evaluated according to AHA model. Operators were blinded to coronary angiography results. Patients were considered as positive for the presence of significant CAD if there was a significant stenosis in any artery.
Reference standard (or Gold standard)	**Coronary angiography** Routine invasive CAG via the femoral or radial artery was performed and images evaluated by 2 independent, blinded cardiologists. For both imaging modalities, all evaluable segments were classified as normal (smooth borders) as having non-significant disease (luminal irregularities resulting in narrowing <50%) or as having significant stenosis (luminal narrowing ≥50%).
Time between testing & treatment	Within 1 month
Length of follow-up	May 2006 to May 2007 (although due to machine failure inclusion was not possible during a total period of 4 months).
Location	The Netherlands
Diagnostic accuracy measures (2 x 2 table)	**Dual source CT (Siemens Definition)**

	TP FP FN TN SENS% SPEC% CTCA (dual source) 38 12 0 10 100.0 45.5 No mention of any adverse events.
Source of funding	Not mentioned
Comments	**Study Limitations** 1A – HIGH Lack of clarity of inclusion/exclusion criteria relating to population characteristics. Unclear if known CAD were excluded. 1B – HIGH. Suspected CAD, no other detail and patients recruited based on being referred for coronary angiography. 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – LOW

Table 34 Pontone 2014

Bibliographic reference	**Author: Pontone et al** **Coronary Artery Disease: Diagnostic Accuracy of CT Coronary Angiography – A comparison of High and Standard Spatial Resolution Scanning** **Year: 2014**
Study type	Cross-sectional
Aim	To compare the image quality, evaluability, diagnostic accuracy and radiation exposure of high-spatial resolution (HR) CT with standard spatial resolution (SR) CT 64 section imaging in patients at high risk of coronary artery disease (CAD) by using invasive coronary angiography (ICA) as the reference method.
Patient characteristics	210 consecutive patients at high risk for CAD who were scheduled for ICA were randomly assigned for study with SR (n=99) or HR (n=98) coronary CT angiography before they underwent ICA. NB As the study protocol excluded new generation scanners, including the Discover 750CT used here as the HR scanner, only the data from the SR scanner is included. **Exclusion criteria**

	Contraindications to contrast agents or impaired renal function, inability to sustain a breath hold, pregnancy, HR >65 BPM despite IV beta blockade treatment during CTCA or cardiac arrhythmias, previous history of PCI or CABG, BMI >35kg/m^2 No patient characteristics provided
Number of patients	99-8= 91
Index test	**CTCA** Spatial resolution 0.6mm. If resting HR>65bpm before scan, metoprolol was administered IV. 8 patients were excluded in whom this was not achieved. 90ml contrast medium (Iomeron 400mg/ml) was given via antecubital vein at 5ml/sec followed by 50ml saline solution. Scan was performed according to bolus tracking technique. Prospective ECG triggering was performed and a post-processing an iterative algorithm was used. Images were reconstructed independently by two experienced, blinded radiologists. Image segmentation was performed based on AHA segmentation method. Images were rated for image quality on a scale of 1-4. Stenosis was classified according to the following percentage categories. 0=0% luminal stenosis 1=1-24% 2=25-49% 3=50-69% 4=70-99% 5=100%
Reference standard (or Gold standard)	**Coronary Angiography** Was performed using standard techniques and same classification system as above. Quantification of the severity of coronary stenosis included the following. Minimum diameter and reference diameter for all stenosis and the percentage of stenosis was derived according to following formula: $D_{ref} - D_{min})/D_{ref} \bullet 100$, where D_{ref} is the reference diameter and D_{min} is the minimum diameter. The severity of luminal stenosis was graded using the same semi-quantitative score as above. 50% stenosis was used as the cut-off off.
Time between testing & treatment	Within 7 days
Length of follow-up	Duration : January 2010 to September 2010
Location	Italy
Diagnostic accuracy measures (2 x 2 table)	**64 slice CTCA (Light Speed VCT XTe)** **TP** **FP** **FN** **TN** **SENS%** **SPEC%** CTCA all segments * 78 8 0 5 100.0 38.5

	CTCA diagnostic segments 78 7 0 6 100.0 46.2 *censored non-evaluable segments classed as positive results No mention of any adverse events.
Source of funding	Not mentioned
Comments	**Study Limitations** 1A – Population not well defined. Unclear if known CAD excluded. HIGH. 1B – HIGH. High risk (of CAD) patients made up the study population. Patients were recruited on basis of referral for coronary angiography. 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – LOW

Table 35 Pugliese 2008

Bibliographic reference	**Author: Pugliese et al** **Diagnostic performance of coronary CT Angiography by Using Different Generations of Multi-section Scanners** **Year: 2008**
Study type	Cross-sectional
Aim	To retrospectively compare sensitivity and specificity of four generations of multi-detector CT scanners for diagnosing significant (≥50%) coronary artery stenosis with quantitative conventional coronary angiography as the reference standard.
Patient characteristics	A total of 204 patients with stable angina pectoris or atypical chest pain underwent coronary multi-detector CT angiography. The first 51 consecutive patients examined with each scanner were included in four equally sized groups. **Exclusion criteria** Patients with bypass grafts and coronary stents were excluded. **Patient characteristics** (64-Section scanner group only)

	Age (y) mean (SD) 59 (11) Men/women 39/12 *Cardiovascular risk factors* mean (SD) Obesity 14 (27) Smoking 14 (27) Hypertension 16 (31) Cholesterol >200mg/dL 25 (49) Diabetes mellitus 7 (14) Family History 12 (24) *No of risk factors* mean (SD) 0– 11 (22) 1 – 7 (14) 2 – 16 (31) ≥3 - 17 (33)
Number of patients	51 (in the 64 slice CTCA group)
Index test	**CTCA (Somatom Sensation 64, Siemens)** Metoprolol 100mg was given to patients with HR >65bpm (unless contraindicated). Independent review of the scans was performed by two experienced, blinded readers. Scan thickness 0.6mm (32 x 2 detectors). All image evaluation was performed on an offline workstation. 17-segment AHA classifications. Image quality was rated as good, adequate or poor or non -valuable. Images were reconstructed using mono-segmental ECG gating and multi-planar reconstruction. Blood vessels of 2mm or larger were considered.
Reference standard (or Gold standard)	**Coronary Angiography** One experienced, blinded observer identified coronary artery segments using 17-segment modified AHA classification. Stenoses were evaluated and classified as significant if the mean luminal narrowing was 50% or greater using a validated quantification algorithm.
Time between testing & treatment	Mean (SD) 7 days (3)
Length of follow-up	Duration of recruitment for the study group of interest May 2004 – March 2006. (Study started in February 2000)
Location	Rotterdam, The Netherlands
Diagnostic accuracy measures (2 x 2 table)	**64 slice CTCA** Patient based analysis (including all segments*)

	TP FP FN TN SENS% SPEC% CTCA 38 0 0 13 100.0 100.0 *No segments were judged as unevaluable. No mention of any adverse events.
Source of funding	Not mentioned. All study authors reported no financial relationship to disclose.
Comments	**Study Limitations** 1A – Does not state whether known CAD were excluded. HIGH 1B – No breakdown of patient characteristics relating to symptoms/chest pain. Study population included patients referred for coronary angiography who would have higher prevalence of disease. HIGH 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – LOW

Table 36 Raff 2005

Bibliographic reference	**Author: Raff et al** **Diagnostic Accuracy of Noninvasive Coronary Angiography Using 64-slice Spiral Computed Tomography** **Year: 2005**
Study type	Cross sectional
Aim	To evaluate the diagnostic accuracy of multi-slice CT coronary angiography using a new 64 slice scanner.
Patient characteristics	**Inclusion** Consecutive patients scheduled for elective invasive coronary angiography for suspected CAD. **Exclusion** Irregular HR, at risk patients for iodinated contrast (congestive heart failure, dye allergy, elevated serum creatinine) or contraindications to beta-blocking drugs. (14 additional patients were screened but met exclusion criteria and were thus not enrolled). **Other** Age (y) mean (SD) 59 (11) range (22-81)

Bibliographic reference	**Author: Raff et al** **Diagnostic Accuracy of Noninvasive Coronary Angiography Using 64-slice Spiral Computed Tomography** **Year: 2005**
	Males 53/70 (73%) Calcium score, Mean (SD) 326 (472) (Agatston Units)
Number of patients	70
Index test	**MSCT (Index test 2)** Patients not already on beta-blocking drugs received 100mg atenolol for HR > 65bpm or 50mg for HR 51-64bpm 1hr before MSCT imaging. HR, ECG and BP were monitored and IV metoprolol (5-30mg) was administered to achieve a target heart rate <65bpm. (No patient excluded due to HR above target). Sublingual nitroglycerin 0.4mg was given 1 min before image acquisition. 64 slice scanner used (Sensation 64, Siemens). Patients were given initial bolus timing single-slice scan using 10ml of contrast and 40ml saline chaser then a 100ml dose of contrast via antecubital vein at 5ml/s in order to obtain a contrast enhanced scan. Estimated radiation was 13mSv for men and 18mSv for women. ECG gated data sets were reconstructed automatically at 65% and 35% of R-R cycle length. Additional reconstruction windows were constructed after examination of datasets if motion artefacts were present. MSCT angiograms were analysed on a 3D workstation by 2 observers blinded to results of the reference standard. 15 segment AHA model was employed. Lesions were classified as 0= no stenosis, 1= 1% to 25% stenosis 2= 26% to 50% stenosis 3= 51% to 75% stenosis 4= 75% to 99% stenosis 5 = total occlusion Patients were classified as positive for the presence of significant coronary artery disease if there was a stenosis of >50% in any artery. **Calcium Scoring** Scores analysed using SYNGO software using Agatston units and were rated as 0 = not calcified 1 = calcium present, no image impairment 2 = calcium covering <50% of lumen

Bibliographic reference	**Author: Raff et al** **Diagnostic Accuracy of Noninvasive Coronary Angiography Using 64-slice Spiral Computed Tomography** **Year: 2005**
	3 = calcium covering >50% of lumen in all planes including in cross section.
Reference standard (or Gold standard)	**Coronary Angiography** Evaluated by a single observe blinded to MSCT results. Segmental disease analysed in same 15 segment model described above. Severity of stenosis was classified in each segment using maximum luminal diameter and lesions were classified using an automated edge-detection system.
Time between testing & treatment	Within 30 days
Length of follow-up	Study period September 2004 – February 2005.
Location	Michigan, USA
Diagnostic accuracy measures (2 x 2 table)	Per patient analysis only **MSCT only (n=70)** TP 38, FP 3, FN 2, TN 27 Sensitivity 95%, Specificity 90%, PPV 93%, NPV 93% **Calcium Scoring (using MSCT) (NB the following data are extracted but not used in analysis as calcium scoring is not used as a diagnostic test).** ***Score 0-100 (n=35)*** TP 15, FP 1, FN 1, TN 18 Sensitivity 94%, Specificity 95%, PPV 94%, NPV 95% ***Score 101-400 (n=17)*** TP 9, FP 1, FN 1, TN 7 Sensitivity 100%, Specificity 88%, PPV 90% NPV 100% ***Score 401-1,804 (n=18)*** TP 14, FP 1, FN 1, TN 2 Sensitivity 93%, Specificity 67%, PPV 93%, PPV 67% No mention of any adverse events.

Bibliographic reference	**Author: Raff et al** **Diagnostic Accuracy of Noninvasive Coronary Angiography Using 64-slice Spiral Computed Tomography** **Year: 2005**
Source of funding	Supported by the Ministrelli Cardiovascular Research Fund.
Comments	**Study limitations:** 1a. LOW 1b. Patients were all suspected to have CAD with no breakdown of numbers with chest pain. Patients were recruited into study on basis of referral to coronary angiography. HIGH 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

Table 37 Rixe 2009

Bibliographic reference	**Author: Rixe et al 2009** **Detection of Relevant Coronary Artery Disease Using Dual-Source Computed Tomography in a High Probability Patient Series – Comparison with Invasive Angiography** **Year: 2009**
Study type	Cross sectional
Aim	To assess the feasibility of dual-source CT (DSCT) for the detection of relevant coronary artery stenoses in a cohort of 76 patients with clinically suspected coronary artery disease (CAD).
Patient characteristics	76 consecutive patients referred for invasive coronary angiography due to suspected CAD were included. Clinical signs of CAD included typical chest pain in 50 patients (65.8%), positive stress testing in 15 (19.7%) and both indicators in 11 (14.5%). Positive stress test was not mandatory for inclusion in the study. **Other inclusion criteria** Stable clinical condition Absence of a contraindication for administration of iodinated contrast agents **Exclusion criteria**

	CABG, prior stent implantation, valve prosthesis and cardiac pacemakers. AF **Clinical characteristics** HR>65/>70BPM (n) 36/24 Mean (SD) HR (BPM) 68 (9) (range 49-85) Mean Agatston score 100 (560) (range 0-2,650) Male gender 57 (62%) Mean (SD) age(y) 65 (10) Diabetes mellitus 21 (28) Arterial hypertension 64 (84%) Hypercholesterolemia 45 (59%) Family history of CAD 21 (28%) Smoking 9 (12%) Obesity 33 (43%)
Number of patients	76
Index test	**DSCT (Siemens Somatom Definition) 64 Slice** Heart rate modulation was not performed but 45 patients were on continuous beta blocker medication. 0.8mg isosorbide dinitrate was given sublingually immediately before scanning. 10ml of iopamidole contrast followed by 50ml of isotonic saline, both at 5ml/s was administered via antecubital vein using a tests bolus approach to establish maximum enhancement in the ascending aorta. 60ml of contrast was then injected at 5ml/s followed by 50ml saline. ECG gated current modulation and automatic radiation exposure control was used in all patients. Retrospective ECG gated image reconstruction was performed. Slice thickness 0.6mm. Data were transferred to an offline workstation and images were assessed by 2 experienced, blinded investigators. Segments were defined using AHA/ACC 16 segment model. Segments <1.5mm in diameter were excluded and all segments were classified as evaluable or unevaluable and assessed for presence of stenoses >50% lumen reduction as well as for the presence of occlusions.
Reference standard (or Gold standard)	**Coronary angiography** Standard technique used by an experienced, blinded observer. Quantitative evaluation was performed using an offline workstation using AHA 16 segment coronary model. Coronary segments with a diameter of <1.5mm were excluded from analysis and a reduction of >50% of the luminal diameter compared with the reference diameter was considered a significant stenosis.

Time between testing & treatment	24-48 hours
Length of follow-up	Duration 2 months
Location	Germany
Diagnostic accuracy measures (2 x 2 table)	**64 slice dual source CT angiography** **TP FP FN TN SENS% SPEC%** DSCTA 40 6 0 30% 100 83.3 8 segments were classed as unevaluable and were estimated as having significant stenosis. 1072/1080 segments were evaluable. *Back calculated by reviewer No complications from CTA were observed.
Source of funding	Not mentioned
Comments	**Study Limitations** 1A – LOW 1B – HIGH. Suspected CAD with breakdown of those with chest pain was provided but all patients were recruited due to referral for coronary angiography increasing the prevalence of disease. 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – LOW

Table 38 Ropers 2006

Bibliographic reference	**Author: Ropers et al** **Usefulness of Multidetector Row Spiral Computed Tomography With 64- X 0.6mm Collimation and 330-ms Rotation for the Noninvasive Detection of Significant Coronary Artery Stenoses** **Year: 2006**
Study type	Cross sectional

Aim	To analyse the accuracy of 64 slice MDCTA for the detection of significant coronary artery stenosis compared with quantitative coronary angiography.
Patient characteristics	84 patients had been referred to the study institution for a first invasive coronary angiography due to suspected CAD. **Exclusion criteria** Acute coronary syndromes, contraindications to administration of contrast agent, cardiac arrhythmias, possible pregnancy, or an unstable clinical situation. **Clinical characteristics** Men/Women 52/32 Age years (SD) 58 (10), range 35-77 BMI (kg/m^2) 29 (5) (range 22-44) No of coronary arteries narrowed 1 - 16 (19%) 2 - 8 (10%) 3 - 2 (2%)
Number of patients	84
Index test	**MSCT 64 Slice (Sensation 64, Siemens)** Patients with HR >60bpm received 100mg of atenolol orally 1 hour before scanning. If remained >60 at time of scanning, up to 4 doses of 5mg metoprolol were administered IV to lower HR. In Addition all patients received 0.8mg isosorbide dinitrate sublingually immediately before scanning. Contrast agent time was determined using a bolus injection of 10ml of contrast agent. A total of 65ml of contrast agent was administered at a rate of 5ml/s followed by 50ml saline. ECG gated tube current modulation was used in all patients. Average radiation doses were determined to be 7.45mSv for men and 10.24mSv for women. Slice thickness (overlapping axial cross-sectional images) were reconstructed with a medium-sharp convolution kernel. All data sets were evaluated on an off-line image analysis workstation by 1 experienced, blinded observer. MDCTdata were evaluated for the presence of coronary artery stenosis within 17 coronary artery segments (per modified AHA model). First each segment was judged to be evaluable or non evaluable. The former were visually assessed for the presence or absence of significant stenosis which was defined as a diameter increase of ≥50%.
Reference standard (or Gold	**Coronary angiography**

standard)	Performed 1-3 days after MDCT Standard projections were obtained after intracoronary injection of 0.2mg of isosorbide dinitrate and evaluated offline by an independent observer using angiographic software. Segments with a diameter <1.5mm were excluded. Lesions with a luminal decrease of ≥50% in all other vessels were considered to represent significant stenosis.
Time between testing & treatment	1-3 days
Length of follow-up	Study duration not specified
Location	Germany
Diagnostic accuracy measures (2 x 2 table)	26/84 patients had CAD according to ICA. **64 slice dual source CT angiography** **TP FP FN TN SENS% SPEC%** MSCTA 25 5 1 50 96.2 90.9 MDCT was performed in all patients without complications. 45/1128 segments were unevaluable.
Source of funding	Not mentioned
Comments	**Study Limitations** 1A – Consecutive enrolment not specified - UNCLEAR 1B – Suspected CAD population with no breakdown, recruitment carried out via referral for coronary angiography. - HIGH 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – LOW

Table 39 Sheikh 2009

Bibliographic reference	**Author: Sheikh et al**

	Accuracy of 64-Multidetector-row Computed Tomography in the Diagnosis of Coronary Artery Disease Year: 2009
Study type	Cross sectional
Aim	To assess the accuracy of 64-multidetector-row computed tomography coronary angiography (CTA) in the diagnosis of coronary artery disease (CAD).
Patient characteristics	Patients with suspected CAD referred for coronary angiography were given the option of CTA prior to coronary angiography. **Exclusion Criteria** AF High baseline heart rate (>70BPM) with contraindication to beta-blockade, known allergic reaction to iodinated contrast agents, renal insufficiency, severe chronic congestive heart failure and any previous percutaneous coronary intervention or CABG. Patients with HR>70BPM were prescribed 50-100mg oral metoprolol to keep the HR <60. **Patient characteristics** Male/Female 60/13. Age (y) mean (SD) 60 (9). Range (32-67). Allergies 4 (5.5%) Diabetes Mellitus 38 (52.1%) Hypertension 39 (53.4%) Hyperlipidaemia 65 (89%) Smoking 37 (50.7%) Peripheral vascular disease 3 (4.10)
Number of patients	73
Index test	**64-slice CT scanner.** 100-120ml contrast medium followed by 50-60ml or normal saline was injected through and arm vein at 4-5mls/s using a dual injector. 20mls contrast was injected at ascending aortic level. All data sets were reconstructed using retrospective ECG gating.
Reference standard (or Gold standard)	**Coronary angiography (CCA).** Interventional radiologists evaluated reconstructed images for both the CTA and the CCA using visual estimation. Accessibility of segments and arteries was recorded and for the accessible areas, presence of significant stenosis

	(≥50% reduction lumen diameter) was determined. (Segments per modified AHA criteria were used). Disagreement between the two reporters was resolved by consensus. Interventional cardiologist blinded to the results of CTA performed the CCA within 1 month. Visual inspection led to recording of degree of stenosis. A significant lesion was defined as 50% or more reduction in lumen diameter. 92 patients underwent CTA. Of these 5 were considered non-diagnostic. The remaining 87 were considered diagnostic but 14 patients subsequently refused to undergo CCA.
Time between testing & treatment	Within 1 month.
Length of follow-up	Duration of study not specified
Location	Kuwait
Diagnostic accuracy measures (2 x 2 table)	**Patient based analyses** **TP FP FN TN SENS% SPEC%** MSCTA 48 1 3 21 95.0 96.0 No mention of adverse events.
Source of funding	Supported by a Kuwait university research grant.
Comments	**Study Limitations** 1A – Unclear if patients were consecutively approached for inclusion UNCLEAR 1B – suspected CAD with no breakdown of numbers with chest pain. Patients recruited into study after referral for coronary angiography – high prevalence group. HIGH 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – LOW

Table 40 Swailam 2010

Bibliographic reference	**Author: Swailam et al** **Multi-slice computed tomography@ Can it adequately rule out left main coronary disease in patients with an intermediate probability of coronary artery disease?** **Year: 2010**
Study type	Cross-sectional
Aim	To explore the diagnostic accuracy of MSCT angiography for the detection of significant stenosis of the left main coronary artery (LMCA) in a series of patients with an intermediate pre-test likelihood of CAD, based on an intention to diagnose analysis.
Patient characteristics	30 consecutive patients were prospectively enrolled who were referred to the catheter laboratories to undergo elective invasive coronary angiography for suspected CAD. Patients were considered for inclusion if they had 1) Ischemic-type chest pain or other symptoms suggestive of myocardial ischemia in the absence of a positive stress test or with an equivocal stress test for myocardial ischemia, or 2) Asymptomatic patients with a positive stress test **Exclusion** History of CAD as defined by significant coronary artery stenosis shown in prior coronary angiogram, prior MI, prior PCI, prior CABG. AF Allergies to iodinated contrast material. **Patient Characteristics** Age (y) Mean (SD) 52.6 (6.3) Males 24 (80%) Diabetes 12 (50%) Hypertension 26 (86.7%) Smoking 19 (63.3%) Dyslipidaemia 15 (50%) Mean (SD) Agatston score 227 (688)
Number of patients	30
Index test	**MSCT – 64 Slice scanner (Aquilion 64).** 80-120mL contrast (Iopromide) was injected into antecubital vein followed by 50ml saline chaser both injected at

	rate of 5mL/s. Automated detection of peak enhancement in the aortic root was used to time the scan. Imagining was performed with breath held in inspiration and under retrospective ECG gating. In patients with HR>65 BPM beta blockers were given (unless contraindicated). Slice thickness 0.5mm. All data were evaluated on remote workstation by two experienced, blinded, independent investigators. A semiautomatic tool was used for the assessment of severity of LMCA stenosis on curved multi-planar reformations and cross-sections orthogonal to the vessel. Significant stenosis of the LMCA was defined by at least 50% luminal diameter obstruction.
Reference standard (or Gold standard)	**Invasive Coronary angiography** Standard technique used. Data retrospectively analysed by a single expert, independent interventionist, blinded to all other data. No intracoronary pharmacologic agents were given. Significant stenosis of the LMCA was defined as at least 50% luminal diameter obstruction seen in two different projections. An automated edge detection system was applied to determine lesion severity.
Time between testing & treatment	Within 1 week.
Length of follow-up	Duration March – August 2007
Location	Cairo, Egypt
Diagnostic accuracy measures (2 x 2 table)	Based on diagnostic criteria of LMA only. (Numbers were reported for other arteries in isolation but no per patient analysis was reported overall). **TP FP FN TN SENS% SPEC%** MSCTA 3 1 0 26 100 96.3 According to an intention to diagnose based analysis, arteries with inconclusive segments were considered as significantly diseased. No patient reported any adverse events during either procedure.
Source of funding	Not mentioned
Comments	**Study Limitations** 1A – LOW 1B – HIGH. Included people only with intermediate pre-test probability for CAD and included some asymptomatic patients with a positive stress test only. Breakdown of numbers with chest pain is not provided. Patients recruited on basis of referral for coronary angiography. 2A – LOW

	2B – LOW 3A – LOW 3B – LOW 4 – LOW

Table 41 van Werkhoven 2009

Bibliographic reference	**Author: van Werkhoven et al** **Diagnostic Accuracy of 64-slice multi-slice Computed Tomographic Coronary Angiography in Patients with an Intermediate Pre-test Likelihood for Coronary Artery Disease** **Year: 2009**
Study type	Cross sectional
Aim	To determine the diagnostic accuracy of CTA in patients without known coronary artery disease with an intermediate pre-test likelihood.
Patient characteristics	Prospective recruitment of patients who had an intermediate pre-test likelihood of CAD who had been referred for invasive diagnostic coronary angiography. **Exclusion criteria** Cardiac arrhythmias Renal insufficiency Known hypersensitivity to iodine contrast media Pregnancy Cardiac event in period between the two investigations **Patient characteristics** Men/women 37/24 Age (y) mean (SD) 57 (9) (Range 35-75) HR mean (SD) 58 (8) (Range 41-78) Average calcium score (SD) 198 (323) (Range 0-1,505) Beta blockers n(%) 37 (61) Diabetes 15 (25%) Hypertension 38 (62%) Hypercholesterolaemia 38 (62%)

	Current smoker 20 (33%) BMI ≥30kg/m^2 14 (23%) Non angina chest pain 8 (13%) Atypical angina pectoris 50 (82%) Typical angina pectoris 3 (5%)
Number of patients	61
Index test	**MSCTA – 64 Slice (Lightspeed VR 64, GE Healthcare)** HR and BP were monitored before each scan. In the absence of contraindications, patients with a HR >65BPM were given beta blockers (50-100 metoprolol orally or 5-10mg IV). Non-enhanced ECG gated scan was performed to measure coronary calcium score and to determine the start and end positions of the helical scan. A bolus of 80mls iomeprol was injected at 5ml/s followed by 40ml saline flush. The helical scan was automatically triggered using a bolus tracking technique when the attenuation level in the region of interest reached the predefined threshold. Data sets were reconstructed from the retrospectively gated raw data with an effective slice thickness of 0.625mm. Post scan processing was performed on a dedicated workstation . Coronary arteries were divided into modified-AHA 17 segment classifications. All studies were interpreted by 2 experienced, blinded observers. Image quality was assessed as good, average and poor. Next the presence of significant stenosis (≥50% luminal narrowing) was evaluated using multi-planar reconstructions and maximum intensity projections.
Reference standard (or Gold standard)	**Invasive coronary angiography** Performed using standard techniques and angiograms were evaluated by a blinded observer using offline quantitative software. Arteries were evaluated according to above segment model and quantitative angiography was performed in lesions with >30% luminal narrowing on visual assessment. Obstructive CAD was defined as luminal narrowing of ≥50%.
Time between testing & treatment	Within 14 days
Length of follow-up	Duration not specified
Location	The Netherlands
Diagnostic accuracy measures (2 x 2 table)	**Patient based analysis** **TP FP FN TN SENS% SPEC%** MSCTA 16 5 0 40 100 89 No patient level results were excluded from the per patient analysis. (885/920 segments were evaluable, thus 35

	segments were not included in the per segment analysis). No mention of any adverse events.
Source of funding	Dr van Werkhoven was financially supported by a research grant from The Netherlands Society of Cardiology. Dr Boogers was supported by a grant from the Dutch Heart Foundation and Dr Bax received various research grants including one from GE Healthcare.
Comments	**Study Limitations** 1A – UNCLEAR – unclear if known CAD was excluded (not specified). 1B – HIGH – Only includes people with intermediate pre-test probability who had been referred for invasive diagnostic coronary angiography. 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – LOW

G.1.2 Calcium Scoring

Table 42 Budoff 2013

Bibliographic reference	**Author: Budoff MJ et al** **Diagnostic accuracy of coronary artery calcium for obstructive disease: results from the accuracy trial** **Year: 2013**
Study type	Cross sectional
Aim	To assess whether the coronary artery calcium scores obtained with 64 multi-detector CT (MDCT) has the same high sensitivity and negative predictive value to prior electron beam tomography (EBT) data. The diagnostic accuracy of coronary artery calcium by 64 row CT to detect obstructive coronary stenosis compared to quantitative coronary angiography was evaluated.
Patient characteristics	**Inclusion** - ≥18 years of age - Experienced typical or atypical chest pain - Being referred for non-emergent invasive coronary angiography

<table>
<tr><td>Bibliographic reference</td><td>Author: Budoff MJ et al
Diagnostic accuracy of coronary artery calcium for obstructive disease: results from the accuracy trial
Year: 2013</td></tr>
<tr><td></td><td>Exclusion
Not reported

Other characteristics
Mean age in years (SD) 57 (10)
Gender, % males 59.1</td></tr>
<tr><td>Number of patients</td><td>N=230</td></tr>
<tr><td>Index test</td><td>1. Calcium scoring determined by 64 row CT – corresponds to tests 2 and 3 on review protocol
- All CCTA scans performed with a 64 detector row Lightspeed VCT scanner
- 2.5 mm slice thickness
Agatston scoring system used.</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Selective invasive coronary angiography
- Performed by standard transfemoral arterial catheterisation
- Images interpreted without knowledge of index test results
- Significant stenosis defined as ≥50% luminal narrowing of the coronary artery diameter</td></tr>
<tr><td>Time between testing & treatment</td><td>Index tests were performed ‘prior’ to conventional invasive coronary angiography – unclear what rough time interval was.</td></tr>
<tr><td>Length of follow-up</td><td>Study dates not reported</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>1. Accuracy of coronary artery calcium (CAC) by 64-row CT compared to coronary angiography to detect stenosis (per patient analysis)

Coronary artery calcium >0
TP: 56; FP: 101; TN: 1; FN: 72
<table><tr><td>Sensitivity (95%CI)*:</td><td>98.2 (90.7 to 99.7)</td></tr><tr><td>Specificity (95%CI)*:</td><td>41.6 (34.5 to 49.1)</td></tr></table>
Coronary artery calcium >100
TP: 50; FP: 50; TN: 123; FN: 7</td></tr>
</table>

Bibliographic reference	**Author: Budoff MJ et al** **Diagnostic accuracy of coronary artery calcium for obstructive disease: results from the accuracy trial** **Year: 2013**
	<table><tr><td>Sensitivity (95%CI)*:</td><td>87.7 (76.8 to 93.9)</td></tr><tr><td>Specificity (95%CI)*:</td><td>71.1 (63.9 to 77.3)</td></tr></table> **Coronary artery calcium >400** TP: 34; FP: 20; TN: 153; FN: 23 <table><tr><td>Sensitivity (95%CI)*:</td><td>59.6 (46.7 to 71.4)</td></tr><tr><td>Specificity (95%CI)*:</td><td>88.4 (82.8 to 92.4)</td></tr></table> No mention of any adverse events.
Source of funding	Not reported
Comments	**Statistical methods** Standard 2x2s for various calcium scores **Study limitations (as assessed using QUADAS-2)** 1a. HIGH – consecutive recruitment not reported, exclusion criteria not reported 1b. HIGH – patients recruited on basis or referral for coronary angiography (higher prevalence population) 2a. UNCLEAR – unclear if index test results interpreted without knowledge of reference standard results 2b. LOW 3a. LOW 3b. LOW 4. LOW

Table 43 Javadrashid 2009

Bibliographic reference	**Author: Javadrashid et al** **Diagnostic efficacy of coronary calcium score in the assessment of significant coronary artery stenosis.** **Year: 2009**
Study type	Case control
Aim	To evaluate the diagnostic accuracy of coronary artery calcium score (CCS) to detect significant stenosis in

Bibliographic reference	**Author: Javadrashid et al** **Diagnostic efficacy of coronary calcium score in the assessment of significant coronary artery stenosis.** **Year: 2009**
	coronary arteries in symptomatic patients.
Patient characteristics	**Inclusion** Symptomatic patients with suspected CAD referred for conventional coronary angiography to the University Hospital of Tabriz. **Exclusion** Previous percutaneous angioplasty, surgical revascularisation, valve replacement, pacemaker implantation and cardiac arrhythmia. Strong evidence for the existence of non-cardiac chest pain. Renal impairment (serum creatinine level above normal range). Allergy to IV contrast materials. **Other** Age (mean (SD) 58 (10) Male gender n(%) 102 (65) Risk factors: n(%) Hypertension 67 (42) Dyslipidaemia 47 (30 Diabetes 36 (23) Smoking 29 (18) Family history of CAD 16 (10) Distribution of CAD by conventional coronary angiography n(%) None 36 (23) One vessel 41(26) Two vessels 44 (28) Three vessels 37 (24) (total with CAD = 122)
Number of patients	158 consecutive patients.
Index test	**Multi-detector computed tomography (MDCT)** Somatom 64 (Siemens).

<table>
<tr><td>Bibliographic reference</td><td>Author: Javadrashid et al
Diagnostic efficacy of coronary calcium score in the assessment of significant coronary artery stenosis.
Year: 2009</td></tr>
<tr><td></td><td>The best quality images were obtained from datasets reconstructed with retrospective ECG gating. The Agatston algorithm was used and total CCS was the sum of the scores from all coronary arteries.
Scanned slice thickness – 3mm.</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography. Performed by the same independent cardiologist using digital fluorography system (Siemens Axiom Artis) using a femoral approach.
Measurements involved the right coronary artery (RCA), left main (LM), left anterior descending (LAD) and left circumflex (LCX) coronary arteries. Stenosis ≥50% of the main coronary arteries on conventional angiography (as the reference standard) was considered significant.</td></tr>
<tr><td>Time between testing & treatment</td><td>Time delay between tests did not exceed 24hrs.</td></tr>
<tr><td>Length of follow-up</td><td>Study duration September 2008 to September 2009.</td></tr>
<tr><td>Location</td><td>Tabriz, Iran.</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>122/158 patients had CAD according to reference standard.

AUC and 95%CI for diagnostic accuracy of CCS of each coronary artery for diagnosing stenosis in this individual artery.
<table>
<tr><th></th><th>AUC for Coronary Calcium Score of individual artery (95% CI)</th><th>AUC for total CCS (95% CI)</th></tr>
<tr><td>RCA</td><td>0.8 (0.71-0.88)</td><td>0.74 (0.65-0.82)</td></tr>
<tr><td>LM</td><td>0.72 (0.38-1.06)</td><td>0.50 (0.20-0.81)</td></tr>
<tr><td>LAD</td><td>0.73 (0.62-0.82)</td><td>0.66 (0.56-0.76)</td></tr>
<tr><td>LCX</td><td>0.76 (0.67-0.85)</td><td>0.78 (0.69-0.85)</td></tr>
<tr><td>OVERALL (At least one artery)</td><td>n/a</td><td>0.83 (0.74-0.92)</td></tr>
</table>

Analysis of ROC curves for CCS in each coronary artery to establish optimal cut-off value for diagnosing significant stenosis in that artery.
<table>
<tr><th></th><th>Optimal cut off point</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th><th>NPV (%)</th></tr>
<tr><td>RCA</td><td>3.1</td><td>75.0</td><td>73.1</td><td>68.8</td><td>79.4</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Author: Javadrashid et al** **Diagnostic efficacy of coronary calcium score in the assessment of significant coronary artery stenosis.** **Year: 2009**

LM	7.7	66.7	82.2	66.6	82.7
LAD	9.5	70.9	66.7	78.6	58.5
LCX	4.5	73.9	69.2	58.6	83.3
Overall (at least one artery using CCS cut off value of ≥7.7)	n/a	86%	71%	NR	NR

Overall (all arteries) Data for CCS ≥7 - TP 105, FP 10, TN 26, FN 17.*

No mention of any adverse events.

Source of funding	Not mentioned
Comments	**Statistical analysis:** Calcium score cut-offs values for the presence of significant stenosis was set using ROC curves and the related area under the curve (AUC) was provided. **Study limitations:** 1a. LOW 1b. did not explicitly state proportion of population with chest pain. Patients recruited on basis of positive referral for coronary angiography. HIGH 2a. Unclear if results were interpreted without knowledge of reference test (order of tests unclear). UNCLEAR 2b. LOW 3a. Unclear if results were interpreted without knowledge of index test (order of tests unclear). UNCLEAR 3b. LOW 4. LOW

**calculated by reviewer*

Table 44 von Ziegler 2014

Bibliographic reference	**Author: von Ziegler et al** **Distribution of coronary calcifications in patients with suspected coronary heart disease**

	Year: 2014
Study type	Cross sectional
Aim	To characterize the coronary calcium distribution in this particular patient population and to establish a possible clinical implication using calcium scoring (CS) for the diagnosis of CHD
Patient characteristics	Prospective study 8177 consecutive patients were screened. 2,849 patients refused to participate. 313 had an aggravation of symptoms leading to exclusion, In 878 scheduling was impossible. This left a total of 4,137 patients. **Eligibility / inclusion criteria:** Typical/atypical or non-angina chest pain and/or signs of myocardial ischemia in non-invasive stress tests and thus a clinical indication for ICA. **Exclusion criteria** Acute coronary syndrome including MI Unstable angina Positive troponin in blood testing Unstable clinical condition Known CHD (prior stent implantation procedure or CABG) <18 years Pregnancy **Patient characteristics** Mean age (y) (SD) 60.5 (12.4) (RANGE 18-95) No risk factors 696 (16.8%) Hypertension 3199 (77.3%) Diabetes 612 (14.8) Hypolipoproteinaemia 2025 (49.0%) FH 1682 (40.7%) Current smoking 1249 (30.2%) Mean no. of risk factors 2.1 *Chest Pain symptoms* Typical/atypical 3756 (90.8%) Non angina 381 (9.2%) Mean Diamond and Forrester Score 42.4 (11.8)

Number of patients	4,137
Index test	**Coronary calcium screening (CS)** Performed using either a Sensation 64 or a Definition CT scanner (Siemens) in thin section mode according to a standardized protocol. ECG triggered images were acquired. 40, 3mm thick slices were obtained covering the whole heart and all images were transferee do a dedicated workstation for CS evaluation. Calcifications were automatically defined as lesions with attenuations >130 Hounsfield units in >4 adjacent pixels. For quantification of CS the Agatston method was applied. All scans were evaluated by a physician blinded to the patient's clinical diagnoses.
Reference standard (or Gold standard)	**Invasive Coronary Angiography** Judkin's technique was used. Significant CHD was defined as luminal stenosis ≥50% stenosis in quantitative coronary analysis in ≥epicardial vessel. Decisions for coronary intervention in the case of obstructive CHD (≥70% stenosis) was made by the examiner who was blinded to the CS results.
Time between testing & treatment	All within 30 days but 82% were within 4 days and 91% within 10 days.
Length of follow-up	Duration June 2005 – June 2011
Location	Germany (single-centre)
Diagnostic accuracy measures (2 x 2 table)	**Patient based analysis** 2089/4137 patients had ≥50% stenosis and 732/4137 patients had ≥70% stenosis based on ICA. **Stenosis % TP FP FN TN * SENS% SPEC%** CCS score >0 50 2068 2747 21 3438 99.0 55.6 CCS score >10 50 1917 1753 172 4432 91.8 71.7 CCS score >100 50 1474 1062 615 5123 70.6 82.8 CCS score >400 50 1134 768 955 5417 54.3 87.6 CCS score >0 70 723 4357 9 3185 98.7 42.2 CCS score >10 70 708 3485 24 4057 96.7 53.8 CCS score >100 70 658 1911 74 5631 89.9 74.7 CCS score >400 70 618 1226 114 6316 84.5 83.7 *back calculated by reviewer No complications were reported with any test.

Source of funding	Not mentioned
Comments	**Study Limitations** 1A – LOW 1B – While positive stress test did form part of the inclusion criteria, 100% of study population had chest pain. Patients recruited based on referral for invasive coronary angiography. HIGH 2A – LOW 2B – LOW 3A – LOW 3B – LOW 4 – LOW

G.1.3 Stress Echocardiography

Table 45 Hennessy 1998

Bibliographic reference	**Author: Hennessy et al** **Dobutamine stress echocardiography for the assessment of patients without history or electrocardiographic evidence of myocardial infarction. Journal of Noninvasive Cardiology 2: 7-11.** **Year: 1998**
Study type	Cross sectional
Aim	To assess the value of dobutamine stress echocardiography (DSE) for diagnosing coronary artery disease in patients with no prior history or ECG evidence of MI
Patient characteristics	**Inclusion:** - Undergoing coronary angiography (CA) for detection of CAD - No ECG evidence or prior history of MI **Exclusion:** - Unstable angina - Valvular heart disease - Cardiac arrhythmia

<table>
<tr><td>Bibliographic reference</td><td>Author: Hennessy et al
Dobutamine stress echocardiography for the assessment of patients without history or electrocardiographic evidence of myocardial infarction. Journal of Noninvasive Cardiology 2: 7-11.
Year: 1998</td></tr>
<tr><td></td><td>- Uncontrolled hypertension (>160/110mm Hg)

Other characteristics:

<table>
<tr><td></td><td>N=157</td></tr>
<tr><td>Age in years - mean (SD)</td><td>59 (11)</td></tr>
<tr><td>Gender: male/female, n (%)</td><td>101/56 (64% male)</td></tr>
<tr><td>Hypertension – n (%)</td><td>62 (39%)</td></tr>
<tr><td>Diabetes– n (%)
- Insulin
- Oral hypoglycaemic
- Diet-controlled</td><td>
18 (11.5%)
10 (6%)
3 (2%)</td></tr>
<tr><td>Hypercholesterolemia– n (%)</td><td>53 (34%)</td></tr>
<tr><td>Smoker– n (%)
- Current
- Quitter
- Never</td><td>
19 (12%)
77 (49%)
61 (39%)</td></tr>
<tr><td>Family history – n (%)</td><td>70 (45%)</td></tr>
<tr><td>Angina – n (%)
- Typical
- Atypical
- Noncardiac
- None</td><td>
72 (49%)
49 (31%)
6 (4%)
30 (19%)</td></tr>
</table>
</td></tr>
<tr><td>Number of patients</td><td>157 patients</td></tr>
<tr><td>Index test</td><td>Dobutamine stress echocardiography
- Beta-blockers withheld for 24hrs prior to DSE examination
- 2D baseline images obtained in parasternal long and short axes, and in apical four- and two-chamber views
- Graded dobutamine infused at 10, 20 and 40µg/kg/min, each for 3 mins
- Infusion increased to 50µg/kg/min if heart rate response was inadequate; atropine (1mg) administered</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Author: Hennessy et al
Dobutamine stress echocardiography for the assessment of patients without history or electrocardiographic evidence of myocardial infarction. Journal of Noninvasive Cardiology 2: 7-11.
Year: 1998</td></tr>
<tr><td></td><td>thereafter, if response was still suboptimal
- Metoprolol and glycerol trinitrate given as needed
- Online analysis system (Nova Microsonics pre-vue) used to acquire and store digital echocardiographs
- Images arranged on quad screen display to facilitate resting, low, medium and peak infusion comparisons
- For analysis, images of left ventricle (LV) were divided into 16 segments, each scored for wall motion: 1 = normal, 2=hypokinetic, 3=akinetic, 4=dyskinetic, 5=aneurysmal
- LV score index derived by summing scores and dividing by number of segments evaluated
- Positive test (indicative of CAD) was defined as deterioration in score by 1 grade in two segments compared with baseline
- DSEs were analysed and scored offline by two independent assessors blind to other investigative findings</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography
Significant CAD defined as >50% luminal diameter stenosis of the three major epicardial vessels or branches
Performed using Judkins technique.
CAD assessed by two independent assessors blind to other investigative findings</td></tr>
<tr><td>Time between testing & treatment</td><td>Index test performed within 2 weeks of CA</td></tr>
<tr><td>Length of follow-up</td><td>Dates of study not reported</td></tr>
<tr><td>Location</td><td>UK (single centre)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Dobutamine stress echocardiography*
<table>
<tr><td></td><td>CAD present on CA</td><td>CAD absent on CA</td></tr>
<tr><td>+ve index test result</td><td>86 (TP)</td><td>17 (FP)</td></tr>
<tr><td>-ve index test result</td><td>24 (FN)</td><td>30 (TN)</td></tr>
</table>
Sensitivity 78%; specificity 64%; PPV 84%; NPV 56%

Tests were terminated in cases of intolerable symptoms, severe hypertension, substantial increase in systolic BP, tachycardia. (Numbers not reported).</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Study limitations:</td></tr>
</table>

Bibliographic reference	**Author: Hennessy et al** **Dobutamine stress echocardiography for the assessment of patients without history or electrocardiographic evidence of myocardial infarction. Journal of Noninvasive Cardiology 2: 7-11.** **Year: 1998**
	1a. Unclear if patients were enrolled consecutively – UNCLEAR 1b. Patients recruited on basis of referral for coronary angiography HIGH 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

*=calculated by reviewer

Table 46 Hoffman 1993

Bibliographic reference	**Author: Hoffman et al** **Comparative Evaluation of bicycle and Dobutamine Stress Echocardiography with perfusion Scintigraphy and Bicycle electrocardiogram for Identification of Coronary Artery Disease.** **Year: 1993**
Study type	Cross-sectional
Aim	To compare the accuracy of exercise ECG, exercise echocardiography, dobutamine stress echocardiography and ^{99m}Tc-MIBI for detecting CAD.
Patient characteristics	**Inclusion** Prospective patients without prior Q-wave myocardial infarction referred for evaluation of suspected CAD. **Exclusion** **Other** Male/Female 51/15 Mean age (y) (SD) 57 (10)
Number of patients	66
Index test	Medication (types not specified) was discontinued 24 hours before examination.

Bibliographic reference	**Author: Hoffman et al** **Comparative Evaluation of bicycle and Dobutamine Stress Echocardiography with perfusion Scintigraphy and Bicycle electrocardiogram for Identification of Coronary Artery Disease.** **Year: 1993**
	Exercise stress Echo (Index test 4) Patients performed symptom-limited bicycle exercise with ECG and BP monitoring. Before exercising resting sequences were acquired with the patient in the parasternal short- and long-axis and apical 4- and 2-chamber views with the patient in the left lateral decubitus position and images were digitized. Exercise was continued until 85% of expected maximal HR was achieved but stopped in cases of exhaustion, development of severe angina, significant electrocardiographic changes, serious arrhythmia or hypotension. Recording was completed within 60 seconds of exercise termination for each of the 4 views.
Reference standard (or Gold standard)	**Coronary angiography** Judkins technique was applied. Interpretation by angiographers blinded to other clinical data. CAD was defined as luminal area stenosis of >70% in at least 1 major artery branch. Two orthogonal planes were used to measure the luminal area narrowing. Measurements were performed manually with calipers.
Time between testing & treatment	Within 2 weeks
Length of follow-up	Study duration not specified
Location	Germany
Diagnostic accuracy measures (2 x 2 table)	Post exercise echocardiography showed insufficient endocardial border definition in 6/66 patients, but data for all 66 patients were included. **TP* FP* FN* TN * Sens% Spec%** Exercise Echo (4) 40 2 10 14 80.0 87.0 *calculated by reviewer from sensitivity, specificity, total sample size (66) and number with gold standard test (50) No mention of serious adverse events relating to ICA or numbers of adverse events in relation to exercise echo.
Source of funding	Not mentioned
Comments	While dobutamine stress echo and MIBI-SPECT were also carried out on 64/66 and 55/64 patients respectively, the corresponding numbers of those with and without by coronary angiography were not provided therefore it was not possible to back calculate the 2x2 data and the results for these tests are not reported. **Study limitations:** 1a. Prospective enrolment but no mention of consecutive, no exclusion criteria stated HIGH

Bibliographic reference	**Author: Hoffman et al** **Comparative Evaluation of bicycle and Dobutamine Stress Echocardiography with perfusion Scintigraphy and Bicycle electrocardiogram for Identification of Coronary Artery Disease.** **Year: 1993**
	1b. Patients all had suspected CAD but no breakdowns with chest pain provided. Patients were recruited on basis of referral for coronary angiography. HIGH 2a. diagnostic thresholds not specified and unclear how those patients with insufficient border definition were classified. HIGH 2b. LOW 3a. Degree of stenosis measured manually with calipers. LOW 3b. LOW 4. LOW

*=calculated by reviewer

Table 47 Marangelli 1994

Bibliographic reference	**Author: Marangelli et al** **Detection of coronary artery disease by digital stress echocardiography: comparison of exercise, transesophageal atrial pacing and dipyridamole echocardiography.** **Year: 1994**
Study type	Cross-sectional
Aim	To assess and compare the diagnostic potential of exercise, trans-esophageal atrial pacing and dipyridamole echocardiography in a clinical setting
Patient characteristics	**Inclusion:** - suspected CAD scheduled for CA evaluation of chest pain - underwent routine exercise echocardiography **Exclusion:** - Valvular heart disease; congenital heart disease, cardiomyopathies - Previous history of MI - Left ventricular wall motion abnormalities in baseline conditions - Patients with technically inadequate resting echo images to assess left ventricular wall motion **Other characteristics:**

Bibliographic reference	**Author: Marangelli et al** **Detection of coronary artery disease by digital stress echocardiography: comparison of exercise, transesophageal atrial pacing and dipyridamole echocardiography.** **Year: 1994**
	Age in years (n=82) – mean (SD) 68 (8) Gender (n=82) – m/f (%) 69/13 (84% male)
Number of patients	104 consecutive patients met inclusion/exclusion 82 (79%) agreed to undergo both transesophageal atrial pacing and dipyridamole echocardiography 60 (58%) included in final analyses (all patients who had usable results on all three index tests) 44 (42%) overall patient exclusions from analysis sample. Exclusion reasons as follows: • Exercise (exclusions n=24): - 4 due to musculoskeletal diseases - 16 echo images were not interpretable - 4 submaximal exercise yielded non-diagnostic results • Dipyridamole echocardiography (exclusions n=3) - 2 due to difficulties finding superficial veins for drug infusion - 1 due to inadequate imaging • Transesophageal atrial pacing (exclusions n=19) - 9 unable to tolerate transesophageal catheter or electrical stimulation of oesophagus - 7 difficulty obtaining stable atrial capture - 3 appearance of 2nd degree Luciani-Wenckebach atrioventricular block at suboptimal heart rates
Index test	**Exercise stress** - Echo performed using standard equipment (Hewlet Packard Sonos 1000). - Digital and video imaging of both apical (four-chamber, two-chamber and long-axis views) and tomographic planes - After echo at rest, patients exercised on treadmill (DelMar E17 and Cardioovit CS12/M, Excel software, Schiller) according to the Bruce protocol - Echocardiographic recording repeated post-exercise using same views as baseline, within first 2 minutes of stress interruption (95% within first minute) - Images also stored in quad screen format for rest vs. stress comparisons **Transesophageal atrial pacing (TAP)**

Bibliographic reference	**Author: Marangelli et al** **Detection of coronary artery disease by digital stress echocardiography: comparison of exercise, transesophageal atrial pacing and dipyridamole echocardiography.** **Year: 1994**
	- Bipolar catheter connected to transesophageal atrial stimulator (Arzco model 7A) - Starting at 100bpm, heart rate was increased every 2 minutes by 10 beats/min until chest pain or severe wall abnormalities appeared or maximal step of 150bpm for 5 min was completed - Apical and tomographic planes (two- and four-chamber and long-axis) and precordial long or short-axis images recorded before and throughout TAP **Dipyridamole echocardiography** - After baseline echocardiographic examination (apical two- and four-chamber, long-axis) and precordial long or short-axis dipyridamole was infused at 0.56mg/kg body weight in 4 mins - Echo examination started immediately after start of infusion and continued throughout - If by 8 minutes after start of infusion no ECG or echocardiographic wall motion abnormalities appeared, a second dose of 0.28mg/kg in 2 mins was administered - Digital baseline images were visualised throughout and compared with stress wall motion images with videotape recording at 4 min intervals - Patients were monitored for 20 mins after end of drug infusion - Aminophylline or nitrates administered et end of test where necessary All stress procedures performed after adequate withdrawal of all cardioactive drugs. **Interpretation:** - Digital images from all three stress tests interpreted by a single experienced observer independent of the person performing the test and blind to patient history, clinical data (including previous tests and ECG findings) - Left ventricular wall divided into 16 myocardial segments; wall motion score assigned to each (according to American Society of Echocardiography guidelines) - Positive test defined as onset of left ventricular wall motion abnormalities
Reference standard (or Gold standard)	**Coronary angiography (CA)** CAD defined as lumen narrowing ≥75% of one or more major epicardial vessels. Multiple projections of coronary arteries obtained using Judkins technique. Coronary vessels visually assessed by one experienced observer
Time between testing &	Dipyridamole and transesophageal atrial pacing echocardiography were scheduled to be performed in a random

<table>
<tr><td>Bibliographic reference</td><td>Author: Marangelli et al
Detection of coronary artery disease by digital stress echocardiography: comparison of exercise, transesophageal atrial pacing and dipyridamole echocardiography.
Year: 1994</td></tr>
<tr><td>treatment</td><td>sequence at the same time on 2 consecutive days; 1 to 3 days before CA.</td></tr>
<tr><td>Length of follow-up</td><td>Study dates: November 1991 to January 1993.</td></tr>
<tr><td>Location</td><td>Italy (single centre)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>(a) Exercise 2D echo (n=60)*
<table>
<tr><td></td><td>CAD present on CA</td><td>CAD absent on CA</td></tr>
<tr><td>+ve index test result</td><td>31 (TP)</td><td>3 (FP)</td></tr>
<tr><td>-ve index test result</td><td>4 (FN)</td><td>22 (TN)</td></tr>
</table>
Sensitivity 89%; specificity 88%

(b) Transesophageal atrial pacing 2D echocardiography (n=60)*
<table>
<tr><td></td><td>CAD present on CA</td><td>CAD absent on CA</td></tr>
<tr><td>+ve index test result</td><td>29 (TP)</td><td>6 (FP)</td></tr>
<tr><td>-ve index test result</td><td>6 (FN)</td><td>19 (TN)</td></tr>
</table>
Sensitivity 83%; specificity 76%

(c) Dipyridamole 2D echocardiography (n=60)*
<table>
<tr><td></td><td>CAD present on CA</td><td>CAD absent on CA</td></tr>
<tr><td>+ve index test result</td><td>15 (TP)</td><td>2 (FP)</td></tr>
<tr><td>-ve index test result</td><td>20 (FN)</td><td>23 (TN)</td></tr>
</table>
Sensitivity 43%; specificity 92%

Side Effects: Aminophylline required to stop cephalea or flushing. N=5 required nitroglycerine and n=2 required IV nitrates to stop angina, ST depression or severe wall motion abnormalities.
No mention of adverse events associated with ICA.</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
</table>

Bibliographic reference	**Author: Marangelli et al** **Detection of coronary artery disease by digital stress echocardiography: comparison of exercise, transesophageal atrial pacing and dipyridamole echocardiography.** **Year: 1994**
Comments	Only 60 patients (58%) were included in analyses due to exclusions for various test- and non-test specific reasons (see 'Number of patients' above). All patients being assessed for chest pain, but limited reporting of other study sample characteristics **Study limitations:** 1a. LOW 1b.Patients recruited to study on basis of referral for coronary angiography HIGH 2a. LOW 2b. LOW 3a. Not clear if observer assessing CA results was independent of the one who interpreted index tests - HIGH 3b. LOW 4. LOW

*=calculated by reviewer

Table 48 Mazeika 1991

Bibliographic reference	**Author: Mazeika et al** **Uses and limitations of high dose dipyridamole stress echocardiography for evaluation of coronary artery disease..** **Year: 1991**
Study type	Cross-sectional
Aim	To establish the sensitivity and specificity, safety and efficacy of high dose dipyridamole stress echocardiography in the detection of CAD and to compare these results with dipyridamole stress electrocardiography (ECG) and exercise.
Patient characteristics	**Inclusion:** - Patients referred for coronary angiography for suspected CAD **Exclusion:** - Cardiac failure

Bibliographic reference	**Author: Mazeika et al** **Uses and limitations of high dose dipyridamole stress echocardiography for evaluation of coronary artery disease..** **Year: 1991**
	- Unstable angina - Bronchospasm - Left bundle branch block - ≥1mm ST segment deviation from isoelectric on the baseline ECG **Other characteristics:** Age in years (n=55) – mean (SD) 55 (9) Gender (n=55) – m/f (%) 41/14 (75% male)
Number of patients	58 patients screened for inclusion 55 included in analyses 3 exclusions due to inadequate baseline imaging
Index test	**High dose dipyridamole stress echocardiography** - Antianginal medication and caffeine avoided prior to examination - After collection of baseline cross-sectional echocardiographic data, iv dipyridamole (0.6mg/kg) was infused over 5 mins, followed by a 5 minute interval, then a further 0.4mg/kg infusion over 5 minutes - Continuous cross-sectional echocardiography conducted for up to 30 mins after administration of dipyridamole - Parasternal long- and short-axis views and the apical four- and two-chamber views obtained; images recorded on videotape for analysis Image analysis: - Performed blind from video playback by two experienced observers – disagreements resolved by consensus - 11 segment (Hammersmith Hospital) model of left ventricle applied to analysis of wall motion - Echocardiograms read baseline and peak stress; each segment graded as normal / hyperkinetic / hypokinetic / akinetic / dyskinetic Positive test interpreted on basis of (a) new abnormality of wall motion compared with baseline, or (b) worsening asynergy (hypokinesis in any segment at baseline deteriorating to akinesis or dyskinesis with dipyridamole stress)

<table>
<tr><td>Bibliographic reference</td><td>Author: Mazeika et al
Uses and limitations of high dose dipyridamole stress echocardiography for evaluation of coronary artery disease..
Year: 1991</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography (CA)
- Using Philips Poly Diagnostic C imaging system and Judkins' technique (multiple views).
- Evaluated blind to other results by a single experienced observer.
- CAD defined as ≥70% reduction in diameter of a major epicardial vessel</td></tr>
<tr><td>Time between testing & treatment</td><td>Mean of 17 days (SD 10) between CA and index test</td></tr>
<tr><td>Length of follow-up</td><td>Study dates not reported</td></tr>
<tr><td>Location</td><td>UK (single centre)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>High dose dipyridamole stress echocardiography

<table><tr><td></td><td>CAD present on CA</td><td>CAD absent on CA</td></tr><tr><td>+ve index test result</td><td>16</td><td>1</td></tr><tr><td>-ve index test result</td><td>24</td><td>14</td></tr></table>Sensitivity 40%; specificity 93%; PPV 94%; NPV 37%

Serious Adverse events: 1 cardiac arrest.
Other Side effects: chest pain n=27, headache n=17, dizziness n=9, dyspnoea n=5, nausea n=5, arrhythmia n=4, hypotention with syncope n=2, vomiting n=1.

No mention of adverse events in relation to ICA.</td></tr>
<tr><td>Source of funding</td><td>CORDA (heart charity)</td></tr>
<tr><td>Comments</td><td>Study limitations:
1a. Not clear if patients were consecutively enrolled - UNCLEAR
1b. 'Suspected CAD' study population (does not mention chest pain or give further clinical characteristics). Patients recruited on basis of referral for coronary angiography. HIGH
2a. LOW
2b. LOW
3a. LOW</td></tr>
</table>

Bibliographic reference	**Author: Mazeika et al** **Uses and limitations of high dose dipyridamole stress echocardiography for evaluation of coronary artery disease..** **Year: 1991**
	3b. LOW 4. LOW

*=calculated by reviewer

Table 49 Miszalski-Jamka 2012

Bibliographic reference	**Author: Miszalski-Jamka et al** **Quantitative myocardial contrast supine bicycle stress echocardiography for detection of coronary artery disease** **Year: 2012**
Study type	Cross-sectional
Aim	To determine the feasibility and accuracy of quantitative supine bicycle stress myocardial contrast echocardiography (MCE), and assess its incremental benefit over 2D echocardiography for detection of CAD.
Patient characteristics	**Inclusion:** - Suspected CAD and scheduled for coronary angiography **Exclusion:** - Known CAD including prior MI - Poor acoustic window - Contraindications to exercise testing - Contraindications to SonoVue (sulphur hexafluoride microbubbles for contrast imaging; Bracco, Milan) **Other characteristics:** Age in years – mean (SD) 57 (12) Gender – m/f (%) 47/14 (77% male) Background treatment (n=61), n (%): - beta-blockers 44 (72%) - angiotensin converting enzyme inhibitors 38 (62%) - calcium blockers 11 (18%)

<table>
<tr><td>Bibliographic reference</td><td>Author: Miszalski-Jamka et al
Quantitative myocardial contrast supine bicycle stress echocardiography for detection of coronary artery disease
Year: 2012</td></tr>
<tr><td></td><td>- nitrates 15 (25%)
- statins 36 (59%)

<table><tr><td></td><td>n=61</td></tr><tr><td>Hypertension – n (%)</td><td>39 (64%)</td></tr><tr><td>Diabetes mellitus – n (%)</td><td>4 (7%)</td></tr><tr><td>Hypercholesterolemia – n (%)</td><td>51 (84%)</td></tr><tr><td>Cigarette smoking - n (%)</td><td>25 (41%)</td></tr><tr><td>Family history of CAD– n (%)</td><td>41 (67%)</td></tr><tr><td>Angina pectoris – n (%)</td><td>32 (53%)</td></tr><tr><td>BMI > 25 (kg/m2)</td><td>33 (54%)</td></tr><tr><td>Exertional dyspnoea</td><td>23 (38%)</td></tr><tr><td>NYHA class 1</td><td>16 (26%)</td></tr><tr><td>NYHA class 2</td><td>29 (48%)</td></tr></table></td></tr>
<tr><td>Number of patients</td><td>61 consecutive patients</td></tr>
<tr><td>Index test</td><td>Supine Bicycle Stress MCE:
- Using Sonos 5500 (Philips Medical Systems, MA, USA)
- Antianginal medications not discontinued before exercise test.
- Initial workload set at 50 W and increased in 25-W increments every 2 minutes until endpoints achieved, in accordance with AHA/ACC guidelines.
- After obtaining peak-stress 2DE images, peak-stress MCE was acquired.
- Following termination of exercise, each subject remained supine on bicycle and another MCE was performed when subject’s heart rate returned to pre-exercise value.

Myocardial Contrast Echocardiography:
- Using low power imaging in apical four-chamber, two-chamber, and long-axis views
- SonoVue (Bracco) contrast agent administered via infusion pump (BR-INF100; Bracco, Geneva): initial bolus of 1 ml over 15 seconds then infusion at rate of 1.6 ml/min (adjusted to provide uniform myocardial contrast opacification without attenuation)</td></tr>
</table>

Bibliographic reference	Author: Miszalski-Jamka et al Quantitative myocardial contrast supine bicycle stress echocardiography for detection of coronary artery disease Year: 2012
	- After reaching a steady state of myocardial contrast opacification, consecutive 5–10 high power frames (mechanical index 1.5) emitted to disrupt contrast within myocardium - Subsequently, mechanical index switched back to low power to visualize myocardial contrast replenishment - Imaging sequences of at least 15 cardiac cycles (including steady state, flash frames, and replenishment) were stored digitally for each apical view at peak exercise and post-stress. **MCE assessment - Qualitative:** - MCE sequences assessed offline for presence and location of WMAs (left ventricular opacification [LVO] component) and/or perfusion abnormalities (myocardial perfusion component) by 2 independent, experienced viewers blinded to other investigations and clinical data. **Wall motion abnormalities (WMAs)** - Used a 17-segment model of left ventricle, and segments were assigned to coronary artery territories - WMAs scored as follows: (1) normal, (2) hypokinetic, (3) akinetic, (4) dyskinetic - Positive test result = increase in score from rest to stress in at least one segment. **Perfusion abnormalities** - Myocardial perfusion assessed in terms of contrast opacification and/or replenishment (uninterpretable segments excluded from analysis) - Contrast opacification of interpretable segments graded using a 3-point scale: 1 – normal, 2 – reduced, or 3 – none, based on relative assessment (in comparison with the best opacified segment) - Segmental replenishment evaluated in terms of number of heart cycles required to refill a segment after microbubble destruction. - A perfusion defect was considered present if peak-stress myocardial contrast opacification was graded as reduced or none and/or peak-stress contrast replenishment exceeded 3 cardiac cycles - Perfusion defects were defined as reversible when myocardial contrast opacification score was higher at peak-stress than at post-stress and/or when difference between peak-stress and post-stress contrast replenishment exceeded 0 cardiac cycles - A reversible perfusion defect in 1 segment was considered to indicate ischemia. - Cut-off values for replenishment analysis were determined in previous study using ROC and reference intervals analysis.

<table>
<tr><td>Bibliographic reference</td><td>Author: Miszalski-Jamka et al
Quantitative myocardial contrast supine bicycle stress echocardiography for detection of coronary artery disease
Year: 2012</td></tr>
<tr><td></td><td>Quantitative MCE Analysis:
- Myocardial blood flow quantified using dedicated software (QLAB; Philips Medical Systems, Bothell, WA, USA) by an independent experienced observer blinded to other investigations and clinical data
- MCE sequences were analysed in end systolic frames starting in frame immediately after the flash and including subsequent cardiac cycles, manually placing and tracking regions of interest within the myocardium of each left ventricular segment with careful exclusion of epicardial and endocardial borders
- MCE intensity data in each left ventricular segment were automatically fitted to the monoexponential function y = A[1 – exp(–ßt)] + C, where A represents the peak plateau signal intensity, ß is the rate of signal increase, and C the offset for signal intensity (intercept at origin of replenishment curve). Curves not fitting the monoexponential function were considered uninterpretable.
- An index of myocardial blood flow was calculated as the product of A and ß. The A, ß, and Aß were expressed as average values of all segments in individual coronary artery territories. The A, ß, and Aß reserves were calculated as the ratio of peak stress to baseline values, respectively.
- ROC curves were used to determine the best cut-off values to identify ischemia.</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography
CAD defined as stenosis of ≥ 50% diameter
Performed by an experienced interventional cardiologist blinded to clinical and echocardiographic results
Undertaken with CAAS software (CAAS II; Pie Medical Imaging, Maastricht)
Quantitative analysis - measurements expressed as % of diameter narrowing with the nearest normal-appearing region as a reference</td></tr>
<tr><td>Time between testing & treatment</td><td>CA performed within 15 days of index test</td></tr>
<tr><td>Length of follow-up</td><td>Study dates not reported</td></tr>
<tr><td>Location</td><td>Poland (single centre)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>(a) Exercise myocardial contrast echo (MCE) - left ventricular opacification (LVO) analysis*
<table>
<tr><td></td><td>CAD present on CA</td><td>CAD absent on CA</td></tr>
<tr><td>+ve index test result</td><td>32 (TP)</td><td>4 (FP)</td></tr>
<tr><td>-ve index test result</td><td>9 (FN)</td><td>16 (TN)</td></tr>
</table>
Sensitivity: 78%; specificity 80%</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Author: Miszalski-Jamka et al
Quantitative myocardial contrast supine bicycle stress echocardiography for detection of coronary artery disease
Year: 2012</td></tr>
<tr><td></td><td>(b) Exercise myocardial contrast echo (MCE) - qualitative perfusion analysis*
<table><tr><td></td><td>CAD present on CA</td><td>CAD absent on CA</td></tr><tr><td>+ve index test result</td><td>35 (TP)</td><td>4 (FP)</td></tr><tr><td>-ve index test result</td><td>6 (FN)</td><td>16 (TN)</td></tr></table>Sensitivity 85%; specificity 80%

(c) Exercise myocardial contrast echo (MCE) - quantitative (Aß reserve) perfusion analysis*
<table><tr><td></td><td>CAD present on CA</td><td>CAD absent on CA</td></tr><tr><td>+ve index test result</td><td>38 (TP)</td><td>4 (FP)</td></tr><tr><td>-ve index test result</td><td>3 (FN)</td><td>16 (TN)</td></tr></table>Sensitivity 93%; specificity 80%
Above results all for ≥50% stenosis.

Sensitivity only reported for ≥70% stenosis 89%, 89% and 94% respectively (unable to back calculate 2x2 table).

No mention of side effects/adverse events.</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Study limitations:
1a. LOW
1b. Patients recruited on basis of referral for coronary angiography HIGH
2a. LOW
2b. LOW
3a. LOW
3b. LOW
4. LOW</td></tr>
</table>

*=calculated by reviewer

Table 50 Nixdorff 2008

Bibliographic reference	**Author: Nixdorff et al.** **Head-to-head comparison of dobutamine stress echocardiography and cardiac computed tomography for the detection of significant coronary artery disease.** **Year: 2008**
Study type	Cross-sectional
Aim	To compare the validity of dobutamine stress echocardiography (DSE) versus electron beam cardiac computed tomography (EBCT)* versus both together in a prospective study design to detect significant coronary artery disease *note: EBCT data not extracted as outside the remit of this review
Patient characteristics	**Inclusion:** - suspected CAD - admitted for elective, invasive coronary angiography as primary diagnostic procedure - stable, regional clinical condition - normal global left ventricular function in echocardiography **Exclusion:** - previous myocardial infarction, coronary intervention, or surgery - severe arterial hypertension - severe arrhythmia, - atrial fibrillation, - valve disease, - contraindications to iv dobutamine or X-ray contrast **Other characteristics:** Mean age in years 62 Gender – m/f (%): 47/32 (60% male)
Number of patients	79 consecutive patients 71 patients (90%) included in final analyses 8 exclusions due to technical issues (images not evaluable): - atrial flutter during DSE (n=1) - suboptimal heart rate in DSE (n=2)

<table>
<tr><td>Bibliographic reference</td><td>Author: Nixdorff et al.
Head-to-head comparison of dobutamine stress echocardiography and cardiac computed tomography for the detection of significant coronary artery disease.
Year: 2008</td></tr>
<tr><td></td><td>- developed limited echogenicity in DSE (n=2)
- limited compliance in DSE (n=1)
- experienced respiratory artefacts in EBCT (n=2)</td></tr>
<tr><td>Index test</td><td>Dobutamine stress echocardiography
- Performed with HP Sonos 5500 (Philips, The Netherlands)
- Dobutamine infusion: 5–40µg/kg/min (plus 0.25–1.0 mg atropine if necessary) as per standard protocol
- All echocardiographic images digitized and displayed as continuous cine loops using quad-screen display for review of pre-, low, and high dose, as well as post-dobutamine infusion steps

Assessment and interpretation:
- Observers blind to other investigations
- Regional wall motion analysed according to 16-segment model of the American Society of Echocardiography
- A positive finding for significant CAD was defined by induced wall motion abnormalities in ≥1 segment</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography (CA)
Quantitative CA using QuantCOr.QCA V 2.0 (Pie Medical Imaging, Maastricht, The Netherlands)
Observer blinded to the noninvasive tests

Significant CAD defined as coronary diameter reduction of ≥70% in at least 2 projections (NHLBI class II)</td></tr>
<tr><td>Time between testing & treatment</td><td>CA within 1-3 days of index test</td></tr>
<tr><td>Length of follow-up</td><td>Study dates not reported</td></tr>
<tr><td>Location</td><td>Not reported (study authors from Germany, Italy and Belgium)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Dobutamine stress echocardiography (n=71)*
<table>
<tr><td></td><td>CAD present on CA</td><td>CAD absent on CA</td></tr>
<tr><td>+ve index test result</td><td>23 (TP)</td><td>6 (FP)</td></tr>
<tr><td>-ve index test result</td><td>10 (FN)</td><td>32 (TN)</td></tr>
</table>
Sensitivity 70%; specificity 84%; PPV 79%; NPV 76%</td></tr>
</table>

Bibliographic reference	**Author: Nixdorff et al.** **Head-to-head comparison of dobutamine stress echocardiography and cardiac computed tomography for the detection of significant coronary artery disease.** **Year: 2008**
	Side effects: atrial flutter n=6, No mention of adverse events in relation to ICA.
Source of funding	Supported by grants from the ELAN-Program, University of Erlangen, Germany
Comments	**Study limitations:** 1a. LOW 1b Not clear whether patients have chest pain ('suspected CAD' but no further clinical breakdown and limited reporting of other patient characteristics). Patients recruited on basis of referral for coronary angiography. HIGH. 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

*=calculated by reviewer

Table 51 Onishi 2010

Bibliographic reference	**Onishi T, Uematsu M, Watanabe T, Fujita M, Awata M, et al. (2010) Objective interpretation of dobutamine stress echocardiography by diastolic dyssynchrony imaging: a practical approach. Journal of the American Society of Echocardiography 23: 1103-1108.**
Study type	Cross-sectional
Aim	To investigate whether diastolic dyssynchrony imaging is useful for the objective interpretation of dobutamine stress echocardiography
Patient characteristics	**Inclusion:** - referred for dobutamine stress echocardiography for suspected CAD - agreed to undergo coronary angiography **Exclusion:**

<table>
<tr><td>Bibliographic reference</td><td>Onishi T, Uematsu M, Watanabe T, Fujita M, Awata M, et al. (2010) Objective interpretation of dobutamine stress echocardiography by diastolic dyssynchrony imaging: a practical approach. Journal of the American Society of Echocardiography 23: 1103-1108.</td></tr>
<tr><td></td><td>- abnormal echocardiographic results at rest (wall motion abnormalities, significant valvular diseases, dilated or restrictive cardiomyopathies, left ventricular hypertrophy, pulmonary hypertension)
- previous MI, coronary angioplasty or bypass grafting
- atrial fibrillation or flutter
- pacemaker implantation
- left bundle branch block
- congestive heart failure

Other characteristics:
<table>
<tr><td></td><td>n=59</td></tr>
<tr><td>Mean age in years (SD)</td><td>64 (11)</td></tr>
<tr><td>Gender – m/f, (%)</td><td>39/20 (66% male)</td></tr>
<tr><td>Hypertension</td><td>46 (78%)</td></tr>
<tr><td>Dyslipidaemia</td><td>36 (61%)</td></tr>
<tr><td>Hyperuricemia</td><td>10 (17%)</td></tr>
<tr><td>Diabetes mellitus</td><td>27 (46%)</td></tr>
<tr><td>Current smoker</td><td>22 (37%)</td></tr>
<tr><td>Medication:
- beta-blockers
- Ca antagonists
- nitrates</td><td>
8 (14%)
27 (46%)
23 (39%)</td></tr>
</table></td></tr>
<tr><td>Number of patients</td><td>62 patients enrolled
59 patients included in analysis
3 exclusions due to inadequate ultrasound images</td></tr>
<tr><td>Index test</td><td>Dobutamine stress echocardiography
Standard dobutamine stress echo protocol used:
- Dobutamine given in 3 min increments from 10-40µg/kg/min
- Up to 2mg atropine given, as needed, to achieve 85% of age-predicted maximum heart rate</td></tr>
</table>

Bibliographic reference	**Onishi T, Uematsu M, Watanabe T, Fujita M, Awata M, et al. (2010) Objective interpretation of dobutamine stress echocardiography by diastolic dyssynchrony imaging: a practical approach. Journal of the American Society of Echocardiography 23: 1103-1108.**
	Routine echocardiography and colour-coded tissue Doppler imaging (TDI): - Using Aplio SSA-770A (Toshiba, Japan) with 3.6NHz transducer - Performed in standard apical planes, including four- and two-chamber and long-axis views - TDI images digitally recorded at both rest and peak dobutamine Two methods of analysis were compared: (i) Classic wall motion analysis: - Assessed by expert blinded to clinical and angiographic data - Regional wall motion score obtained for each segment of standard 16 segment model (myocardial performance classed as: normal, mildly hypokinetic, severely hypokinetic, akinetic, dyskinetic) - Positive test indicated by new or worsening wall motion abnormalities with stress (ii) Diastolic dyssynchrony imaging: - Utilised the stored digital TDI images at rest and peak stress and software developed by study team - Software provides a measure of post-systolic shortening: delay of the displacement peak from the end-systole is colour coded from green (no delay) to red (delay greater than selected time window) - Positive test indicated when the part of the left ventricle was segmentally colour-coded red - Assessed intra-observer agreement (97% n=30); inter-observer agreement (90%, n=30).
Reference standard (or Gold standard)	**Coronary angiography (CA)** Quantitative CA using an automated edge detection system (CASS; Pie Medical Imaging BV, Maastricht) Performed by independent expert cardiologist blinded to other investigations and clinical data Significant CAD defined as >50% maximal luminal stenosis in any plane
Time between testing & treatment	CA performed within 3 weeks of dobutamine stress echocardiography
Length of follow-up	Study dates: May 2006 to July 2008
Location	Japan (single centre)
Diagnostic accuracy measures (2 x 2 table)	**(i) Dobutamine stress echocardiography – analysis by diastolic dyssynchrony imaging at peak dobutamine stress, with time window of 80msec used as cut-off value (n=59)*** | | CAD present on CA | CAD absent on CA |

Bibliographic reference	**Onishi T, Uematsu M, Watanabe T, Fujita M, Awata M, et al. (2010) Objective interpretation of dobutamine stress echocardiography by diastolic dyssynchrony imaging: a practical approach. Journal of the American Society of Echocardiography 23: 1103-1108.**
	<table><tr><td>+ve index test result</td><td>33 (TP)</td><td>5 (FP)</td></tr><tr><td>-ve index test result</td><td>4 (FN)</td><td>17 (TN)</td></tr></table> Sensitivity 89%; specificity 77%; PPV 79%; NPV 81% **(ii) Dobutamine stress echocardiography – classic wall motion analysis (n=59)*** <table><tr><td></td><td>CAD present on CA</td><td>CAD absent on CA</td></tr><tr><td>+ve index test result</td><td>26 (TP)</td><td>3 (FP)</td></tr><tr><td>-ve index test result</td><td>11 (FN)</td><td>19 (TN)</td></tr></table> Sensitivity 70%; specificity 86%; PPV 87%; NPV 62% *=calculated by reviewer No serious adverse events associated with dobutamine infusion. CP and early termination n=7, wall motion abnormalities n=4, intolerable heart pounding n=10. No mention of any adverse events with ICA.
Source of funding	Not reported
Comments	**Study limitations:** 1a. LOW 1b. Patient population are ‘suspected CAD’ but chest pain is not reported as a symptom at baseline - UNCLEAR 2a. LOW 2b. LOW 3a. Not clear if analysis by diastolic dyssynchrony imaging was performed blind to results of angiographic testing and classic wall motion analysis of stress echo (which it was also being compared with) - UNCLEAR 3b. LOW 4. LOW

Table 52 Parodi 1999

Bibliographic reference	**Author: Parodi et al** **High dose dipyridamole myocardial imaging: simultaneous sestamibi scintigraphy and two-dimensional echocardiography in the detection and evaluation of coronary artery disease.** **Year: 1999**
Study type	Cross sectional
Aim	To compare the relative accuracy of high-dose dipyridamole stress imaging with 2D-Echo and sestamibi perfusion scintigraphy in detecting coronary artery disease.
Patient characteristics	**Inclusion** Prospective patients with history of chest pain on effort. **Exclusion** No previous MI, clear ECG signs of previous MI, unstable angina, heart failure, severe hypertension, valvular or other cardiac diseases, aged >70 years or taking methylxantines were not included. Previous PCI, CAGG. **Other** Men/Women 81/20. Mean age (y) (SD) 55 (9)
Number of patients	101
Index test	Calcium antagonists and nitrates were withdrawn 24 hrs before each tests. In patients receiving beta-blockers, therapy was discontinued 48hrs before tests. Patients underwent MCE and SPECT however only the results of MCE are reported here. This is because this study population was part of previously published work (Parodi et al 1991) whereby identical results for SPECT are reported. See separate evidence table for this study. **Echo** IV dipyridamole 0.56mg/kg/min over 4 mins (low dose) was administered the morning after an overnight fast (plus avoidance of caffeine for min 3hrs prior to test). ECG and BP monitoring took place. The test was interrupted if there was down sloping ST segment depression or if there was angina-like chest pain. In the absence of signs or symptoms of ischaemia, after a 4 min interval, an additional dose of 0.28mg/kg dipyridamole was given over 2 mins.

Bibliographic reference	**Author: Parodi et al** **High dose dipyridamole myocardial imaging: simultaneous sestamibi scintigraphy and two-dimensional echocardiography in the detection and evaluation of coronary artery disease.** **Year: 1999**
	Echos continually regarded during stress test and up to 15mins after. Appearance of wall motion abnormalities or extension of resting dissynergies were identified on multiple views. The studies were then analysed by to independent observers blinded to other test results. LV was divided into 13 segments (adapted American Soc. Of Echocardiography) to match nuclear segmentation and scored as follows. Wall motion was graded as 1=normal/hyperkinetic, 2=hypokinetic, 3=akinetic, 4=dyskinetic. The test was considered positive for myocardial ischemia in the presence of transient wall motion abnormalities. A wall motion index was derived by summing the total scores from all segments and dividing by number of interpretable segments. Each score was expressed as a percentage of maximal possible score.
Reference standard (or Gold standard)	**Coronary Angiography** Multiple projections and biplane contrast using Judkins or Sones technique. Anatomy was evaluated quantitatively by two experienced, independent observers in each centre, blinded to all other test/clinical data. Disagreement was resolved by consensus. Coronary artery stenosis was considered significant in the presence of luminal diameter narrowing of >50% (visual assessment). Duke scoring system was also used to evaluate number of diseased vessels, location of diseased vessels and involvement of the left anterior descending coronary artery. (0-100 scale 0=no disease 100=most severe disease).
Time between testing & treatment	Within 3 weeks.
Length of follow-up	Study duration not reported
Location	7 centres, Italy.
Diagnostic accuracy measures (2 x 2 table)	21 patients had non-significant lesions and 80 had significant lesions. (37 had single, 19 double and 24 triple vessel disease). **TP FP FN TN * Sens% Spec%** dipyridamole stress echo 62 5 18 16 78.0 76.0 No serious adverse events after low or high dose dipyridamole. Minor side effects: headache, flushing, nausea (52 and 57%) No mention of adverse events associated with ICA.
Source of funding	No mention

Bibliographic reference	**Author: Parodi et al** **High dose dipyridamole myocardial imaging: simultaneous sestamibi scintigraphy and two-dimensional echocardiography in the detection and evaluation of coronary artery disease.** **Year: 1999**
Comments	**Study limitations:** 1a. People aged >70 were excluded. Valid limitation? UNCLEAR 1b. All had history of typical chest pain. Unclear whether patients were recruited on basis of referral for coronary angiography. UNCLEAR. 2a. Carried out in 7 institutions with documented variability in quality control of echocardiography procedures/readings. UNCLEAR 2b. LOW 3a. LOW 3b. LOW 4. LOW

Table 53 San Roman 1996

Bibliographic reference	**Author: San Roman et al .** **Dipyridamole and Dobutamine-atropine Stress Echocardiography in the Diagnosis of Coronary Artery disease** **Year: 1996**
Study type	Cross-sectional
Aim	To compare the usefulness of dipyridamole echocardiography, dobutamine-atropine echocardiography, and exercise stress testing in the diagnosis of coronary artery disease and to analyse the agreement among the tests.
Patient characteristics	Consecutively enrolled patents Men 57, Women 45 with mean (SD) age 64 (11) years Admitted to the hospital for evaluation of chest pain and had no previous diagnosis of CAD. **Exclusion:** Previous MI, proven CAD, cardiac failure, angina uncontrolled with medical treatment, congential or valvular disease and cardiomyopathy. **Other characteristics**

Bibliographic reference	**Author: San Roman et al .** **Dipyridamole and Dobutamine-atropine Stress Echocardiography in the Diagnosis of Coronary Artery disease** **Year: 1996**
	Chest pain on exertion n=25, at rest in 61 and both on exertion and at rest in 16. Patients were receiving antianginal treatment when indicated by their referring physicians (21 beta-blockers, 35 on calcium antagonists and 55 on no treatment).
Number of patients	102
Index test	**(a) Dipyridamole echocardiography** – (index test 4b) Dipyridamole was infused 0.84mg/kg over 5 mins. IV aminophylline was given when myocardial ischemia developed. Nitroglycerin was administered if needed. **(b) Dobutamine echocardiography** – (index test 4b) Dobutamine was administered IV at 10mcg/kg/min and was increased at 10mcg increments up to max 40mcg/kg/min which was maintained for 6 mins. 1mg atropine was infused when the test result was still negative and HR was under 85% of age-gender-predicted max. HR. Propranolol (0.5-1.0mg IV) was given if a positive response appeared. Infusions of both the above medications were immediately interrupted if areas of transient asynergy, severe hypertension, severe hypotension or sustained ventricular arrhythmias developed. 2D Echocardiographic monitoring was performed during and up to 10 mins after dipyridamole or dobutamine drug infusion. New wall motion abnormalities were sought. BP and 12 lead-ECG were obtained every 3mins. All studies were evaluated by 2 independent and experienced reviewers who were blinded to patients' clinical data. Segmentation was carried out according to American Society Echocardiography recommendations. Wall motion was graded as normal, mild hypokinesia, severe hypokinesia, akinesia and dyskinesia. A test result was considered positive when areas of transient asynergy were visualized in one or more segments that were absent or of lesser degree in the baseline examination. The absence of hyperkinesia in response to dobutamine infusion was not interpreted as a positive result.
Reference standard (or Gold standard)	**Coronary Angiography** Carried out on all patients using Judkin's technique. Coronary angiograms were evaluated by hand-held electronic calipers. Significant coronary stenosis was considered when at least 50% reduction in the luminal

Bibliographic reference	**Author: San Roman et al . Dipyridamole and Dobutamine-atropine Stress Echocardiography in the Diagnosis of Coronary Artery disease Year: 1996**
	diameter in 1 or more of the major vessels or the main branches was present.
Time between testing & treatment	Maximum of 7 days, performed in random order.
Length of follow-up	Study duration not specified.
Location	Madrid, Spain.
Diagnostic accuracy measures (2 x 2 table)	Per patient analysis. 63 patients had significant CAD. **TP FP FN TN * Sens% Spec%** Dipyridamole 49 1 14 38 77.0 97.0 Dobutamine-atopine 49 2 14 37 77.0 95.0 No cardiac events occurred between tests. The incidence of major complications was slightly higher during dobutamine-atropine testing compared with dipyridamole (7% vs 2%). During dobutamine-atropine, one patient had left-sided heart failure, 2 needed pharmacologic support due to severe hypotension and 2 developed a sustained ventricular tachycardia. 2 Patients had increased systolic arterial pressure. Minor side effects with both drugs were palpitations, headache, nausea, vomiting, flushing (dipyridamole 37%, dobutamine-atropine 35%)
Source of funding	Not reported
Comments	Study limitations: 1a. LOW 1b. UNCLEAR whether recruitment was based on referral for coronary angiography. 2a. LOW 2b. LOW

Bibliographic reference	**Author: San Roman et al .** **Dipyridamole and Dobutamine-atropine Stress Echocardiography in the Diagnosis of Coronary Artery disease** **Year: 1996**
	3a. LOW 3b. LOW 4. LOW

Table 54 Severi 1993

Bibliographic reference	**Author: Severi et al** **Diagnostic and Prognostic Value of Dipyridamole Echocardiography in Patients With Suspected Coronary Artery Disease. Comparison with Exercise Electocardiography.** **Year: 1993**
Study type	Cross sectional
Aim	To assess the relative diagnostic and prognostic accuracies of high dose dipyridamole echocardiography.
Patient characteristics	1,049 inpatients without previous bypass surgery admitted to coronary clinic between 1986 and June 1991 for coronary angiographic evaluation because of chest discomfort were initially considered. **Inclusion criteria** History of chest pain, off antianginal therapy for at least 2 days (1 week for beta blockers), no previous myocardial infarction and/or obvious regional left ventricular dyssynergy of contraction at baseline and acceptable acoustic window under resting conditions. **Exclusion** Unequivocal history of previous MI or ECG evidence of previous transmural MI, unstable angina, need to continue antianginal or xanthine meds, inability to exercise adequately or hypertension or presence of ECG alterations preventing interpretation of the ECG, technically poor acoustic window at baseline and presence of an obvious regional dyssenergy detected by 2D echo under resting conditions. **Clinical characteristics** Age, Y (mean (SD)) 55 (4.1) Sex male/female 307/122 Family history of IHD **(no (%))** 194 (45)

Bibliographic reference	**Author: Severi et al** **Diagnostic and Prognostic Value of Dipyridamole Echocardiography in Patients With Suspected Coronary Artery Disease. Comparison with Exercise Electocardiography.** **Year: 1993**
	Smoking 238 (55) Cholesterol 66 (15) Diabetes 44(10 Obesity 63(14) Hypertension 124 (28) Canadian Angina class 1 - 65(15) 2 – 237 (55) 3 – 127 (29) 4 - ….. Clearly typical angina 132 (30) Abnormal resting ECG 138 (32)
Number of patients	429
Index test	**Dipyridamole echo** (performed within one week of coronary angiography) 2D with 12 lead ECG monitoring performed in combination with a dipyridamole infusion 0.56mg/kg over 4 mins. Followed by 4 mins of no dose then 0.28mg/kg in 2 mins. Echocardiograms were obtained during and up to 10 mins after dipyridamole. Wall motion score index was derived by the summation of individual segment scores divided by the number of interpreted segments (score 1= hyperkinesis; score 2=hypokinetic, marked reduction in endocardial motion, score 3=akinetic, virtual absence of inward motion or score 4=dyskinetic, paradoxical wall motion away from left ventricular center in systole). Inadequately visualised segments were not scored.
Reference standard (or Gold standard)	**Coronary angiography** Judkins or Sones technique. A vessel was considered to have significant obstruction if its diameter was narrowed by ≥75% with respect to the prestenotic tract (50% for left main). Two independent observers who were blind to results of index tests.
Time between testing & treatment	Within 1 week

Bibliographic reference	**Author: Severi et al** **Diagnostic and Prognostic Value of Dipyridamole Echocardiography in Patients With Suspected Coronary Artery Disease. Comparison with Exercise Electocardiography.** **Year: 1993**
Length of follow-up	Study duration 1986 and June 1991
Location	Italy
Diagnostic accuracy measures (2 x 2 table)	**TP FP FN TN * Sens% Spec%** Dipyridamole echo 185 18 62 165 75.0 90.0 No major side effects reported for index test or reference standard. 3 patients were unable to tolerate the higher dose of dipyridamole but their results were still included in the analysis. Minor side effects, excessive tachycardia and palpitations n=1, hypotension and symptomatic bradycardia n=2.
Source of funding	Not mentioned
Comments	**Study limitations:** 1a. appears prospective but consecutive sample not specifically mentioned. Known CAD not clearly part of exclusion criteria. HIGH 1b. Patients recruited on basis of referral for coronary angiography HIGH. 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

Table 55 Shaikh 2014

Bibliographic reference	**Author: Shaikh et al** **Feasibility, safety and accuracy of regadenoson-atropine (REGAT) stress echocardiography for the diagnosis of coronary artery disease: an angiographic correlative study.** **Year: 2014**
Study type	Cross-sectional
Aim	To study the feasibility, safety, and accuracy for CAD detection of the REGAT stress echocardiography protocol (regadenoson (REG) plus adjunctive atropine (AT) to achieve adequate chronotropy in addition to vasodilator

Bibliographic reference	**Author: Shaikh et al** **Feasibility, safety and accuracy of regadenoson-atropine (REGAT) stress echocardiography for the diagnosis of coronary artery disease: an angiographic correlative study.** **Year: 2014**
	stress), using coronary angiography (CA) as the gold standard.
Patient characteristics	**Inclusion:** - aged ≥18 years old with suspected CAD - scheduled for a clinically indicated cardiac catheterization (with or without a prior functional stress imaging study) **Exclusion:** - history of acute MI, unstable angina, prior percutaneous coronary intervention in last 3 months, non-sinus rhythm, left bundle branch block, electronic paced rhythm, or bypass surgery - typical listed contraindications to REG and AT - patients with bronchospastic lung disease **Other characteristics:** Age in years – mean (SD): 61 (7) Gender – m/f (%): 26/19 (58% male) Body Surface Area (m2) – mean (SD): 2.04 (0.23) Dyslipidaemia – n/N (%): 40/45 (89%) Hypertension– n/N (%): 31/45 (69%) Diabetes– n/N (%): 16/45 (36%) Family history of CAD– n/N (%): 29/45 (64%) Smoker– n/N (%): 6/45 (13%) History of stroke– n/N (%): 2/45 (4%) History of CHF– n/N (%): 1/45 (2%) Background treatment– n/N (%) - Aspirin use 36/45 (80%) - Statin use 31/45 (69%) - Beta blocker use 29/45 (64%) - Ace inhibitor or angiotensin receptor blocker use 21/45 (47%) Background diagnostics – n/N (%) - Prior exercise stress echocardiogram 17/45 (38%)

Bibliographic reference	**Author: Shaikh et al** **Feasibility, safety and accuracy of regadenoson-atropine (REGAT) stress echocardiography for the diagnosis of coronary artery disease: an angiographic correlative study.** **Year: 2014**
	- Prior pharmacologic MPI 7/45 (16%) - Prior dobutamine stress echocardiogram 7/45(16%) - Prior exercise MPI 5/45 (11%) - Prior treadmill ECG 2/45 (4%) - Prior regadenoson PET stress 1/45 (2%) - Total number of prior positive stress tests 30/45 (67%)
Number of patients	45 patients Note: 54/1596 consecutive patients (3.4%) met study inclusion/exclusion criteria and were initially enrolled; 9 subsequent exclusions due to: - severe hypertension (1) - increased pulmonary artery pressure (1) - tachycardia (1) - admitted for syncope day of scan (1) - glaucoma (2) - withdrew consent (3)
Index test	S**tress echocardiography using regadenoson (REG) plus atropine (AT) drug protocol** - Standard echocardiographic imaging planes were performed at rest using Acuson Sequia C512 (Siemens Medical Solutions, Malvern, USA). - All patients required to stop beta-blockers and nitrates at least 24hr prior to study. - Atropine (AT) used as follows: 5 initial patients: 0.25mg doses cumulative to 2mg; 4 patients (to test safety): 0.5 boluses to total of 2mg; 36 patients: 1mg bolus x 2 - After administration of 2mg AT, a single iv bolus dose of 400µg of regadenoson (REG) over 10 seconds was given followed by a saline flush - Standard stress echocardiographic views (apical 4, 3, 2 chamber views and parasternal long and short axis

<table>
<tr><td>Bibliographic reference</td><td>Author: Shaikh et al
Feasibility, safety and accuracy of regadenoson-atropine (REGAT) stress echocardiography for the diagnosis of coronary artery disease: an angiographic correlative study.
Year: 2014</td></tr>
<tr><td></td><td>windows) obtained 30-40 seconds later for side-by-side digital comparison to rest images
- Additional images obtained at 2 min post-REGAT to document any new changes not noted in initial imaging.
- Recovery images obtained when heart rate was around 100bpm
- Echocardiographic contrast was used as needed

Analysis:
- Interpreted independently by two experienced echocardiography readers blinded to clinical and angiographic data (disagreements resolved by consensus)
- Analysed off-line on a digital workstation (Syngo Dynamics, Siemens Medical Solution, Malvern, USA)
- Standard 16-segment model used for left ventricular wall motion and wall motion score index
- Positive stress study defined as new or worsening wall motion abnormality seen in 2 or more adjacent myocardial segments</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography (CA)
CAD defined as >70% luminal stenosis in any coronary vessel or >50% left main stenosis.</td></tr>
<tr><td>Time between testing & treatment</td><td>All patients had CA within 7 days of index test.
If CA was performed on same day, there was a minimum recovery period of one hour after REGAT prior to CA.
Images assessed qualitatively by independent angiographer blinded to clinical and echo data.</td></tr>
<tr><td>Length of follow-up</td><td>Study dates: October 2009 and January 2012</td></tr>
<tr><td>Location</td><td>USA (single centre)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Stress echocardiography using regadenoson (REG) plus atropine (AT)*

<table>
<tr><td></td><td>CAD present on CA</td><td>CAD absent on CA</td></tr>
<tr><td>+ve index test result</td><td>14 (TP)</td><td>3 (FP)</td></tr>
<tr><td>-ve index test result</td><td>9 (FN)</td><td>19 (TN)</td></tr>
</table>
Sensitivity 60.9%; specificity 86.4%

Safety analysis: dry mouth n=28, shortness of breath n=27, headache n=20, dizziness n=18, chest pain n=13,</td></tr>
</table>

Bibliographic reference	**Author: Shaikh et al** **Feasibility, safety and accuracy of regadenoson-atropine (REGAT) stress echocardiography for the diagnosis of coronary artery disease: an angiographic correlative study.** **Year: 2014**
	flushing n=9, blurry vision n=2, aminophylline use n=9, MI/death n=0. No mention of adverse events associated with ICA.
Source of funding	Astellas Pharma US, Inc.
Comments	Study terminated early due to slow recruitment (intended to recruit 110 patients) Only 30% of tested patients achieved target heart rate – may have affected sensitivity A study author receives research grants from funders (Astellas Pharma US, Inc) **Study limitations:** 1a. Patient recruitment was not consecutive; high number of patients refused to participate due to burden of testing or unwillingness to undergo a previously untested combination of agents (REG + AT); high proportion of study sample (67%) had positive prior tests – HIGH 1b. Unclear population applicability – 'suspected CAD'; no symptom breakdown given; chest pain not mentioned as a criterion. Patients recruited on basis of referral for coronary angiography. HIGH. 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

*=calculated by reviewer

G.1.4 Cardiac magnetic resonance (perfusion)

Table 56 Kawase 2004

Bibliographic reference	**Author: Kawase et al** **Assessment of Coronary Artery Disease with Nicorandil Stress Magnetic Resonance Imaging** **Year: 2004**

Bibliographic reference	**Author: Kawase et al** **Assessment of Coronary Artery Disease with Nicorandil Stress Magnetic Resonance Imaging** **Year: 2004**
Study type	Cross sectional
Aim	To evaluate the diagnostic accuracy of nicorandil stress perfusion MRI in detecting significant coronary stenosis in patients with suspected CAD.
Patient characteristics	**Inclusion** Consecutive patients who underwent coronary angiography for assessment of coronary artery disease. **Exclusion** History of MI, atrial fibrillation, ventricular extra-systole or contraindications to MR examination (claustrophobia, artificial pacemaker). **Other** Male/Female 29/21 Mean age (SD) 66.5 (11.7)
Number of patients	50
Index test	**Stress MRI** 1.5tesla (Philips) scanner used. Perfusion was assessed with a multi-slice turbo field echo with multi shot echo-planar-imaging. Immediately after a bolus dose of 0.1mg/kg of nicorandil diluted to 1mg/ml with physiological saline was intravenously injected for 5 seconds, breath-held dynamic MR image acquisition was initiated while 0.1ml gadolinium based contrast material was injected into the antecubital vein at 4ml/s. Breath-hold was from the start of the image acquisition for as long as possible. Cine images of cardiac function were obtained. After 10 minutes (to allow for clearance of contrast agent) the perfusion scan at rest was repeated. Images were evaluated by two readers blinded to other imaging results and clinical history. Rest and stress perfusion images were compared to differential low enhancement caused by coronary artery stenosis from artifacts. Segments showing reduced peak signal intensity or delayed wash-in when stressed by not at rest were regarded as pathological. Coronary artery territories were defined according to AHA guidelines.
Reference standard (or Gold standard)	**Coronary angiography** Performed in left and right coronary arteries according to standard Judkins technique. Quantitative analysis of coronary angiograms was carried out using CMS analysis software. Luminal diameter of stenosed artery showing maximal severity was measured at end diastole. Significant CAD was defined as 70% or more of lumen diameter stenosis.

Bibliographic reference	**Author: Kawase et al** **Assessment of Coronary Artery Disease with Nicorandil Stress Magnetic Resonance Imaging** **Year: 2004**
Time between testing & treatment	Within 1 week
Length of follow-up	Study duration / dates not reported
Location	Osaka, Japan
Diagnostic accuracy measures (2 x 2 table)	**Stress perfusion MRI (nicorandil)** TP 31, FN 1, FP 2, TN 16 Sensitivity 93.4% Specificity 94.1% No adverse effects during nicorandil stress in any patients.
Source of funding	Not mentioned
Comments	**Study limitations** 1a. LOW 1b. No mention of chest pain in the recruited patients (only suspected CAD). Patients recruited on basis of referral for coronary angiography. HIGH 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

Table 57 Klein 2008

Bibliographic reference	**Author: Klein et al.** **Combined magnetic resonance coronary artery imaging, myocardial perfusion and late gadolinium enhancement in patients with suspected coronary artery disease. Journal of Cardiovascular Magnetic Resonance 10: 4554** **Year: 2008**
Study type	Cross sectional
Aim	To assess the feasibility and diagnostic accuracy of CMR stress/res adenosine perfusion, infarct imaging and coronary angiography and their combination for the detection of significant stenosis in patients with suspected

Bibliographic reference	**Author: Klein et al.** **Combined magnetic resonance coronary artery imaging, myocardial perfusion and late gadolinium enhancement in patients with suspected coronary artery disease. Journal of Cardiovascular Magnetic Resonance 10: 4554** **Year: 2008**
	CAD scheduled for invasive coronary angiography.
Patient characteristics	**Inclusion** Consecutive patients with suspected CAD who were referred for invasive coronary angiography were prospectively included. **Exclusion** Contraindications for CMR, known myocardial infarction, atrial fibrillation, unstable angina, Av block, obstructive lung disease or claustrophobia. **Other** Age 60 (10) (37-78) BMI kg/m^2 mean (SD) 27.6 (4.1) N (%) Typical angina 30 (56) (significantly more people with angina in the group who had CAD) Atypical angina 15 (28) Dyspnoea on exertion 21 (39) (significantly fewer people with dyspnoea in the group who had CAD) Diabetes 12 (22) Hypertension 37 (69) (significantly more people with hypertension in the group who had CAD) Smoker 18 (33) Hypercholesterolaemia 41 (76) Family history 17 (31) Pathological ECG 17 (31)
Number of patients	54
Index test	**MRI (CMR)** Supine position. 1.5Tesla Philips scanner. A sufficient number of strictly transversal slices (120-140) were obtained to cover the whole heart. For the visual assessment of coronary artery stenosis quality was graded as excellent, good, moderate or non-diagnostic. The latter were not included in the analysis. For the final results only vessels with a diameter ≥2mm (suitable for revascularisation) were included.

Bibliographic reference	**Author: Klein et al.** **Combined magnetic resonance coronary artery imaging, myocardial perfusion and late gadolinium enhancement in patients with suspected coronary artery disease. Journal of Cardiovascular Magnetic Resonance 10: 4554** **Year: 2008**
	PERF – first pass stress perfusion – gating window 6mm. 1 saturation per pulse per slice, 2 short axis slices/heart beat) was begun after 3 minutes of IV adenosine infusion (140µg/min/kg body weight. After 10mins, rest perfusion (0.05mmol/kg GD-BOPTA) was performed, followed by additional 0.1mmol/kg. Late Gadolinium enhancement **(LGE)** was imaged in short axis and the standard long axis views after 10 minutes using an inversion recovery 3D turbo-gradient-echo-technique. A perfusion defect was graded visually as sub-endocardial (<75%) or transmural (≥75%). Any regional stress induced defect or LGE in any segment was considered positive. All **CMR** images were evaluated visually on ViewForum using 16 segment model by 2 experienced observers blinded to the other tests results. For the combination of tests, a patient was classified as having CAD if any of the tests was positive.
Reference standard (or Gold standard)	**Coronary angiography** Two experienced interventional cardiologists visually evaluated the cardiograms. They were blinded to the results of the other tests. A haemodynamically significant coronary stenosis was defined as >50% luminal narrowing.
Time between testing & treatment	Within 24 hours
Length of follow-up	Duration not specified.
Location	Hamburg, Germany
Diagnostic accuracy measures (2 x 2 table)	26/54 had significant CAD. 5 patients were not included in PERF analysis (not performed in 3 patients due to possible aortic stenosis not previously known or dyspnoea and analysis could not be performed in 2 due to non-diagnostic image quality). 8 patients were not included in MRCA due to non-diagnostic images. **CMR/PERF (n=49)** TP 20, FP 3, FN 3, TN 23* Sensitivity and specificity 87% and 88% respectively. (Accuracy 88%).

Bibliographic reference	**Author: Klein et al.** **Combined magnetic resonance coronary artery imaging, myocardial perfusion and late gadolinium enhancement in patients with suspected coronary artery disease. Journal of Cardiovascular Magnetic Resonance 10: 4554** **Year: 2008**
	CMR with LGE (n=54) TP 13, FP 1, FN 13, TN 27*. Sensitivity and specificity 50% and 96% respectively. (Accuracy 88%). **MR Coronary Angiography (MRCA) (n=46)** TP 20, FP 11, FN 2, TN 13* Sensitivity and specificity 91% and 54% respectively. (Accuracy 70%). **PERF/LGE (n=51)** TP 22, FP 3, FN 3, TN 23* Sensitivity and specificity 88% and 88% respectively. (Accuracy 88%). **PERF/LGE/MRCA (n=51)** TP 24, FP 10, FN 2, TN 15* Sensitivity and specificity 92% and 60% respectively. (Accuracy 75%). Adverse events/side effects: Severe dyspnoea during adenosine n=2. No mention of adverse events associated with ICA.
Source of funding	Not mentioned but one competing interest – One author is an employee of Philips Medical Systems.
Comments	**Study limitations:** 1a. LOW 1b. Patients with suspected CAD with breakdown by symptoms. Patients were recruited on basis of referral for coronary angiography. HIGH 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. All patients had reference tests but not all patients had all index tests/data suitable for analysis, however

Bibliographic reference	**Author: Klein et al.** **Combined magnetic resonance coronary artery imaging, myocardial perfusion and late gadolinium enhancement in patients with suspected coronary artery disease. Journal of Cardiovascular Magnetic Resonance 10: 4554** **Year: 2008**
	reasons were clearly stated and did not exceed 20% of total population. LOW

**=calculated by reviewer*

Table 58 Klem 2006

Bibliographic reference	**Author: Klem et al** **Improved Detection of Coronary Artery Disease by Stress Perfusion with Cardiovascular Magnetic Resonance With the Use of Delayed Enhancement Infarction Imaging** **Year: 2006**
Study type	Cross-sectional
Aim	To devise and test a predefined visual interpretation algorithm that combines cardiovascular magnetic resonance3 (CMR) data from perfusion and infarction imaging for the diagnosis of coronary artery disease (CAD).
Patient characteristics	**Inclusion** Consecutive patients with suspected CAD referred for elective coronary angiography screened for enrolment 3 days/week. **Exclusion** People with known CAD, previous MI or revascularization procedures. MRI related (e.g. pacemaker). Adenosine related (AV block). **Other** Age (y) Mean (SD) 58 (11.5) Number of risk factors 2.3 (1.1) **N (%)** Male gender 45 (49) **CAD risk factors** Diabetes 21 (23) Hypertension 59 (64)

Bibliographic reference	**Author: Klem et al** **Improved Detection of Coronary Artery Disease by Stress Perfusion with Cardiovascular Magnetic Resonance With the Use of Delayed Enhancement Infarction Imaging** **Year: 2006**
	Cigarette smoker 36 (39) Hypercholesterolaemia 50 (54) Family history of CAD 47 (52) Typical angina 31 (34) (Rose questionnaire) Numbers with other types of chest pain not reported **Medications** Statins 35 (38) Beta-blockers 30 (33) Aspirin 51 (55) ACE inhibitors 40 (43) **Indication for angiography** Positive stress nuclear study 44 (48) Positive stress echo study 19 (21) Positive treadmill ECG study 7 (8) Clinical symptoms 22 (24) Framingham risk score , triglycerides and fasting glucose were all significantly higher in the CAD vs non CAD groups (p=0,008, 0.04 and 0.03 respectively) 8 people did not undergo CMR. 3 = CMR related (did not fit into scanner (1), ECG cable malfunctioned (1), Unavailable scanner software (1). 5 = Non CMR related (consumed caffeine that morning (1), withdrew consent (1), IV access could not be obtained (1), contrast injection pump failure (1), adenosine-induced dyspnoea (1).
Number of patients	92 (100 patients enrolled, 8 excluded)
Index test	**Index test 6 (CMR)** - **Interpretation algorithm (including perfusion CMR (PERF) and Delayed enhancement (DE)-CMR)** - **PERF only** Adenosine gadolinium first-pass imaging for stress perfusion - **DE-CMR only** Signal to noise ratio Preparation: Blood samples were drawn after overnight fast for glucose, lipid profile and hsCRP. 12 lead ECG was

Bibliographic reference	**Author: Klem et al** **Improved Detection of Coronary Artery Disease by Stress Perfusion with Cardiovascular Magnetic Resonance With the Use of Delayed Enhancement Infarction Imaging** **Year: 2006**
	performed and scored for Q waves and bundle-branch block. 1.5Tesla scanner was used. Adenosine was infused 140µg/kg/min under ECG and continuous BP monitoring. Perfusion sequence was then applied. Gadolinium contrast (0.065mmol/kg) followed by saline flush was infuse via antecubital vein. Breath-holding stated from the appearance of contrast in the right ventricular cavity. Once the gadolinium bolus had transited the LV myocardium, adenosine was stopped and imaging completed 10-15s later. 4-5 short axis slices were obtained per heartbeat with a saturation-recovery, gradient echo sequence. 5mins after rest perfusion, DE-CMR was performed with a segment inversion-recovery technique. Scans were analysed by two observes, blinded to angiography results. Regional parameters were assessed with a 17 segment model. For perfusion images these were scored with a 4-point scale (0=normal, 1=probably normal, 2=probably abnormal, 3=definitely abnormal). CAD n= 37 patients. No CAD n=55.
Reference standard (or Gold standard)	**Coronary angiography** Performed using standard techniques. Operators blinded to CMR results. Luminal narrowing estimated visually. In cases of disagreement, quantitative analysis was performed. Significant CAD was defined as ≥70% narrowing of the luminal diameter of at least one major epicardial artery ≥50% narrowing of the left main artery. To tests the accuracy of the interpretation algorithm for each individual coronary lesion, the readers also evaluated the level of stenosis for each segment of the 17-segment model, the artery perfusing that segment and the maximum level of stenosis.
Time between testing & treatment	Within 24 hours
Length of follow-up	Duration January 2003 and January 2004.
Location	North Carolina, USA

Diagnostic accuracy measures (2 x 2 table)	**Index Test 6 (different variants)**	**TP**	**FP**	**FN**	**TN ***	**Sens%**	**Spec%**
	≥70% stenosis/≥50% LMA PERF+DE-CMR	33	7	4	48	89.2	87.3
	≥70% stenosis/≥50% LMA PERF only	31	23	6	32	83.8	58.2
	≥70% stenosis/≥50% LMA DE-CMR only	18	1	19	54	48.6	98.2
	≥60% stenosis/≥50% LMA PERF+DE-CMR	33	7	6	46	92.8	86.8

Bibliographic reference	**Author: Klem et al** **Improved Detection of Coronary Artery Disease by Stress Perfusion with Cardiovascular Magnetic Resonance With the Use of Delayed Enhancement Infarction Imaging** **Year: 2006**						
	≥60% stenosis/≥50% LMA PERF only	33	21	6	32	84.6	60.4
	≥60% stenosis/≥50% LMA DE-CMR only	18	1	21	52	46.2	98.1
	≥50% stenosis/≥50% LMA PERF+DE-CMR	34	6	10	42	77.3	87.5
	≥50% stenosis/≥50% LMA PERF only	36	18	8	30	81.8	62.5
	≥50% stenosis/≥50% LMA DE-CMR only	18	1	26	47	40.9	97.9
	Side Effects/Adverse events: Severe adenosine dyspnoea n=1. No mention of adverse events in relation to ICA.						
Source of funding	Not mentioned						
Comments	**Study limitations:** 1a. LOW 1b. Population suspected CAD (34% had typical angina symptoms) but indications for angiography reveal that majority of patients (total of 77%) had received a previous positive stress tests. Also patients recruited on basis of referral for coronary angiography. HIGH 2a. LOW 2b. LOW 3a. LOW 3b.LOW 4. LOW						

**=calculated by reviewer*

Table 59 Krittayaphong 2009

Bibliographic reference	**Author: Krittayaphong et al** **Myocardial perfusion cardiac magnetic resonance for the diagnosis of coronary artery disease: do we need rest images?** **Year: 2009**
Study type	Cross sectional

Bibliographic reference	**Author: Krittayaphong et al** **Myocardial perfusion cardiac magnetic resonance for the diagnosis of coronary artery disease: do we need rest images?** **Year: 2009**
Aim	To determine the accuracy of visual assessment and myocardial perfusion reserve index (MPRI) in the diagnosis of CAD and the accuracy of analysis based on rest-stress and stress images (from CMR) comparing to coronary angiography.
Patient characteristics	**Inclusion** Over 30 yrs old Referred for coronary angiography for suspected CAD **Exclusion** Contraindications to CMR such as pacemaker or implantable defibrillator implantation, history of claustrophobia or allergy to gadolinium History of MI History of revascularisation. Need for urgent revascularisation Clinical unstable condition **Other** Mean age 61.3 (SD 11.7) years. Male 38 (58%) Diabetes 18 (27%) Systemic hypertension 41 (62%) Cigarette smoking 4 (7%) Hypercholesterolaemia 41 (62%) History of heart failure 6 (9%) Chest pain 34 (52%) Medications: beta-blockers 32, calcium antagonists 11, nitrate 18, aspirin or clopidogrel 43, ACEI/ARB 34, statin 39.
Number of patients	66 (total screened n=78, 12 met at least one of exclusion criteria).
Index test	**CMR (Adenosine stress CMR)** Gyroscan NT Intera 1.5 tesla Philips scanner.

<table>
<tr><td>Bibliographic reference</td><td>Author: Krittayaphong et al
Myocardial perfusion cardiac magnetic resonance for the diagnosis of coronary artery disease: do we need rest images?
Year: 2009</td></tr>
<tr><td></td><td>Medications that might influence myocardial perfusion were withheld for at least five half-lives prior to the perfusion study.
CMR was started with gradient echo technique. All analyses (semi-quantitative) were performed by two readers with any disagreement solved by the third reader. All experienced readers. Segmentation of each slice was performed according to the recommendation of the AHA with the exclusion of segment 17 (most apical part) from the analysis.
Analysis of MPRI – signal intensity was determined for all dynamics and segments. Cut off value of 1.2 was applied based on ROC analysis in a pilot group of 20 patients. If the value was ≤1.2 (calculated for all segments) the segment was classed as ischemic. The test was considered abnormal when at least one segment was found to be ischemic.
Analysis by visual assessment – myocardial ischemia defined as a perfusion delay for at least five consecutive phases in at least one myocardial segment during peak myocardial enhancement.</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography
Left-sided cardiac catheterisation and coronary angiography by the Judkins technique. Coronary stenosis was filmed in the centre of the field from multiple projections. Reduction of luminal diameter of each lesion was reported as a percentage. Significant CAD was defined as 50% or more reduction.</td></tr>
<tr><td>Time between testing & treatment</td><td>Within one week (CMR first)</td></tr>
<tr><td>Length of follow-up</td><td>Time period of study not specified</td></tr>
<tr><td>Location</td><td>Thailand</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>38/66 patients diagnosed with CAD.
MPRI and Stress analysis only reported (per study protocol).

<table>
<tr><th></th><th>MPRI (CMR)*</th><th>Visual method (Stress)</th></tr>
<tr><td>TP</td><td>34</td><td>33</td></tr>
<tr><td>TN</td><td>22</td><td>21</td></tr>
<tr><td>FP</td><td>6</td><td>7</td></tr>
<tr><td>FN</td><td>4</td><td>5</td></tr>
<tr><td>Sensitivity (%, 95% CI)</td><td>89.5 (79.5, 95.9)</td><td>86.8 (72.7, 94.3)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Author: Krittayaphong et al
Myocardial perfusion cardiac magnetic resonance for the diagnosis of coronary artery disease: do we need rest images?
Year: 2009</td></tr>
<tr><td></td><td colspan="3">
<table>
<tr><td>Specificity (%, 95% CI)</td><td>78.6 (60.5, 89.5)</td><td>75 (56.6, 87.3)</td></tr>
<tr><td>PPV (%, 95% CI)</td><td>85 (70.9, 92.9)</td><td>82.5 (68.1, 91.3)</td></tr>
<tr><td>NPV (%, 95% CI)</td><td>84.6 (66.5, 93.9)</td><td>80.8 (62.1, 91.5)</td></tr>
<tr><td>Accuracy</td><td>84.8 (74.3, 91.6)</td><td>81.8 (70.9, 89.3)</td></tr>
<tr><td>Prevalence of CAD</td><td>57.6</td><td>57.6</td></tr>
</table>
*Data used in analysis

No mention of any side effects or adverse events for either test.</td></tr>
<tr><td>Source of funding</td><td colspan="3">Study funded by the research fund of Her Majesty Cardiac Centre, Siriraj Hospital. Bangkok, Thailand.</td></tr>
<tr><td>Comments</td><td colspan="3">Study limitations
1a. UNCLEAR if consecutive screening/enrolment – UNCLEAR
1b. Not all patients had chest pain (52%) and 6 patients had history of heart failure. Patients were recruited on basis of referral for coronary angiography. HIGH
2a. LOW
2b. LOW
3a. LOW
3b. LOW
4. LOW</td></tr>
</table>

G.1.5 Myocardial perfusion scintigraphy (MPS) SPECT/PET

Table 60 Budoff 1998

Bibliographic reference	**Author: Budoff et al** **Comparison of Exercise Electron Beam Computed Tomography and Sestamibi in the Evaluation of Coronary Artery Disease.** **Year: 1998**
Study type	DTA Cross-sectional study
Aim	To compare the sensitivity and specificity of 2 different imaging modalities using a single exercise protocol for the detection of obstructive CAD.
Patient characteristics	**Inclusion criteria:** • Patients undergoing routine cardiac catheterization for the diagnosis of chest pain. **Exclusion criteria:** • Patients with previous revascularization, recent myocardial infarction (≤3 months), and valvular or congenital heart disease. • Patients unable to exercise, those with a creatinine kinase level elevated ≥2 times normal or with known contrast allergies. **Medication:** • Not reported.
Number of patients	Total = 33 Gender: male = 19; female = 14 Mean age = 55 (SD: 9, range 30 to 73) years old
Index test	Stress technetium-99m (Tc-99m) Sestamibi single photon emission computed tomography (SPECT) Tc-99m isonitrile (20 to 25 mCi) was injected at peak exercise stress in all patients, and images were obtained 60 to 90 minutes later. A second injection of 20 mCi of sestamibi was given 1 to 2 days after the stress studies for imaging at rest. Threshold: Areas of significant hypo-perfusion were defined as those volume elements within the computer defined myocardium in each slice that fell below 45% of the maximum counts in the ventricle. Two SPECT scans were then interpreted using visual assessments of regional abnormalities.

Bibliographic reference	**Author: Budoff et al** **Comparison of Exercise Electron Beam Computed Tomography and Sestamibi in the Evaluation of Coronary Artery Disease.** **Year: 1998**
	Blinding: Reversible perfusion defects were evaluated by 2 nuclear medicine specialists; disagreements were resolved by consensus with a third investigator. All investigators were blinded to the results of the angiogram.
Reference standard (or Gold standard)	**Coronary arteriography** Threshold for stenosis: ≥50% narrowing of luminal diameter of at least one coronary vessel. The coronary angiograms were analysed by an experienced reader blinded to the results of the single-photon emission computed tomography (SPECT).
Time between testing & treatment	Time flow between index test and reference standard = within 4 weeks.
Length of follow-up	Not reported.
Location	Harbor-UCLA Medical Center, Torrance, California, US.
Diagnostic accuracy measures (2 x 2 table)	Total = 33 TP = 12; FP = 5; FN = 4; TN = 12 Sensitivity = 75% (95%CI: 50.5-89.8%) Specificity = 71% (95%CI: 46.9-86.7%); Prevalence = 70% Note: 2x2 was back calculated by the reviewer. No mention of adverse events.
Source of funding	Not reported.
Comments	<u>Study limitations (QUADAS-2):</u> 1a. (yes/yes/yes) = LOW 1b. Patients recruited on basis of referral for coronary angiography = High 2a. (yes/yes) = LOW 2b. LOW 3a. (yes/yes) = LOW 3b. LOW 4. (yes/yes/yes/yes) = LOW

Table 61 Budoff 2007

Bibliographic reference	**Author: Budoff et al** **Cardiac CT angiography and nuclear myocardial perfusion imaging – a comparison in detecting significant coronary artery disease** **Year: 2007**
Study type	Cross sectional
Aim	To compare the accuracy of cardiac CT angiography (CTA) and coronary artery calcification (CAC) with myocardial perfusion imaging (MPI) using conventional catheter angiography as the gold standard for assessing significant stenosis of the coronary arteries
Patient characteristics	**Inclusion** - Symptomatic outpatients with exertional angina or dyspnoea scheduled for cardiac catheterisation - CTA to be done within 1 month of coronary angiographic studies - Normal baseline electrocardiography without left bundle branch block, resting ST segment or T wave changes - At least 85% of the maximum predicted heart rate achieved during treadmill ECG - No history of cardiac valve replacement, coronary stenting procedures or coronary artery bypass grafting before the completion of all testing methods **Exclusion** - Renal insufficiency - Refusal to participate - Known allergy to iodinated contrast - Lack of diagnostic cardiac catheterisation **Other characteristics** Age in years, mean (SD) 54 (9) Gender, % males 70 Breakdown of number of participants with chest pain not reported
Number of patients	n=30
Index test	**1. Cardiac CT angiography** – corresponds to test 2a on review protocol however 2x2 results were not reported and used used non-protocol version of CTCA (electron beam). **2. Myocardial perfusion imaging** – corresponds to test 7 on review protocol - MPI (SPECT) images acquired 60 to 120 minutes after injection of 99mTc sestamibi using a large field of view,

<table>
<tr><td>Bibliographic reference</td><td>Author: Budoff et al
Cardiac CT angiography and nuclear myocardial perfusion imaging – a comparison in detecting significant coronary artery disease
Year: 2007</td></tr>
<tr><td></td><td>dual headed gamma camera equipped with a high resolution collimator</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Invasive coronary angiography
- Blinded to index test results
- Significant CAD defined as >50% left main artery stenosis or >70% stenosis in any other epicardial vessel</td></tr>
<tr><td>Time between testing & treatment</td><td>MPI and CTA performed before coronary angiography in all cases. CTA studies were done within 1 month of the coronary angiographic studies.</td></tr>
<tr><td>Length of follow-up</td><td>Study dates not reported</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>1. Accuracy of myocardial perfusion imaging to detect significant CAD defined as >50% left main artery stenosis or >70% stenosis in any other epicardial vessel
TP: 17; FP: 2; TN: 7; FN:4

<table><tr><td>Sensitivity (95%CI)*:</td><td>81.0 (60.0 to 92.3)</td></tr><tr><td>Specificity (95%CI)*:</td><td>77.8 (45.3 to 93.7)</td></tr></table>
*Calculated by analyst based on data reported in article

No mention of adverse events in either test.</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Study limitations (as assessed using QUADAS-2 checklist)
1a. UNCLEAR – consecutive recruitment not reported
1b. Patients recruited based on referral for coronary angiography HIGH.
2a. LOW
2b. LOW
3a. LOW
3b. LOW
4. LOW</td></tr>
</table>

Table 62 Cramer 1997

Bibliographic reference	**Author: Cramer et al** **SPECT versus planar 99m-Tc-sestamibi myocardial scintigraphy: comparison of accuracy and impact on patient management in chronic ischemic heart disease.** **Year: 1997**
Study type	DTA Cross-sectional study
Aim	To compare the extent and localisation of planar and SPECT perfusion defects and to relate the scintigraphic findings to its impact on patient treatment.
Patient characteristics	Inclusion: • Patients referred for the evaluation of chest pain who required coronary arteriography. Exclusion: • Not reported. Medication: • Not reported.
Number of patients	Total = 78 Gender: male = 50; female = 28 Mean age = 58 (range: 28 to 74) years old
Index test	**Myocardial perfusion scintigraphy (SPECT)** SPECT imaging was performed with a GE-400 AT tomographic camera equipped with a low energy general purpose collimator. Energy discrimination was provided by a 15% window centred over the 140 keV photopeak of 99m-Tcsestamibi. Imaging began 60 mins after the dipyridamole low level exercise protocol, and 60 mins after the injection at rest. Resting studies and the dipyridamole 99m-Tcsestamibi studies were either performed on a separate day, using 740-920 MBq (20-25 mCi) for each injection. Or a one day rest-stress protocol using 260 MBq (7mCi) 99m-Tc-sestamibi for the rest study. Threshold: An image was considered abnormal if there was a decrease of uptake in any of the segments on at least 2 consecutive slices. Blinding: No mention of blinding.
Reference standard (or	**Coronary arteriography**

Bibliographic reference	**Author: Cramer et al** **SPECT versus planar 99m-Tc-sestamibi myocardial scintigraphy: comparison of accuracy and impact on patient management in chronic ischemic heart disease.** **Year: 1997**
Gold standard)	Threshold for stenosis: ≥50% narrowing of luminal diameter of at least one coronary vessel. The coronary angiograms were analysed by 2 cardiologists independently, disagreement was resolved by an independent third interpreter.
Time between testing & treatment	Time flow between index test and reference standard = within 3 months
Length of follow-up	Varied between 1 week to 11 months.
Location	The Netherlands.
Diagnostic accuracy measures (2 x 2 table)	Total = 78 TP = 55; FP = 2; FN = 12; TN = 9 Sensitivity = 82.1% (95%CI: 71.3 to 89.4%); Specificity = 81.8% (95%CI: 52.3 to 94.9%); Prevalence = 90% Note: 2x2 was back calculated by the reviewer. No serious adverse events reported for either test. Minor events associated with index test: headache n=2, vertigo n=1, aminophylline requirement n=24, nitroglycerine sublingual n=3.
Source of funding	Not reported.
Comments	<u>Study limitations (QUADAS-2):</u> 1a. (yes/yes/unclear) = LOW [very limited information on inclusion criteria and no information on exclusion criteria]. 1b. HIGH [no information on exclusion criteria, baseline unclear]. Patients recruited on basis of referral for coronary angiography. 2a. (no/yes) = HIGH [no mention of blinding]. 2b. LOW 3a. (yes/no) = HIGH [no mention of blinding]. 3b. LOW 4. (yes/yes/yes/yes) = LOW

Table 63 Fleming 1992

Bibliographic reference	**Author: Fleming et al** **Using quantitative coronary arteriography to redefine SPECT sensitivity and specificity.** **Year: 1992**
Study type	DTA Cross-sectional study
Aim	To determine the accuracy of SPECT in diagnosing CAD.
Patient characteristics	Inclusion: • Patients suspected of having CAD. Exclusion: • History of cardiomyopathy, severe valvular disease, unstable angina, recent MI, morbid obesity, pregnant. Medication: • Not reported.
Number of patients	Total = 44 Gender: male = 27; female = 17 Mean age = 56.6 (SD: 11.2) years old
Index test	**Thallium SPECT or Teboroxime SPECT** GE 400 AC Starcam, 64x64 Matrix Hanning Filter multipurpose collimator. Thallium SPECT: 3mCi dose, with exercise continued for one minute, then redistribution 4 hours later. With 40 seconds/image acquisition. Teboroxime SPECT: Tebo dose was 20-25 mCi, exercise stopped immediately after injection, rest study with the same dose as stress 1 hour later. With 15 seconds/image acquisition. Threshold: Perfusion was scored on 0 to 5 (0 = normal, 5 = sever defects). Averaged values from 2 observers ranging from 0 to 2 were reported as not significant for perfusion abnormalities. Blinding: Images were analysed by 2 observers blinded to clinical and CA data.
Reference standard (or Gold standard)	**Coronary arteriography** Threshold for stenosis: ≥50% narrowing of luminal diameter of at least one coronary vessel.

Bibliographic reference	**Author: Fleming et al** **Using quantitative coronary arteriography to redefine SPECT sensitivity and specificity.** **Year: 1992**
	The coronary angiograms were analysed by a DEC VAX 11/780 computer and Tektronics 4207 graphics computer.
Time between testing & treatment	Time flow between index test and reference standard = Not reported.
Length of follow-up	Not reported
Location	Houston, US.
Diagnostic accuracy measures (2 x 2 table)	Total = 44 TP = 29; FP = 4; FN = 3; TN = 8 Sensitivity = 90.6% (95%CI: 75.8 to 96.8%); Specificity = 66.7% (95%CI: 39.1 to 86.2%); Prevalence = 70% Note: 2x2 was back calculated by the reviewer. Minor effects: Angina (43%) relieved by nitroglycerin. 48% demonstrated significant ST segment changes during or after exercise. No mention of adverse events in relation to ICA.
Source of funding	Not reported.
Comments	<u>Study limitations (QUADAS-2):</u> 1a. (unclear/yes/unclear) = HIGH [very limited information on inclusion/exclusion criteria, unclear whether consecutive]. 1b. HIGH [limited information on inclusion/exclusion criteria, baseline unclear]. 2a. (yes/yes) = LOW 2b. UNCLEAR [the index tests were a mixture of thallium SPECT and Teboroxime SPECT, cannot separate out the data for the 2 different index tests]. 3a. (unclear/unclear) = HIGH [computer system was used for CA, unclear the validity of interpretation]. 3b. LOW 4. (unclear/yes/yes/yes) = LOW

Table 64 Kaminek 2015

Bibliographic reference	**Author: Kaminek M et al** **Diagnosis of high risk patients with multivessel coronary artery disease by combined cardiac gated SPET imaging and coronary calcium score** **Year: 2015**
Study type	Cross sectional
Aim	To investigate coronary artery calcium (CAC) as an adjunct to gated single photon emission tomography (G-SPET) in the detection of multi-vessel coronary artery disease.
Patient characteristics	**Inclusion** - High risk patients referred for cardiac gated single photon emission tomography (GSPET) **Exclusion** - Known CAD - Myocardial infarction - Coronary revascularisation **Other characteristics** Gender male/female, n (%) 123 (75) / 60 (37) Age in years, mean (SD) 61 (12) Diabetes mellitus, n (%) 26 (16) Chronic renal failure treated by dialysis, n (%) 26 (16) Left ventricular dilatation, n(%) 41 (25)
Number of patients	N=164
Index test	1. Coronary artery calcium scoring – corresponds to test 3 on review protocol 2. Gated single photon emission tomography (GSPET) – corresponds to test 7 on review protocol
Reference standard (or Gold standard)	**Coronary angiography** **-** Details not reported
Time between testing & treatment	Timing of tests not reported
Length of follow-up	Study dates not reported
Location	Czech Republic
Diagnostic accuracy measures (2 x 2 table)	**1. Accuracy of gated SPET to detect CAD defined as ≥50% stenosis of epicardial coronary arteries or their major branch**

<table>
<tr><td>Bibliographic reference</td><td>Author: Kaminek M et al
Diagnosis of high risk patients with multivessel coronary artery disease by combined cardiac gated SPET imaging and coronary calcium score
Year: 2015</td></tr>
<tr><td></td><td>TP:98; TN:39; FP:14; FN:13
<table><tr><td>Sensitivity (95%CI)*:</td><td>88.3 (81.0 to 93.0)</td></tr><tr><td>Specificity (95%CI)*:</td><td>73.6 (60.4 to 83.6)</td></tr></table>
2. Calcium scoring
Insufficient data to back calculate 2x2 table for calcium scoring alone. Sensitivity of 81% (60/84) only reported with perfusion plus function plus calcium score of >1000). No specificity reported.

No mention of adverse events with either test.</td></tr>
<tr><td>Source of funding</td><td>European Regional Development Fund Project</td></tr>
<tr><td>Comments</td><td>Statistical methods
Standard 2x2 data reported in text for GSPET.

Study limitations (as assessed using QUADAS-2 checklist)
1a. UNCLEAR – consecutive recruitment not reported
1b. HIGH – high risk patients, chest pain not reported
2a. HIGH – unclear if index test results were interpreted without knowledge of reference standard results
2b. LOW
3a. HIGH – reference standard details not reported and unclear if results were interpreted without knowledge of index test results
3b. UNCLEAR – reference standard details not reported
4. LOW – timing of tests not reported</td></tr>
</table>

Table 65 Yao 2004

Bibliographic reference	**Author: Yao et al** **Comparison of 99m-Tc-methoxyisobutylisonitrile myocardial single photon emission computed tomography and electron bean computed tomography for detecting coronary artery disease in patients with no myocardial infarction.** **Year: 2004**
Study type	DTA Cross-sectional study
Aim	To compare SPECT with EBCT in detection of CAD in patients with no MI.
Patient characteristics	Inclusion: • Patients with suspected CAD who underwent coronary angiography. • With no history of myocardial infarction. Exclusion: • Not reported. Medication: • Not reported.
Number of patients	Total = 73 Mean age = 52.62 (SD: 10.59) 24 patients ≤45 years old; 49 patients >45 years old.
Index test	**Stress-rest 99m-Tc-MIBI myocardial SPECT** At the peak of exercise, 20 mCi 99m-Tc-MIBI was injected IV and the exercise was continued for one more minute. Myocardial SPECT was performed 75 mins later, and a rest myocardial SPECT was performed 90 mins after 20mGi 99m-Tc-MIBI was injected. Myocardial SPECT acquisition was carried out with a GE Starcam 4000 SPECT system that was equipped with low energy, high resolution and parallel-hole collimator. Threshold: Segment with <70% maximal count density on 2 or more continuous slices at 2-axis view was considered abnormal. Blinding: 2 experienced nuclear medicine physicians, who did not know the results of CA, analysed SPECT images together.
Reference standard (or Gold standard)	**Coronary arteriography** Threshold for stenosis: ≥50% narrowing of luminal diameter of at least one coronary vessel. The coronary angiograms were analysed by 2 cardiologists.
Time between testing &	Time flow between index test and reference standard = Not reported.

Bibliographic reference	**Author: Yao et al** **Comparison of 99m-Tc-methoxyisobutylisonitrile myocardial single photon emission computed tomography and electron bean computed tomography for detecting coronary artery disease in patients with no myocardial infarction.** **Year: 2004**
treatment	
Length of follow-up	Not reported.
Location	Beijing Hospital, Beijing, China.
Diagnostic accuracy measures (2 x 2 table)	Total = 73 TP = 28; FP = 3; FN = 7; TN = 35 Sensitivity = 80.0% (95%CI: 64.1 to 90.0%); Specificity = 92.1% (95%CI: 79.2 to 97.3%); Prevalence = 50% Note: 2x2 was back calculated by the reviewer. No mention of any adverse events associated with either test.
Source of funding	Not reported.
Comments	Study limitations (QUADAS-2): 1a. (yes/yes/unclear) = LOW [very limited information on inclusion criteria and no information on exclusion criteria]. 1b. HIGH [no information on exclusion criteria, baseline unclear]. 2a. (yes/yes) = LOW 2b. LOW 3a. (yes/yes) = LOW 3b. LOW 4. (unclear/yes/yes/yes) = UNCLEAR [no information on time flow].

G.1.6 Studies reporting multiple index tests and/or combined analyses

Table 66 Arnold 2010

Bibliographic reference	**Author: Arnold et al, 2010** **Adenosine Stress Myocardial Contrast Echocardiography for the Detection of Coronary Artery Disease. A comparison with coronary angiography and cardiac magnetic resonance.** **Year: 2010**

Bibliographic reference	**Author: Arnold et al, 2010** **Adenosine Stress Myocardial Contrast Echocardiography for the Detection of Coronary Artery Disease. A comparison with coronary angiography and cardiac magnetic resonance.** **Year: 2010**
Study type	Cross-sectional
Aim	To evaluate the accuracy of adenosine myocardial contrast echocardiography (MCE) in diagnosing coronary artery disease (CAD).
Patient characteristics	**Inclusion** Prospectively recruited adults referred to regional tertiary centre for elective diagnostic angiography as part of routine clinical care for further investigation of exertional chest pain. (Suspected CAD). **Exclusion** Recent MI (within 7 days). Contraindications to CMR or adenosine, gadolinium and sulphur hexafluoride. **Baseline Clinical Characteristics (n=62) n (%)** Men 40 (65) Smoker 6 (10) Ex-smoker 20 (32) Hypertension 33 (53) Hypercholesterolaemia 35 (57) Diabetes mellitus 11 (18) Family history of CAD 22 (36) **Mean (SD)** BMI (kg/m^2) 28 (5) Age (y) 64 (9)
Number of patients	65 (from total of 99 consecutive patients screened) were elected to participate. 2 patients did not undergo CMR due to claustrophobia and 1 patient withdrew consent. **62** patients completed both scans.
Index test	MCE and CMR taken on same day in random order. Patients were asked to avoid caffeine 24hrs before exams but routine angina medications were continued. **Myocardial Contrast Echo (MCE) – Index test 4**

Bibliographic reference	**Author: Arnold et al, 2010** **Adenosine Stress Myocardial Contrast Echocardiography for the Detection of Coronary Artery Disease. A comparison with coronary angiography and cardiac magnetic resonance.** **Year: 2010**
	Sulfur hexafluoride was infused at 0.7ml/min and adjusted in 0.1-ml/min steps to achieve optimum myocardial opacification. Images were acquired once "steady state" was reached. Stress images were obtained after infusion of adenosine (140µg/kg/min for 4mins or less if angina was induced or if perfusion/wall motion abnormalities became apparent. Images were obtained sequentially at ~1min intervals. Patients were monitored throughout by ECG, sphygmomantometry and pulse oximetry. Scans were interpreted in random order by a single observer blinded to the CMR/angiography results and clinical information. Assessment of **wall motion and perfusion** was performed using 17-segment AHA model. For **wall motion assessment**, standard segmental scoring was performed (1=normal, 2=hypokinesis, 3=akinesis, 4=dyskinesis) with documentation of progression of wall motion abnormality during stress. For perfusion assessment, rest and images were displayed side by side. A **perfusion** defect was defined as a decrease in contrast relative to another region with comparable image quality. Perfusion defects were considered artifactual if there were attenuation defects, contrast shadowing or artifacts from external shadowing. Inducible ischemia was defined as a stress perfusion defect appearing more extensive than at rest, or progressional of wall motion abnormality. Diagnosis of CAD was determined by the presence of 1) resting akinesis, 2) reversible wall motion abnormalities or 3) perfusion defects (fixed or reversible). For the identification of disease location, a positive diagnosis was determined by the presence of perfusion/wall motion abnormality in any segment ascribed to a coronary artery. The overall diagnosis of CAD on a per patient basis was determined by the presence of any abnormal segment. **Cardiac Magnetic Resonance (CMR) – Index test 6** 3T Siemens machine used. Patients were monitored continuously (as above). After 4 mins of adenosine (or less if angina induced) a bolus of 0.05-mmol/kg gadolinium based contrast was given followed by 15mls normal saline. First pass of contrast - Images were acquired every cardiac cycle using ECG-gated T1 weighted fast gradient echo sequence with generalized auto-calibrating partially parallel acquisitions reconstructions. Breath holding was requested during imaging (as long as possible in end expiration). After 20mins the same sequence was repeated without adenosine for resting perfusion. For **late gadolinium enhancement (LGE)** imaging, further bolus of gadodiamide was given and imagines were acquired (inversion time was adjusted to obtain optimal nulling of non-infarcted myocardium. Scans were visually interpreted by a single blinded reader with assessment of resting wall motion, LGE and perfusion. **Perfusion and LGE data were subsequently combined** according to an algorithm described elsewhere. (Klem et al). No description of perfusion assessment provided. Wall motional scoring performed using scoring system described above. For LGE assessment, segments were graded as normal or abnormal. Diagnosis of CAD was determined on segmental basis by the presence of either perfusion abnormalities or LGE.

Bibliographic reference	**Author: Arnold et al, 2010** **Adenosine Stress Myocardial Contrast Echocardiography for the Detection of Coronary Artery Disease. A comparison with coronary angiography and cardiac magnetic resonance.** **Year: 2010**
Reference standard (or Gold standard)	Coronary angiography was carried out with 2 weeks using standard techniques. Images were obtained in multiple projections, avoiding overlap of side branches and foreshortening of relevant coronary stenoses. Vessel diameters were measured using computer-assisted quantification method. Significant CAD was defined angiographically as ≥50% stenosis in any epicardial coronary artery/branch with diameter ≥2mm.
Time between testing & treatment	Within 2 weeks
Length of follow-up	Study period not specified
Location	Unclear. Authors in multiple locations (UK, Australia, Poland)
Diagnostic accuracy measures (2 x 2 table)	41/62 patients had angiographically defined stenosis ≥50% and 29/62 had ≥70% stenosis) MCE – no exclusions due to inadequate imagine. 1 perfusion image was suboptimal. CMR – no images excluded.

		TP	FP	FN	TN *	Sens%	Spec%
MCE (overall) ≥50%		35	5	6	16	85.0	76.0
MCE (overall) ≥70%		28	12	1	21	97.0	64.0
Individual techniques:							
perfusion	≥50%	31	4	10	17	76.0	81.0
perfusion	≥70%	26	9	3	24	90.0	73.0
Stress wall motion	≥50%	25	3	16	18	61.0	86.0
Stress wall motion	≥70%	22	6	7	27	76.0	82.0
CMR Overall (≥50%)		37	4	4	17	90.0	81.0
CMR Overall (≥70%)		28	13	1	20	97.0	61.0
Individual techniques:							
Perfusion	≥50%	39	8	2	13	95.0	62.0

Bibliographic reference	**Author: Arnold et al, 2010** **Adenosine Stress Myocardial Contrast Echocardiography for the Detection of Coronary Artery Disease. A comparison with coronary angiography and cardiac magnetic resonance.** **Year: 2010**
	Perfusion ≥70% 29 18 0 15 100.0 45.0 LGE-CMR combined ≥50% 18 1 23 20 44.0 95.0 LGE-CMR combined ≥70% 14 5 15 28 48.0 85.0 No significant adverse events occurred during either scan. *back calculations by reviewer
Source of funding	The study was supported by the British Heart Foundation, the UK MRC and the Oxford Partnership Comprehensive Biomedical research Centre with funding from the DoH NIHR Biomedical Research Centres funding Scheme. One author received research funds and has served on the Speakers' Bureau for Philips.
Comments	**Study limitations (as assessed using QUADAS-2 checklist)** 1a. UNCLEAR (although patients could have had higher risk of disease being referred to a tertiary centre?) Exclusion criteria is scant. 1b. HIGH population, suspected CAD with no breakdown of numbers with chest pain AND patients recruited based on referral for coronary angiography. 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

Table 67 Bettencourt 2011

Bibliographic reference	**Author: Bettencourt N et al** **Incremental value of an integrated adenosine stress rest MDCT perfusion protocol for detection of obstructive coronary artery disease** **Year: 2011**
Study type	Cross sectional
Aim	To provide validation data on stress rest CTP protocols as additive tools to improve the accuracy of multidetector computed tomography (MDCT) for coronary artery disease in symptomatic patients
Patient characteristics	**Inclusion** - Referred to cardiology clinic due to clinical suspicion of CAD. 156 patients screened.

Bibliographic reference	**Author: Bettencourt N et al** **Incremental value of an integrated adenosine stress rest MDCT perfusion protocol for detection of obstructive coronary artery disease** **Year: 2011**
	- >40 years - Symptoms compatible with CAD (22% with chest pain, 20% with typical angina, 50% with atypical angina and 8% with dyspnoea on exertion/fatigue) - At least one of the following: 2 or more risk factors or a positive/inconclusive treadmill test **Exclusion** - Known CAD - Atrial fibrillation - Asthma - Renal insufficiency - Known allergy to contrast media **Other characteristics** Mean age in years (SD) 62 (8) % males 66 Hypercholesterolemia, n (%) 70 (78) Hypertension, n (%) 66 (73) Diabetes, n (%) 33 (37) Smoking history, n (%) 31 (34) Family history of CAD, n (%) 20 (22)
Number of patients	N=90
Index test	**1. Multidetector computed tomography (MDCT) – corresponds to test 2 on review protocol** - MDCT scanner Somatom Sensation 64, Siemens - Blinded to results of reference standard test **2. Myocardial perfusion imaging – corresponds to test 9 on review protocol** - Multiphase reconstructions from the retrospective stress acquisition and a single phase reconstruction from the rest acquisition were obtained using the same parameters as the MDCT scan but with an extra smooth filter. - Readers blinded to MDCT and coronary angiography results

<table>
<tr><td>Bibliographic reference</td><td>Author: Bettencourt N et al
Incremental value of an integrated adenosine stress rest MDCT perfusion protocol for detection of obstructive coronary artery disease
Year: 2011</td></tr>
<tr><td></td><td>3. Calcium scoring – corresponds to test 3 on review protocol (data not used in analysis since calcium scoring not used as a diagnostic test)
- Image reconstruction of the calcium score acquisition was performed using an effective slice thickness of 3mm. coronary calcification was reported as the mean Agatston score.

4. Integrated protocol including MDCT and myocardial perfusion imaging</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>X-ray coronary angiography
- Performed by standard techniques
- Blinded to index test results</td></tr>
<tr><td>Time between testing & treatment</td><td>Days from CT to coronary angiography, mean (SD): 5.1 (5.99)</td></tr>
<tr><td>Length of follow-up</td><td>17 month period, February 2010 to June 2011</td></tr>
<tr><td>Location</td><td>Portugal</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td><u>50% stenosis (patient based analyses)</u>

1. Accuracy of <u>MDCT alone</u> (index test 2) in detecting significant coronary artery disease (stenosis ≥50%)
TP: 47; TN: 30; FP: 12; FN: 1
<table><tr><td>Sensitivity (95%CI)*:</td><td>97.9 (89.1 to 99.6)</td></tr><tr><td>Specificity (95%CI)*:</td><td>71.4 (56.4 to 82.8)</td></tr></table>
2. Accuracy of <u>myocardial perfusion imaging alone</u> (index test 9) in detecting significant coronary artery disease (stenosis ≥50%)
TP: 26; TN: 42; FP:0; FN: 22
<table><tr><td>Sensitivity (95%CI)*:</td><td>54.2 (40.3 to 67.4)</td></tr><tr><td>Specificity (95%CI)*:</td><td>100.0 (91.6 to 100.0)</td></tr></table>
3. Accuracy of integrated protocol (MDCT+MPI, Index TESTS 2+9) in detecting significant coronary artery disease (stenosis ≥50%)
TP: 40; TN: 41; FP: 1; FN: 8</td></tr>
</table>

Bibliographic reference	Author: Bettencourt N et al Incremental value of an integrated adenosine stress rest MDCT perfusion protocol for detection of obstructive coronary artery disease Year: 2011

Sensitivity (95%CI)*:	83.3 (70.4 to 91.3)
Specificity (95%CI)*:	97.6 (87.7 to 99.6)

70% stenosis (patient based analysis)

4. Accuracy of MDCT alone (index test 2) in detecting significant coronary artery disease (stenosis ≥70%)

TP: 38; TN: 35; FP: 17: FN: 0

Sensitivity (95%CI)*:	100.0 (90.8 to 100.0)
Specificity (95%CI)*:	67.3 (53.8 to 78.5)

5. Accuracy of myocardial perfusion imaging alone (index test 9) in detecting significant coronary artery disease (stenosis ≥70%)

TP: 25; TN: 51; FP: 1; FN: 13

Sensitivity (95%CI)*:	65.8 (49.9 to 78.8)
Specificity (95%CI)*:	98.1 (89.9 to 99.7)

6. Accuracy of integrated protocol (index tests 2+9) in detecting significant coronary artery disease (stenosis ≥70%)

TP: 36 TN: 49 FP: 3 FN: 2

Sensitivity (95%CI)*:	94.7 (82.7 to 98.5)
Specificity (95%CI)*:	94.2 (84.4 to 98.0)

The following results are extracted but not used in the analysis as they are based on sub populations and not on diagnostic accuracy of calcium scoring alone.

7. Accuracy of MDCT alone in detecting significant coronary artery disease (stenosis ≥50%) in those with calcium score <400

TP: 16; TN: 27; FP: 6; FN: 1

Bibliographic reference	Author: Bettencourt N et al Incremental value of an integrated adenosine stress rest MDCT perfusion protocol for detection of obstructive coronary artery disease Year: 2011

Sensitivity (95%CI)*:	94.1 (73.0 to 99.0)
Specificity (95%CI)*:	81.8 (65.6 to 91.4)

8. Accuracy of myocardial perfusion imaging alone in detecting significant coronary artery disease (stenosis ≥50%) in those with calcium score <400

TP: 11; TN: 33; FP: 0; FN: 6

Sensitivity (95%CI)*:	64.7 (41.3 to 82.7)
Specificity (95%CI)*:	100.0 (89.6 to 100.0)

9. Accuracy of integrated protocol in detecting significant coronary artery disease (stenosis ≥50%) in those with calcium score <400

TP: 15; TN: 32; FP: 1; FN: 2

Sensitivity (95%CI)*:	88.2 (65.7 to 96.7)
Specificity (95%CI)*:	97.0 (84.7 to 99.5)

10. Accuracy of MDCT alone in detecting significant coronary artery disease (stenosis ≥50%) in those with calcium score >400

TP: 31; TN: 3; FP: 6; FN: 0

Sensitivity (95%CI)*:	100.0 (89.0 to 100.0)
Specificity (95%CI)*:	33.3 (12.1 to 64.6)

11. Accuracy of myocardial perfusion imaging alone in detecting significant coronary artery disease (stenosis ≥50%) in those with calcium score >400

TP: 15; TN: 9; FP: 0; FN: 16

Sensitivity (95%CI)*:	48.4 (32.0 to 65.2)
Specificity (95%CI)*:	100.0 (70.1 to 100.0)

12. Accuracy of integrated protocol in detecting significant coronary artery disease (stenosis ≥50%) in those with calcium score >400

Bibliographic reference	Author: Bettencourt N et al Incremental value of an integrated adenosine stress rest MDCT perfusion protocol for detection of obstructive coronary artery disease Year: 2011

TP: 25; TN: 9; FP:0; FN: 6

Sensitivity (95%CI)*:	80.6 (63.7 to 90.8)
Specificity (95%CI)*:	100.0 (70.1 to 100.0)

13. Accuracy of MDCT alone in detecting significant coronary artery disease (stenosis ≥70%) in those with calcium score <400

TP: 13; TN: 29; FP: 8; FN: 0

Sensitivity (95%CI)*:	100.0 (77.2 to 100.0)
Specificity (95%CI)*:	78.4 (62.8 to 88.6)

14. Accuracy of myocardial perfusion imaging alone in detecting significant coronary artery disease (stenosis ≥70%) in those with calcium score <400

TP: 10; TN: 36; FP: 1; FN: 3

Sensitivity (95%CI)*:	76.9 (49.7 to 91.8)
Specificity (95%CI)*:	97.3 (86.2 to 99.5)

15. Accuracy of integrated protocol in detecting significant coronary artery disease (stenosis ≥70%) in those with calcium score <400

TP: 13; TN: 35; FP:2; FN:0

Sensitivity (95%CI)*:	100.0 (77.2 to 100.0)
Specificity (95%CI)*:	94.6 (82.3 to 98.5)

16. Accuracy of MDCT alone in detecting significant coronary artery disease (stenosis ≥70%) in those with calcium score >400

TP: 25; TN: 6; FP: 9; FN:0

Sensitivity (95%CI)*:	100.0 (86.7 to 100.0)
Specificity (95%CI)*:	40.0 (19.8 to 64.3)

17. Accuracy of myocardial perfusion imaging alone in detecting significant coronary artery disease

<table>
<tr><td>Bibliographic reference</td><td>Author: Bettencourt N et al
Incremental value of an integrated adenosine stress rest MDCT perfusion protocol for detection of obstructive coronary artery disease
Year: 2011</td></tr>
<tr><td></td><td>(stenosis ≥70%) in those with calcium score >400
TP: 15; TN: 15; FP: 0; FN: 10
<table><tr><td>Sensitivity (95%CI)*:</td><td>60.0 (40.7 to 76.6)</td></tr><tr><td>Specificity (95%CI)*:</td><td>100.0 (79.6 to 100.0)</td></tr></table>
18. Accuracy of integrated protocol in detecting significant coronary artery disease (stenosis ≥70%) in those with calcium score >400
TP: 23; TN: 14; FP: 1; FN: 2
<table><tr><td>Sensitivity (95%CI)*:</td><td>92.0 (75.0 to 97.8)</td></tr><tr><td>Specificity (95%CI)*:</td><td>93.3 (70.2 to 98.8)</td></tr></table>
No adverse events experienced after any test.</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Statistical methods
Diagnostic accuracy calculated using standard 2x2. All non-evaluable coronary segments in MDCT were coded as being positive for CAD.

Study limitations (as assessed using QUADAS-2 checklist)
1a. LOW
1b. HIGH - all had an intermediate or high pre-test probability of CAD according to the modified Diamond Forrester score. Unclear whether patient selection was based on referral for coronary angiography.
2a. LOW
2b. LOW
3a. LOW
3b. LOW
4. LOW</td></tr>
</table>

Table 68 Di Bello 1996a

Bibliographic reference	**Author: Di Bello et al** **Simultaneous dobutamine stress echocardiography and dobutamine scintigraphy (^{99m}Tc-MIBI-SPET) for assessment of coronary artery disease** **Year: 1996a**
Study type	Cross-sectional
Aim	To evaluate the presence and extent of CAD between simultaneous dobutamine stress echocardiography (DSE) and ^{99m}Tc-MIBI-SPET (DMS) compared to coronary angiography.
Patient characteristics	**Inclusion** Consecutive patients with typical or atypical chest pain referred for evaluation of the presence of CAD. Good acoustic window to basal echocardiographic examination. Not on digitalis therapy. **Exclusion** 120 patients during the study period were excluded due to: Prior MI, history of EKG documentation, other cardiac diseases, severe arterial hypertension, unstable angina, previous CABG, left BBB, WPW syndrome and left ventricular hypertrophy. **Other** Male 33 (73%) Age (y) mean (SD) 53 (7) Angina (positivity) mean (SD) 7 (16) EKG exercise (positive) n=25 (56%) Pre-test probability of disease (Diamond's algorithm using age, gender, clinical symptoms and results of EKG stress test*) 45.6% (12.7) *All studied patients underwent a preliminary EKG exercise stress test
Number of patients	45
Index test	**Dobutamine Stress Echo (Index test 4)** Dobutamine infused IV to antecubital cannula during continuous 2D-Echo with EKG and BP monitoring (maximum of 40mcg/kg/min) adding atropine in patients not achieving 85% of max. predicted HR. Metoprolol was used to reverse the effects if they persisted. Test end points were the achievement of target HR, development of severe ischaemia (increasing angina, extensive worsening wall motion abnormality, ST-segment sift) or the occurrence of intolerable side effects. Echo was performed at risk and stress with Sonos 1000.

Bibliographic reference	**Author: Di Bello et al** **Simultaneous dobutamine stress echocardiography and dobutamine scintigraphy (^{99m}Tc-MIBI-SPET) for assessment of coronary artery disease** **Year: 1996a**
	All echocardiograms were separately reviewed and consensus achieved by two independent, experienced observers, blinded to all other test results. Systolic wall thickening and inward wall motion were evaluated visually. A worsening wall motion abnormality after pharmacological stress was considered to reflect an ischaemic response. **^{99m}Tc-MIBI-SPET (Index test 7)** Within one minute before the end of the dobutamine echocardiographic stress test, 740MBq of ^{99m}Tc-MIBI-SPET was infused. The stress MIBI SPET imaging was acquired one hour after stress. Single photon emission computed tomographic images were obtained with a rotating gamma camera. 32 views were collected. Images were interpreted qualitatively by two independent, experienced observers, blinded to other tests results. Uptake of radio tracer was visually assessed as a perfusional defect during exercise that partially or totally resolved at rest in at least two or more segments.
Reference standard (or Gold standard)	**Coronary Angiography** Performed using Judkins technique 2 weeks after index tests. All arteriograms were independently evaluated by two experienced angiographers, blinded to other tests results. Coronary stenosis was considered significant if the vessel diameter was narrowed >50% in the left main artery, left anterior descending artery, left circumflex artery and right coronary artery and/or in their main branches.
Time between testing & treatment	Within 2 weeks
Length of follow-up	6 month duration
Location	Pisa, Italy.
Diagnostic accuracy measures (2 x 2 table)	**Index tests 4 and 7** **TP FP FN TN * Sens% Spec%** Stress ECHO (dobutamine) (4) 33 2 5 5 86.0 76.0 MIBI-SPECT (7) 33 1 5 6 86.0 87.0 No major complications associated with index test. Minor complications: isolated premature atrial or ventricular contractions n=10, increased angina 15%, ST-segment shift 8%.

Bibliographic reference	**Author: Di Bello et al** **Simultaneous dobutamine stress echocardiography and dobutamine scintigraphy (^{99m}Tc-MIBI-SPET) for assessment of coronary artery disease** **Year: 1996a**
Source of funding	Not mentioned
Comments	**Study limitations:** 1a. LOW 1b. Patients all had chest pain. Unclear whether patients were recruited based on referral for coronary angiography. UNCLEAR 2a. diagnostic thresholds not specified. HIGH 2b. LOW 3a. LOW 3b. LOW 4. LOW

**=calculated by reviewer*

Table 69 Di Bello 1996b

Bibliographic reference	**Author: Di Bello et *al*** **Incremental diagnostic value of dobutamine stress echocardiography and dobutamine scintigraphy (technetium 99m-labeled sestamibi single-photon emission computed tomography) for assessment of presence and extent of coronary artery disease.** **Year: 1996b**
Study type	Cross Sectional
Aim	To compare dobutamine stress echo (DSE) and myocardial scintigraphy (DMS) during dobutamine stress testing, performed by a single-photon emission computed tomographic (SPECT) approach for a better comparison with echo and ^{99m}Tc-labeled sestamibi scintigraphy.
Patient characteristics	**Inclusion** Consecutive patients with typical or atypical chest pain referred for the evaluation of the presence of CAD. Only patients with a good acoustic window were included for basal echocardiographic examination. **Exclusion** ECG documentation of prior MI, other cardiac diseases, severe arterial hypertension, unstable angina, previous CABG, LBBB, Wolff-Parkinson-White syndrome and left ventricular hypertrophy.

Bibliographic reference	**Author: Di Bello et *al*** **Incremental diagnostic value of dobutamine stress echocardiography and dobutamine scintigraphy (technetium 99m-labeled sestamibi single-photon emission computed tomography) for assessment of presence and extent of coronary artery disease.** **Year: 1996b**
	Other All patients had typical angina. 13% of patients also showed atypical angina. Mean (SD) Pre-test probability of disease using (Diamond's algorithm) was 45.6% (12.7). Male n(%) 33 (73) Age (y) mean (SD) 53 (7)
Number of patients	45
Index test	All patients underwent preliminary ECG exercise test and simultaneous echocardiographic scintigraphic dobutamine stress testing. No patient was on digitalis. Adequate pharmacological washout was obtained before each diagnostic procedure. **DSE** Performed during continuous 2-D echo with 12-lead ECG and BP monitoring. Dobutamine infused IV via antecubital vein up to a max. 140µg/kg/min with addition of atropine in patients not achieving 85% of max. predicted HR. Metropolol was used to reverse effects of dobutamine or atropine when they persisted. Test end points – achievement of target HR, development of severe ischaemia, ST segment shift or intolerable side effects. Echo performed at rest and stress with a Sonos 1000. Echocardiograms were reviewed by two independent, experienced observers blinded to other test results. 16 segment system was used and segmental wall motion score index was obtained in both rest and stress using 4 point scale. 0=normal wall motion, 1=hypokinetic, 2=akinetic, 3=dyskinetic wall motion. A worsening wall motion abnormality after stress was considered to reflect an ischemic response. Ischaemia score was calculated from the difference between rest/stress scores. **DMS** Within 1 min before end of the DSE test, 740MBq ^{99m}Tc-MIBI was infused IV. Stress SPECT imaging was acquired 1 hour after stress. Images were obtained with a two-headed rotating gamma camera. 32 views were collected. A series of transaxial slices were reconstructed from the raw data. Qualitative interpretation of the images was performed by two experienced observes blinded to other test results. Uptake of the radiotracer was assess visually and a 4 point scale used. 0=normal uptake, 1=decreased uptake,

Bibliographic reference	**Author: Di Bello et *al*** **Incremental diagnostic value of dobutamine stress echocardiography and dobutamine scintigraphy (technetium 99m-labeled sestamibi single-photon emission computed tomography) for assessment of presence and extent of coronary artery disease.** **Year: 1996b**
	2=severely decreased uptake and 3=absence of uptake. Ischaemia was defined as perfusion defect during exercise that partially or totally resolved at rest in at least two contiguous segments. A score index was generated from the difference between rest and stress indexes. No major complications reported. ST segment shift occurred in 8% of patients and increasing angina in 15%. 15% received atropine. Isolated premature atrial or ventricular contractions occurred in 22%, breathlessness, nausea, palpitation and dizziness rarely occurred and did not reach a level requiring interruption of the test.
Reference standard (or Gold standard)	**Coronary Angiography** Judkins technique used. Multiple views were obtained. All arteriograms were high quality and interpreted independently by two experienced, blinded angiographers. Differences in opinion obtained by consensus. Coronary artery stenosis was considered significant if vessel diameter was narrowed >50% in left main artery, left anterior descending artery, left circumflex artery and the right coronary artery.
Time between testing & treatment	Within 2 weeks.
Length of follow-up	Study duration not mentioned
Location	Pisa, Italy
Diagnostic accuracy measures (2 x 2 table)	7 patients had normal vessels, 19 had one vessel disease and 19 had multi-vessel disease. (Total 38 with disease). **TP FP FN TN * Sens% Spec%** Echo (4) 29 6 9 6 76 86 SPECT (7) 33 1 5 6 87 86 **=calculated by reviewer* No major complications reported. Minor events: isolated premature atrial or ventricular contractions n=10, increased angina 15%, ST-segment shift 8%.
Source of funding	Not mentioned
Comments	**Study limitations:** 1a. LOW 1b. All patients had chest pain and only 13% were atypical. Unclear whether patients were selected based on

Bibliographic reference	**Author: Di Bello et *al*** **Incremental diagnostic value of dobutamine stress echocardiography and dobutamine scintigraphy (technetium 99m-labeled sestamibi single-photon emission computed tomography) for assessment of presence and extent of coronary artery disease.** **Year: 1996b**
	referral for angiography. UNCLEAR 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. Study duration unclear but design was prospective and consecutive. LOW

Table 70 Fujitaka 2009

Bibliographic reference	**Author: Fujitaka K et al** **Combined analysis of multislice computed tomography coronary angiography and stress-rest myocardial perfusion imaging in detecting patients with significant proximal coronary artery stenosis** **Year: 2009**
Study type	Cross sectional
Aim	To evaluate the diagnostic accuracy of detecting patients with proximal coronary artery disease for coronary intervention by combined analysis of multislice computed tomography (MSCT) coronary angiography (CAG) and stress-rest myocardial perfusion imaging (MPI)
Patient characteristics	**Inclusion** - Typical or atypical chest pain suggestive of coronary artery disease who underwent MSCT-CAG, stress-rest MPI and CAG within 4 weeks **Exclusion** - Atrial fibrillation - Impaired renal function - Known intolerance of iodinated contrast agent - Acute myocardial infarction or unstable angina within 48 hours - Coronary artery bypass grafts **Other characteristics** Age in years, mean (SD) 70 (11)

<table>
<tr><td>Bibliographic reference</td><td>Author: Fujitaka K et al
Combined analysis of multislice computed tomography coronary angiography and stress-rest myocardial perfusion imaging in detecting patients with significant proximal coronary artery stenosis
Year: 2009</td></tr>
<tr><td></td><td>Gender, n male/female 80/45
Height in cm, mean (SD) 159 (8)
Weight in kg, mean (SD) 61 (12)
Diabetes mellitus, n (%) 44 (35)
Hypertension, n (%) 110 (88)
Hypercholesterolemia, n (%) 58 (46)</td></tr>
<tr><td>Number of patients</td><td>N=125</td></tr>
<tr><td>Index test</td><td>1. Multislice computed tomography (MSCT) – corresponds to test 2b in review protocol
- 64 slice MSCT scanner, parameters were 64 x 0.6mm collimation
- Blinded to reference standard results

2. MSCT and myocardial perfusion imaging (MPI) combined - tests 2b and 7a in review protocol
- MSCT-CAG performed first followed by stress rest MPI before CAG
- Blinded to reference standard results</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Invasive coronary angiography
- Assessed by 2 observers blinded to the MSCT results
- Significant stenosis defined as ≥75%</td></tr>
<tr><td>Time between testing & treatment</td><td>All tests were within 4 weeks.</td></tr>
<tr><td>Length of follow-up</td><td>Study dates July 2006 to August 2007</td></tr>
<tr><td>Location</td><td>Japan</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>1. Accuracy of MSCT (Index 2) to detect significant stenosis ≥75%
TP: 50; TN: 50; FP: 24; FN: 1
<table><tr><td>Sensitivity (95%CI)*:</td><td>98% (89.7 to 99.7)</td></tr><tr><td>Specificity (95%CI)*:</td><td>67.6% (56.3 to 77.1)</td></tr></table>*Confidence intervals calculated by analyst based on data reported in the article

2. Accuracy of MSCT and MPI (index tests 2 + 9) combined to detect significant stenosis ≥75%
TP: 48; TN: 70; FP: 4; FN: 3</td></tr>
</table>

Bibliographic reference	**Author: Fujitaka K et al** **Combined analysis of multislice computed tomography coronary angiography and stress-rest myocardial perfusion imaging in detecting patients with significant proximal coronary artery stenosis** **Year: 2009**
	Sensitivity (95%CI)*: 94.1% (84.1 to 98.0) Specificity (95%CI)*: 94.6% (86.9 to 97.9) *Confidence intervals and likelihood ratios calculated by analyst based on data reported in the article No adverse events reported.
Source of funding	Not reported
Comments	**Statistical methods** Accuracy measures calculated using standard 2x2. **Study limitations (as assessed using QUADAS-2 checklist)** 1a. LOW 1b.Unclear whether patients recruited on basis of referral for coronary angiography UNCLEAR. 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

Table 71 Marwick 1993

Bibliographic reference	**Author: Marwick et al** **Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography or scintigraphy or both?** **Year: 1993**
Study type	Cross sectional
Aim	To examine the efficacy of dobutamine stress two-dimensional echocardiography and perfusion scintigraphy for the detection of coronary artery disease in routine practice.
Patient characteristics	**Inclusion** Patients presenting for diagnostic coronary angiography prospectively recruited.

Bibliographic reference	**Author: Marwick et al** **Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography or scintigraphy or both?** **Year: 1993**
	Exclusion History of ECG evidence of previous myocardial infarction. Unstable angina, malignant arrhythmias, cardiomyopathy, severe valvular disease or severe hypertension (>200mmHg systolic >120mmHg diastolic) **Other** Men 156, Women 61 Age (y) mean (SD) 58 (10). Typical angina present n% 142 (65). Remaining 75 patients had symptoms sufficiently suggestive of coronary artery disease to warrant coronary angiography. Pre-test probability (calculated on basis of age, gender and the clinical history) High (>80%) 46 Intermediate (20-80%) 131 Low (<20%) 40. Mean overall (SD) 54% (28)
Number of patients	217
Index test	**Dobutamine stress echo (Index test 4)** Undertaken during admission for cardiac catheterisation. Although advised to avoid anti-anginal therapy on the day of the test, 42 took beta-adrenoreceptor antagonists and 55 took nitrates or calcium antagonists or both. The protocol was performed as planned in these situations to correspond to the equivalent clinical circumstance. Pts were routinely prepared, a rest ECG and echo were performed and IV access was secured and dobutamine was infused (3-min dose increments from 5-40µg/kg) under continuous ECG and echocardiographic monitoring. The test was concluded after achievement of peak dose or earlier if patient developed severe ischemia (severe angina or severe impairment of left ventricular function) or intolerable side effects. Technetium-99m methoxyisobutly nitrile (sestamibi) was injected 1 to 2 mins before conclusion of infusion except where severe side effects necessitated termination of the test. **Perfusion Scintigraphy (Index tests 7)**

Bibliographic reference	**Author: Marwick et al** **Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography or scintigraphy or both?** **Year: 1993**
	Performed 1 to 2 hours after the injection of technetium-99m sestamibi. Data were acquired over 180 degrees using a large field, single-crystal camera and high resolution collimator. Trans-axial images were obtained by back-projection then reoriented into short-axis and vertical and horizontal long-axis views. Results were interpreted by experienced observers who had no knowledge of the echo or angiographic characteristics of the patients. Same assumptions were made about the coronary artery distributions. An analogous defect extent score was derived by expressing the number of abnormal segments as a percent of the total. Regions were then interpreted as showing normal perfusion, a stress induced perfusion defect or a fixed perfusion defect.
Reference standard (or Gold standard)	**Coronary angiography** performed using Judkins technique in all patients. All films were read by experienced observers. Quantification of coronary stenosis was performed using manual tracing and measurement using a technique previously validated with computer assisted quantitative angiography. Significant disease was defined as >50% stenosis in a major epicardial coronary artery (present in 142 patients, of whom 68 had single-vessel disease (defined by >50% stenoses confined to one coronary artery or its major branches or both). 66 patients had no significant disease (normal arteries) 9 patients had <50% stenoses (considered to be without CAD).
Time between testing & treatment	All tests performed “during admission”. Exact times not reported.
Length of follow-up	12 month period (dates not specified)
Location	Brussels, Belgium.
Diagnostic accuracy measures (2 x 2 table)	**Stress Echo** TP 102, TN 62, FP 13, FN 40 Sensitivity 72%, Specificity 83% **Mibi-SPECT** TP 108, TN 50, FP 25, FN 34 Sensitivity 76%, Specificity 67% The accuracy of predicting CAD in the high probability group and the absence of disease in the low probability

Bibliographic reference	**Author: Marwick et al** **Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography or scintigraphy or both?** **Year: 1993**
	group were 120/139 (86%) for echo and 99/110 (90%) for scintigraphy. **Side effects** Significant side effects were experienced by 84 patients (39%) and the test was terminated before peak dose in 64 patients (29%). Hypotension 36 (of which asymptomatic in 32), arrhythmias (8) hypertension (9), dyspnea (7), vagal reactions (2) and anxiety (2). The high incidence of side effects was attributable in part to inclusion of ischemia as an end point only in the presence of severe angina or extensive LVF. Milder ischemia was present in 33/64 before the onset of SEs so 31 patients had a non-diagnostic echo due to submaximal stress.
Source of funding	Not mentioned
Comments	**Study limitations:** 1a. Unclear if consecutive enrolment although prospective with clear inclusion/exclusion. UNCLEAR. 1b. All had typical angina/suspected CAD. Patients were recruited on basis of referral for coronary angiography HIGH 2a. 31 patients had a non-diagnostic echo and 64 patients did not complete due to side effects HIGH 2b. LOW 3a. LOW 3b.LOW 4. LOW. All patients were included in the analysis by test and breakdowns reported for combined tests.

Table 72 Nagel 1999

Bibliographic reference	**Author: Nagel et al** **Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high dose dobutamine stress MRI** **Year: 1999**
Study type	Cross sectional
Aim	To compare echocardiography and magnetic resonance imaging for the detection of stress-induced wall motion abnormalities in patients with suspected coronary artery disease.
Patient characteristics	**Inclusion**

Bibliographic reference	**Author: Nagel et al** **Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high dose dobutamine stress MRI** **Year: 1999**
	- Patients with suspected coronary artery disease **Exclusion** - Patients with ECG signs - History of previous myocardial infarction - Unstable angina pectoris (Braunwald classification III) - Arterial hypertension (>220/120mm Hg) - Dilated or obstructive cardiomyopathy - Ejection fraction <20% - Atrial flutter or fibrillation - Ventricular premature beats - Significant valvular disease class ≥II - Patients receiving B-blockers (to ensure an adequate heart rate response to dobutamine) **Other characteristics** Gender, n male/female 147/61 Age in years, mean (SD) 60 (9) Body weight in kg, mean (SD) 66 (34)
Number of patients	208 enrolled; 22 patients excluded from dobutamine stress echo group (DSE) due to insufficient image quality (n=18) and inadequate maximal heart rate (n=4); 22 patients excluded from dobutamine stress magnetic resonance imaging group (DSMR) due to insufficient image quality (n=3); inadequate maximal heart rate n=2); severe obesity (n=5); claustrophobia (n=11) and contraindication e.g.: metallic implants (n=1). Therefore a total of 186 in each group however for comparison, analysis included the **172 patients** in whom DSE and DSMR were obtained in a joint population.
Index test	**1. Dobutamine stress echocardiography (DSE) – corresponds to index test 4b on review protocol** **2. Dobutamine stress magnetic resonance imaging (DSMR) – corresponds to index test 5 on review protocol** - Both echocardiographic and MR images were displayed as continuous cineloops by use of a quadscreen display for review with a 16-segment model

<table>
<tr><td>Bibliographic reference</td><td>Author: Nagel et al
Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high dose dobutamine stress MRI
Year: 1999</td></tr>
<tr><td></td><td>- Images were evaluated by 2 experienced observers blinded to the results of any of other techniques
- Calcium antagonists and nitrates were stopped 24 hours before stress examinations</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Biplane coronary angiography
- Angiograms were reviewed and interpreted by 2 experienced investigators blinded to the results of the non-invasive tests
- Coronary artery disease defined as a 50% narrowing of the luminal diameter with respect to pre-stenotic segment diameters in at least 1 major epicardial coronary artery or a major branch of 1 of these vessel distributions</td></tr>
<tr><td>Time between testing & treatment</td><td>Angiography performed within 14 days after DSE and within 24 hours after DSMR in all patients.</td></tr>
<tr><td>Length of follow-up</td><td>Study dates not reported</td></tr>
<tr><td>Location</td><td>Germany</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>1. Accuracy of dobutamine stress echocardiography (index test 4b) to detect coronary artery disease defined as a 50% narrowing of the luminal diameter (patient based analysis)
TP: 81; TN: 44; FP: 19 FN: 28
<table><tr><td>Sensitivity (95%CI)*:</td><td>74.3 (65.4 to 81.6)</td></tr><tr><td>Specificity (95%CI)*:</td><td>69.8 (57.6 to 79.8)</td></tr></table>*Confidence intervals calculated by analyst based on data reported in the article

2. Accuracy of dobutamine stress magnetic resonance imaging (index test 5) to detect coronary artery disease defined as a 50% narrowing of the luminal diameter (patient based analysis)
TP: 94; TN: 54 FP: 9 FN: 15
<table><tr><td>Sensitivity (95%CI)*:</td><td>86.2 (78.5 to 91.5)</td></tr><tr><td>Specificity (95%CI)*:</td><td>85.7 (75.0 to 92.3)</td></tr></table>*Confidence intervals calculated by analyst based on data reported in the article

No mention of adverse events.</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Statistical methods</td></tr>
</table>

Bibliographic reference	**Author: Nagel et al** **Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high dose dobutamine stress MRI** **Year: 1999**
	Diagnostic accuracy measures were evaluated according to standard definitions and compared between groups. **Study limitations (as assessed using QUADAS-2 checklist)** 1a. LOW 1b. UNCLEAR – suspected CAD but unclear how many had chest pain. Unclear if patients recruited based on referral for coronary angiography. 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

Table 73 San Roman 1998

Bibliographic reference	**Author: San Roman et al.** **Selection of the optimal stress test for the diagnosis of coronary artery disease .** **Year: 1998**
Study type	Cross-sectional
Aim	To compare the value and limitations of exercise stress testing, two types of pharmacological stress echocardiography (dipyridamole and dobutamine) and MIBI-SPECT scintigraphy during dobutamine infusion in the diagnosis of coronary artery disease
Patient characteristics	**Inclusion:** - Typical chest pain with no previous history of CAD **Exclusion:** - Previous: MI; revascularisation; positive stress test; angiographically-proven CAD; - Q wave on ECG; - Unstable angina not controlled by treatment, - Cardiac failure - Congenital or valvular heart disease, or cardiomyopathy

Bibliographic reference	**Author: San Roman et al.** **Selection of the optimal stress test for the diagnosis of coronary artery disease .** **Year: 1998**
	Other characteristics Age in years - mean (SD): 64 (10) Age >70 years – n/N (%) 30/102 (29.4%) Gender: male/female, n (%): 50/52 (49% male) Chest pain – n/N (%) - On exertion only: 14/102 (14%) - At rest only: 53/102 (52%) - Both: 35/102 (34%) Background treatment – n/N (%) - Beta-blockers: 9/102 (9%) - Calcium antagonists: 25/102 (25%) - Both beta-blockers and calcium antagonists: 9/102 (9%) - None: 59/102 (58%) Note: short-acting nitrates given as necessary; sustained release nitrates not used
Number of patients	102 consecutive patients
Index test	**(a) Dipyridamole echocardiography** – (index test 4b) Drug infusion protocol: Weighted dose of dipyridamole (0.84mg/kg) infused over 6 mins. In cases where myocardial ischaemia developed, this was reversed with iv aminophylline (240mg over 1-3 mins) and glycerol tri-nitrate if necessary. Echocardiographic examination: Cross-sectional (2D) echocardiography performed during dipyridamole infusion and up to 10mins after stopping. Used commercially available machines. Obtained parasternal long and short-axis views and apical four and two chamber views to look for new wall motion abnormalities. For analysis, the left ventricle was divided into 7 segments. Segmental wall motion at baseline exam was studied qualitatively and graded as: normal / mild hypokinesia / severe hypokinesia / akinesia / dyskinesia. A positive response was defined as the appearance of areas of transient asynergy that were absent or of lesser degree before the drug infusion. (Note: development of dyskinesia in a previously akinetic segment was not

Bibliographic reference	Author: San Roman et al. Selection of the optimal stress test for the diagnosis of coronary artery disease . Year: 1998
	considered a positive response but a mechanical effect). **(b) Dobutamine echocardiography** – (index test 4b) Drug infusion protocol: Dobutamine initially injected at dose of 10µg/kg/min, with subsequent increments of 10µg/kg/min every 3 minutes up to a total dose 40µg/kg/min, which was then maintained for 6 minutes. Atropine (1mg) was infused if the test was still negative at that point and 85% of max predicted heart rate had not been reached. IV propranolol (0.5-1mg) was given if a positive response appeared. IV glycerol trinitrate was infused when needed. Echocardiographic examination: Cross-sectional (2D) echocardiography performed during dipyridamole infusion and up to 10mins after stopping. Used commercially available machines. Obtained parasternal long and short-axis views and apical four and two chamber views to look for new wall motion abnormalities. For analysis, the left ventricle was divided into 7 segments. Segmental wall motion at baseline exam was studied qualitatively and graded as: normal / mild hypokinesia / severe hypokinesia / akinesia / dyskinesia. A positive response was defined as the appearance of areas of transient asynergy that were absent or of lesser degree before the drug infusion. (Note: development of dyskinesia in a previously akinetic segment was not considered a positive response but a mechanical effect). **(c) MIBI-SPECT** (technetium-99m methoxyisobutyl nitrile single photon emission computed tomography) scintigraphy –(index test 7) Drug infusion protocol: Technetium-99m methoxyisobutyl nitrile (MIBI; 20 mCi) was injected one minute before cessation of the dobutamine infusion (see (b) above). SPECT study: Tomographic imaging (using Siemens Orbiter gamma camera with high resolution collimator) was performed 1 hour after injection of technetium-99m methoxyisobutyl nitrile.

<table>
<tr><td>Bibliographic reference</td><td>Author: San Roman et al.
Selection of the optimal stress test for the diagnosis of coronary artery disease .
Year: 1998</td></tr>
<tr><td></td><td>Resting examination was done on a different day with a 2nd dose.
32 views collected using a 64x64 acquisition matrix for 35 seconds each over 180 degrees, from 45 degrees left posterior to 45 degrees right anterior oblique projections.
Images were reconstructed using back projection with Butterworth filter.
Same segmentation was used as for echocardiography to aid comparison.
Regions were classified as having: normal perfusion / a stress-induced perfusion defect / fixed perfusion defect with both types of defect considered positive responses for presence of CAD.

Notes:
- Situations leading to premature termination of dipyridamole or dobutamine infusion were: systolic BP >220mg Hg; diastolic BP > 120mm Hg; sustained ventricular arrhythmias; symptomatic hypotension; severe angina; ST depression > 3mm or elevation > 2mm.
- All tests were analysed by 2 independent observers blind to clinical data and other test results. Third opinion sought in cases of disagreement (dipyridamole echo: 2 cases; dobutamine echo : 3 cases; scintigraphy: 2 cases)
- Exercise stress testing is not an index test in the review protocol so data are not extracted for this test</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary arteriography (CA)
Significant CAD defined as ≥50% reduction in luminal diameter in one or more major vessels or main branches</td></tr>
<tr><td>Time between testing & treatment</td><td>CA performed after all index tests undertaken (on different days in random order) within 7 day period.</td></tr>
<tr><td>Length of follow-up</td><td>Study dates not reported</td></tr>
<tr><td>Location</td><td>Spain (2 university tertiary care centres)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>(a) Dipyridamole echocardiography (includes 10 patients with left bundle branch block (LBBB))
<table>
<tr><td></td><td>CAD present on CA</td><td>CAD absent on CA</td></tr>
<tr><td>+ve index test result</td><td>54 (TP)</td><td>2 (FP)</td></tr>
<tr><td>-ve index test result</td><td>12 (FN)</td><td>34 (TP)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Author: San Roman et al.** **Selection of the optimal stress test for the diagnosis of coronary artery disease .** **Year: 1998**

(b) Dobutamine echocardiography (includes 10 patients with left bundle branch block (LBBB))

	CAD present on CA	CAD absent on CA
+ve index test result	52 (TP)	4 (FP)
-ve index test result	14 (FN)	32 (TN)

(c) MIBI-SPECT (excludes 10 patients with left bundle branch block (LBBB))

	CAD present on CA	CAD absent on CA
+ve index test result	54 (TP)	9 (FP)
-ve index test result	8 (FN)	21 (TN)

NB/ as LBBB was a protocol exclusion criteria, data for MIBI-SPECT only is included in overall data synthesis.

Major adverse events included left heart failure with dobutamine n=1 and dipyridamole n=1. Severe hypotension (n=2 with each drug), Severe hypertension (3 with dobutamine and none with dipyridamiole) and sustained tachycardia (n=2 with dobutamine and none with dipyridamole).
Minor events: palpitations, headach, flushing or nausea (n=36) during dipyridamole and n=35 during dobutamine.

Source of funding	Not reported
Comments	Study limitations: 1a. LOW 1b. 10% of patients had LBBB – they were included in study samples for dipyridamole and dobutamine echocardiography, but excluded from MIBI-SPECT testing and comparison analyses (due to known limitations of the technique in such patients (unclear if LBBB was known prior to testing). HIGH 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

Table 74 Santoro 1998

Bibliographic reference	**Author: Santoro et al** **Head-to-head comparison of exercise stress testing, pharmacologic stress echocardiography, and perfusion tomography as first line examination for chest pain in patients without history of coronary artery disease** **Year: 1998**
Study type	Cross sectional study
Aim	To evaluate the accuracy of exercise stress testing, dipyridamole and dobutamine stress echocardiography (DIP-ECHO, DOB-ECHO) and dipyridamole and dobutamine technetium 99m sestamibi tomography (DIP-MIBI, DOB-MIBI) for the detection of coronary artery disease in patients evaluated for the first time because of chest pain.
Patient characteristics	**Inclusion** - Chest pain of suspected coronary cause (typical for angina pectoris in 10 (17%) patients and atypical in remaining 50 patients) **Exclusion** - Patients with documented CAD - Known angina pectoris - Previous myocardial infarction - Other cardiac disease including rhythm disturbances, valvular heart disease and cardiomyopathy - Abnormal baseline electrocardiograms (such as those with non isoelectric rest ST segment), - Abnormal baseline echocardiograms (such as those with left ventricular hypertrophy or segmental wall motion abnormalities) - Inability to exercise adequately - Contraindications to exercise or dipyridamole or dobutamine administration and poor acoustic window **Other characteristics** Baseline characteristics e.g.: age, gender not reported
Number of patients	N=60
Index test	**1. Dipyridamole and dobutamine stress echo (DIP-ECHO, DOB-ECHO)** – (index test 4b) - Commercially available equipment (Aloka SSD 870; 2.5 to 3.5 MHz transducers) was used to record images - Normal response to stress was defined as the preservation of the normal wall motion pattern present at rest or the development of homogeneous hyperkinesia. - The response to stress was considered abnormal when segmental deterioration of thickening or wall motion (hypokinesia: reduced thickening and wall motion; akinesia: near or total absence of thickening and wall

<table>
<tr><td>Bibliographic reference</td><td>Author: Santoro et al
Head-to-head comparison of exercise stress testing, pharmacologic stress echocardiography, and perfusion tomography as first line examination for chest pain in patients without history of coronary artery disease
Year: 1998</td></tr>
<tr><td></td><td>motion; dyskinesia: endocardial excursion away from the lumen and systolic thinning) developed

2. Dipyridamole and dobutamine technetium 99m sestamibi tomography (DIP-MIBI, DOB-MIBI) – single photon emission computed tomography – (Index test 7)
- Tomography was collected 60 minutes after technetium 99m sestamibi injection.
- An Elscint Apex SP4 gamma camera equipped with an ultrahigh resolution collimator with a 20% window centered at the 140 keV photopeak of technetium 99m was used.</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography
- Performed in multiple views with Judkins or Sones techniques
- Degree of lumen narrowing visually estimated with the aid of calipers
- Stenosis graded as follows: not significant <70%; moderate: 70 to 89% and severe; >90%.</td></tr>
<tr><td>Time between testing & treatment</td><td>- Exercise stress testing (not of interest to this question) was usually the first test performed.
- Dipyridamole and dobutamine stresses were performed in random order on the following 2 days.
- Coronary angiography was performed according to the study protocol within 15 days of exercise testing.</td></tr>
<tr><td>Length of follow-up</td><td>Study dates not reported</td></tr>
<tr><td>Location</td><td>Italy</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>1. Accuracy of DIP-ECHO (Index test 4b) in detecting significant stenosis defined as >70%
TP: 18; FP: 1; TN: 26; FN: 15
<table><tr><td>Sensitivity (95%CI)*:</td><td>54.5% (36 to 72)</td></tr><tr><td>Specificity (95%CI)*:</td><td>96.3% (81 to 100)</td></tr></table>*Calculated by analyst based on data reported in the article

2. Accuracy of DOB-ECHO (Index test 4b) in detecting significant stenosis defined as >70%
TP: 20; FP: 1; TN: 26; FN: 13
<table><tr><td>Sensitivity (95%CI)*:</td><td>60.6% (42 to 77)</td></tr><tr><td>Specificity (95%CI)*:</td><td>96.3% (81 to 100)</td></tr></table>*Calculated by analyst based on data reported in the article</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Author: Santoro et al
Head-to-head comparison of exercise stress testing, pharmacologic stress echocardiography, and perfusion tomography as first line examination for chest pain in patients without history of coronary artery disease
Year: 1998</td></tr>
<tr><td></td><td>3. Accuracy of DIP-MIBI (Index test 7) in detecting significant stenosis defined as >70%
TP: 32; FP: 3; TN: 24; FN: 1 hoff
<table><tr><td>Sensitivity (95%CI)*:</td><td>97% (84.7 to 99.5)</td></tr><tr><td>Specificity (95%CI)*:</td><td>88.9% (71.9 to 96.1)</td></tr></table>*Calculated by analyst based on data reported in the article

1. Accuracy of DOB-MIBI (Index test 7) in detecting significant stenosis defined as >70%
TP: 30; FP: 5; TN: 22; FN: 3
<table><tr><td>Sensitivity (95%CI)*:</td><td>90.9% (76.4 to 96.9)</td></tr><tr><td>Specificity (95%CI)*:</td><td>81.5% (63.3 to 91.8)</td></tr></table>*Calculated by analyst based on data reported in the article

No major adverse events reported. Minor events: dobutamine was terminated before peak dose because of frequent ventricular ectopic beats (n=2), ventricular tachycardia (n=1), vomiting and hypotension (n=1).</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Statistical methods
Standard 2x2 tables used to calculate accuracy measures

Study limitations (assessed using QUADAS-2 checklist)
1a. UNCLEAR – consecutive recruitment not reported, baseline characteristics not reported
1b. Suspected CAD with chest pain of suspected coronary cause. LOW
2a. LOW
2b. LOW
3a. UNCLEAR - unclear if reference standard results were interpreted without knowledge of index test results
3b. LOW
4. LOW</td></tr>
</table>

Table 75 Schepis 2007

Bibliographic reference	**Author: Schepis et al** **Added value of Coronary Artery Calcium Score as an Adjunt to Gated SPECT for the Evaluation of Coronary Artery Disease in an Intermediate-Risk Population.** **Year: 2007**
Study type	Cross-sectional
Aim	To investigate the added value of the CAC score as an adjunct to gated SPECT for the assessment of CAD in an intermediate risk population.
Patient characteristics	119 patients prospectively recruited who were scheduled for elective coronary angiography because of suspected CAD. 77 fulfilled inclusion criteria. **Inclusion** No previously known CAD Typical or atypical chest pain, dyspnoea or signs of myocardial ischemia on a resting ECG or bicycle stress test; Intermediate risk (10-20%) (determined on the basis of Framingham Heart Study 10-y CAD risk score. Clinically stable condition. Men 45, women 32 Age (mean (SD)) 66(9), range 42-82. **Clinical characteristics** BMI (mean (SD)) 27kg/m^2 (4) Arterial hypertension 56 (73) Diabetes melitus 14 (18) Current smoker 27 (35) Typical angina 26 (34) Atypical angina 18 (23) Asymptomatic 16 (21) Framingham Heart study risk score 13 (5) Total cholesterol (mmol/L) 5.0 (1.1).
Number of patients	77
Index test	**Gated SPECT (Index Test 7)** 1-d stress-rest MPI protocol with doses of 350MBq of 99mTC-tetrofosmin, respectively. Patients were instructed

Bibliographic reference	**Author: Schepis et al** **Added value of Coronary Artery Calcium Score as an Adjunt to Gated SPECT for the Evaluation of Coronary Artery Disease in an Intermediate-Risk Population.** **Year: 2007**
	to refrain from caffeine (12hrs), nitrates (24hrs) and beta blockers for 48hrs before the study. Stress induced using adenosine 0.14mg/kg/min. Data acquisition performed using hybrid SPECT/CT dual head camera. SPECT images were reconstructed with an iterative ordered subsets expectation maximisation algorithm. A low-dose CT scan for attenuation correction was performed. ECG gating was performed at rest. Semi-quantitative visual interpretation of the attenuation corrected stress and rest images was performed by consensus of 2 experienced cardiologists unaware of results of both other tests. Segments were scored for radiotracer uptake with a 5-point score (0=normal, 1=equivocal, 2=moderately reduced, 3=severely reduced and 4=absent). Fixed perfusion defects and reversible defects were considered abnormal findings. The extent of reversible defects was categorised as mild (≤5%), moderate (>5 and ≤10%) or large (>10%). Mild or moderate fixed perfusion defects were not considered to be abnormal if there was normal segmental contraction or thickening. Categorization scale was 1=definitely normal, 2=probably normal, 3=equivocal, 4=possibly abnormal and 5=definitely abnormal. **Calcium Scoring (Index test 3)** A non-enhanced ECG-gated scan was obtained using 64 slice CT scanner. Estimated radiation dose 1-3mSv. Patients with heart rate of >65bpm were given metoprolol at 5-20mg IV prior to CT scan. Image reconstruction was performed at 55% of the R-R interval, with a non-overlapping slice thickness of 3mm. Total calcium burden was measured manually by planimetry according to Agatston scoring algorithm. People were categorised as follows. ≤10 = minimal or insignificant CAC, 11-100 (mild CAC), 101-400 (moderate CAC), 401-1000 (severe CAC) and >1000 (extensive CAC). CAC score threshold was determined as the cut-off that on ROC analysis resulted in the best sensitivity for the detection of significant CAD with an associated specificity of >90%. This score was used to evaluate the diagnostic performance of SPECT alone and of SPECT combined with CAC score for the prediction of significant CAD. The cut off score was >709.
Reference standard (or Gold standard)	**Coronary angiography** Coronary arteries were subdivided into 15 segments (AHA guidelines). Segments were classified as normal, as having non-obstructive disease (<50% stenosis) or as having significant stenosis. Stenosis was evaluated in 2 different views and significant CAD was defined as the presence of at least one coronary vessel stenosis of 50% or greater in major epicardial coronary vessel.

Bibliographic reference	**Author: Schepis et al** **Added value of Coronary Artery Calcium Score as an Adjunt to Gated SPECT for the Evaluation of Coronary Artery Disease in an Intermediate-Risk Population.** **Year: 2007**
Time between testing & treatment	Within 2 weeks. Mean time 7(14) and 4(14) days for coronary angiography and CT and gated SPECT respectively.
Length of follow-up	Study period not specified
Location	Zurich, Switzerland
Diagnostic accuracy measures (2 x 2 table)	42/77 patients had CAD (4 had stenosis level of 50-75% and 38 had stenosis level of >75%). Overall, CAC was deemed accessible in 304/308 coronary arteries in 77 patients. 4 vessels were affected by motion artifacts and were excluded. **TP FP FN TN Sens% Spec%** SPECT (Index test 7) 32 3 10 32 76 91 SPECT plus CAC score (Index tests 3 & 7 combined) 36 5 6 30 86 86 (CAC score threshold >709) No mention of adverse events associated with any test.
Source of funding	One author was supported by a grant from the Swiss National Science Foundation.
Comments	**Study limitations:** 1a. UNCLEAR unclear if enrolment was consecutive 1b. HIGH 21% were asymptomatic, all patients were intermediate risk of CAD according to Framingham Scores. Patients were recruited into study based on referral for coronary angiography. 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW although the time period of the study was not specified

Table 76 Senior 2004

Bibliographic reference	**Author: Senior et al** **Myocardial perfusion assessment in patients with medium probability of coronary artery disease and no prior myocardial infarction: Comparison of myocardial contrast echocardiography with ^{99mT}c single-photon emission computed tomography** **Year: 2004**
Study type	Cross sectional
Aim	To test the hypothesis that MCE is superior to SPECT for the detection of CAD.
Patient characteristics	**Inclusion** Adults with chest pain but without a history of prior MI or resting regional dysfunction on echocardiography scheduled for diagnostic angiography who were then screened for pre-test probability of CAD. People with a medium probability were selected for enrolment into the study. **Exclusion** Previous CABG, valvular disease, cardiomyopathy, atrial fibrillation and contraindications for dipyridamole. Prior MI or abnormal regional function at rest (as assessed with echo). **Other** Pre-test probability of CAD (mean (SD) 64% (26) Age (y) 47-61 (median 61) Male (%) 45 (82) Diabetes (%) 5 (9) Hypertension (%) 22 (40) Hyperlipidaemia (%) 19 (35) Type of Chest pain (%) Typical 18 (33) Atypical 26 (47) Noncardiac 11 (20) ≥3 risk factors 22 (40)
Number of patients	55
Index test	**Echocardiography (Index test 4b)** was performed continuously during dipyridamole infusion and for 5-10mins after its completion. (0.56mg/kg over 4mins, followed 4mins later by 0.28mg/kg over 2mins). Patients who had angina or wall motion abnormalities after the first dose were not given the second dose. When necessary,

Bibliographic reference	**Author: Senior et al** **Myocardial perfusion assessment in patients with medium probability of coronary artery disease and no prior myocardial infarction: Comparison of myocardial contrast echocardiography with ^{99mT}c single-photon emission computed tomography** **Year: 2004**
	intolerable symptoms were reversed with 50-100mg of intravenous aminophylline. Patients were asked to abstain from caffeine and methylxanthines for at least 12 hours and beta blockers for 24 hours before the test. 3 standard apical views using pulse inversion (HDI5000, Phillips Ultrasound). 5 frames acquired (digitally) at each pulse interval. Sonazoid contrast agent was used (0.01ml/kg/min starting 3mins after completion of dipyridamole infusion and just after radio isotope. **SPECT (Index test 7)** Performed 1-2 hours after IV ^{99m}TC-tetrofosomin (600MBq) using multi-head cameras. 32 projections were acquired and tomograms reconstructed in the vertical and horizontal long and short axis planes. 16 and 17 segment model was used for MCE and SPECT respectively. Rest and stress images were viewed side by side by independent and blinded observers. ECHO Normal replenishment (of the ultrasound beam after microbubble destruction) at rest that did not fill in approximately 1 second after dipyridamole was considered to be presence of a reversible perfusion defect On SPECT a perfusion defect was considered to be fixed when its relative magnitude was unchanged between rest and stress. All fixed and reversible defects were considered to be abnormal.
Reference standard (or Gold standard)	**Coronary Angiography** No details about the technique used to carry out. CAD defined as >50% luminal diameter narrowing of ≥1 major epicardial arteries or their major branches. If an artery had >1 stenosis the most severe one was used for definition purposes in both anterior and posterior circulations. Multi-vessel disease was determined to be present when both circulation systems had >50% luminal narrowing.
Time between testing & treatment	Within 4 weeks.
Length of follow-up	Study duration not mentioned
Location	3 centres in Europe (including UK and Germany)
Diagnostic accuracy measures (2 x 2 table)	12 patients had no CAD. 43 patients had CAD (of which, 11 had multi-vessel CAD).

Bibliographic reference	**Author: Senior et al** **Myocardial perfusion assessment in patients with medium probability of coronary artery disease and no prior myocardial infarction: Comparison of myocardial contrast echocardiography with ^{99mT}c single-photon emission computed tomography** **Year: 2004**
	TP FP FN TN * Sens% Spec% Echo stenosis >50% 36 5 7 7 83.0 58.0 SPECT stenosis >50% 21 1 22 11 49.0 92.0 Echo stenosis >75% 36 1 7 11 83.0 88.0 SPECT stenosis >75% 21 4 22 8 49.0 64.0 No mention of adverse events associated with any test.
Source of funding	Supported by a grant from Amersham Health UK and in part by grants from the National Institutes of Health, Bethesda, Md.
Comments	**Study limitations:** 1a. Design described as prospective but it is not stated whether enrolment was consecutive. UNCLEAR 1b. Population all had chest pain. 67% had atypical or non-cardiac chest pain. Only people with medium pre-test probability for CAD were selected. Patients were selected for recruitment based on referral for coronary angiography. HIGH 2a. LOW 2b. LOW 3a. Unclear if operator of the reference standard test was blinded to the index test results. UNCLEAR 3b. LOW 4. LOW

Table 77 Stolzmann 2011

Bibliographic reference	**Author: Stolzmann et al** **Combining cardiac magnetic resonance and computed tomography coronary calcium scoring: added value for the assessment of morphological coronary disease?** **Year: 2011**
Study type	Cross sectional
Aim	To investigate the added value of calcium scoring as adjunct to cardiac magnetic resonance (CMR) for the diagnosis of coronary artery disease (in comparison to coronary angiography).
Patient characteristics	**Inclusion**

Bibliographic reference	**Author: Stolzmann et al** **Combining cardiac magnetic resonance and computed tomography coronary calcium scoring: added value for the assessment of morphological coronary disease?** **Year: 2011**
	Consecutive patients referred to coronary angiography with an intermediate risk of having CAD based on the Diamond and Forrester criteria. **Exclusions** Contraindications for adenosine (second or third AV-block, sick sinus syndrome, symptomatic bradycardia, severe asthma or obstructive pulmonary disease n=4) or MRI (implanted electronic devices, metallic foreign bodies in the eye, severe claustrophobia and other according to local regulations/manufacturer recommendations, n=1). **Other** Male 52 (87%), Female 8 (13%). Age y (mean(SD)) 64 (10) (range 41-85) BMI (kg/m^2) 27.4 (4.3) Obesity 17 (28%) **Cardiovascular risk factors n(%)** Hypertension 46 (77) Nicotine abuse 20 (33) Hyperlipidaemia 43 (72) Family history 11 (18) Diabetes 9 (15) **Symptoms n(%)** Non anginal pain or no chest pain 21 (35) Atypical angina 13 (22) Typical angina 26 (43)
Number of patients	65-5 = 60
Index test	**CMR (Index test 6)** Performed using 1.5Tesla magnetic resonance system using standardized protocols. All data were acquired using breath hold in end inspiration and standardized 17 segment AHA model. Pharmacological stress using adenosine was applied at 140µg/min/kg over 3 mins under ECG, oxygen-saturation and BP monitoring. Gadobutrolum was injected 2.5mins after the start of the adenosine and with the acquisition of perfusion CMR images. Contrast media was administered (0.1mmol/kg) at 5mls/second followed by saline flush. 10 mins later a second bolus was

Bibliographic reference	**Author: Stolzmann et al** **Combining cardiac magnetic resonance and computed tomography coronary calcium scoring: added value for the assessment of morphological coronary disease?** **Year: 2011**
	given and rest perfusion images were obtained with same orientation /positioning as the stress images. Saturation recovery gradient-echo pulse sequence used. Slice thickness 10mm. 10 mins after rest perfusion late gadolinium enhancement (LGE) images were acquired. All images were evaluated using ViewForum (Philips) by two experienced readers blinded to results of other tests. Segmental perfusion and LGE was scored with a 4 point scale (0=definitely normal, 1=probably normal, 2=probably pathological, 3=definitely pathological). A score of 2 or 3 was considered abnormal. (pathological was defined as either reduced peak signal intensity or delayed wash-in during stress/vs rest). **Calcium Scoring (Index test 3)** All CTs performed on Somatom Definition scanner (Siemens). A non-contrast enhanced scan was performed for CS and data were acquired using prospective ECG triggering. Estimated effective radiation dose 1.1±0.3mSV. Image reconstruction was performed using a mon-segment mode with non-overlapping slice thickness of 3mm. Calcifications were semi-automatically quantified with scoring software by a single blinded experienced operator using the Agatston method. On the basis of Agatston score patients were classified into 5 categories. 1. ≤10 = no or minimal calcifications 2. 10 to 100 = mild 3. 101 to 400 = moderate 4. 401 to 1000 = severe 5. >1000 = extensive. CS-related risk was stratified using age and gender related percentiles. Patients with a CS >75th percentile were classified to be at high risk.
Reference standard (or Gold standard)	**Coronary angiography** Angiograms were obtained in at least 2 orthogonal projections according to standard techniques and were evaluated by two experienced readers blinded to results of the index tests. QCA analysis software was used. Arteries were divided into 15 segments per the AHA scheme. An average of the 2 results was taken to obtain the overall percentage stenosis. ≥50% narrowing was considered as morphological stenosis. 36/60 patients had stenosis.
Time between testing & treatment	Same day

Bibliographic reference	**Author: Stolzmann et al** **Combining cardiac magnetic resonance and computed tomography coronary calcium scoring: added value for the assessment of morphological coronary disease?** **Year: 2011**
Length of follow-up	Not specified
Location	Zurich, Switzerland.
Diagnostic accuracy measures (2 x 2 table)	**CMR** TP 28, FP 3, FN 8, TN 21* Sensitivity (%(95%CI) 78% (63-93), Specificity 88 (72-100), PPV 90 (78-100), NPV (54-90. Accuracy 92 (71-92) **Combined CMR and CT calcium scoring** TP 32, FP 4, FN 4, TN 20* Sensitivity (%(95% CI) 89 (77-97), Specificity 83 (66-100), PPV 89 (77-100), NPV 83 (66-100). Accuracy 87 (77-96). No mention of any adverse events associated with any test.
Source of funding	Not mentioned
Comments	**Study limitations:** 1a. LOW 1b. HIGH 35% had no angina pain or no chest pain, all patients were intermediate risk of CAD. Patients were recruited on basis of referral for coronary angiography. 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW although the time period of the study was not specified this should not in itself significantly increase the risk of bias

Table 78 Thomassen 2013

Bibliographic reference	**Author: Thomassen et al** **Hybrid CT angiography and quantitative 15O-water PET for assessment of coronary artery disease: comparison with quantitative coronary angiography** **Year: 2013**
Study type	Cross sectional

Bibliographic reference	**Author: Thomassen et al** **Hybrid CT angiography and quantitative 15O-water PET for assessment of coronary artery disease: comparison with quantitative coronary angiography** **Year: 2013**
Aim	To examine the diagnostic performance of 64-slice CT angiography (CTA) alone, quantitative 15O-water positron emission tomography (PET) alone and hybrid PET/CTA using quantitative coronary angiography (QCA) obtained by invasive coronary angiography (ICA) as reference, and further to determine cut-off values of absolute myocardial blood flow (MBF) yielding the best diagnostic performance
Patient characteristics	**Inclusion** - Outpatients scheduled for ICA because of suspected stable angina pectoris **Exclusion** - Known CAD - Arrhythmia - Dysregulated diabetes - Impaired renal function - Allergy to iodine - Severe asthma or chronic obstructive pulmonary disease - Inability to cooperate **Other characteristics** Gender, male/female, n (%) 23 (52)/21 (48) Age (years), mean ± SD 66±9 Diabetes mellitus, n (%)7 (16) Hypertension, n (%)29 (66) Smoker or ex-smoker, n (%)30 (68) Hypercholesterolaemia, n (%)26 (59) Family history, n (%)21 (48)
Number of patients	N=44
Index test	**1. 64-slice CT angiography (CTA) alone** – corresponds to test 2b on review protocol - Patients were examined using hybrid PET/64-slice CT scanners (GE Discovery VCT XT or GE Discovery RX) with the Agatston score obtained from the CT scan - Stenoses were graded visually considering stenoses of ≥50 % as significant. If CTA was non diagnostic in one or more segments in a vessel, the vessel was considered significantly stenosed, because most non diagnostic CTA

Bibliographic reference	**Author: Thomassen et al** **Hybrid CT angiography and quantitative 15O-water PET for assessment of coronary artery disease: comparison with quantitative coronary angiography** **Year: 2013**
	was a result of heavy calcification. - In symptomatic patients, heavy calcification is associated with increasing probability of having an angiographically significant stenosis **2. Quantitative 15O-water positron emission tomography (PET) alone** – corresponds to test 7 on review protocol - A low-dose CT transmission scan was acquired for attenuation Correction - Data were reconstructed with a 50-cm field of view, a matrix size of 512×512 (pixel size 0.98 mm) and a slice thickness 3.75 mm, using filtered back-projection and a standard GE CT noise filter **3. Hybrid PET/CTA** - Quantitative PET images were fused with CTA images on a GE ADW 4.3 or 4.4 workstation (CardIQ Fusion) to provide a 3-D volumetric model. - The analysis was conducted with full access to the PET and CTA datasets. - All CTA stenoses of ≥50 % were tested for 'haemodynamic significance': if the downstream vascular territory was hypoperfused during hyperaemia as judged by PET (<2.5 ml/min/g), the stenosis was categorized as 'haemodynamically significant'. - Vessels with 0 – 50 % stenosis on CTA were reanalysed if the corresponding vascular territory had impaired MBF by PET and a final decision was made as to whether a stenosis/occlusion was present
Reference standard (or Gold standard)	**Invasive coronary angiography** - Siemens HICOR catheterization equipment (Siemens Medical System, Inc., Erlangen, Germany) was used for standard ICA in two planes - A diameter reduction of 50 % or more indicated an 'angiographically significant' stenosis. In vessels with multiple stenoses, only the most severe stenosis was evaluated.
Time between testing & treatment	Invasive coronary angiography was scheduled for the day after the index tests
Length of follow-up	Study dates not reported
Location	Denmark
Diagnostic accuracy measures (2 x 2 table)	**1. Accuracy of CTA (Index test 2) in detecting significant stenosis (per patient analysis)** TP: 20; TN: 14; FP: 8; FN: 2

Bibliographic reference	**Author: Thomassen et al** **Hybrid CT angiography and quantitative 15O-water PET for assessment of coronary artery disease: comparison with quantitative coronary angiography** **Year: 2013**
	<table><tr><td>Sensitivity (95%CI)*:</td><td>90.9 (72.2 to 97.5)</td></tr><tr><td>Specificity (95%CI)*:</td><td>63.6 (43.0 to 80.3)</td></tr></table> **3. Accuracy of PET (index test 7) in detecting significant stenosis** TP: 20; TN: 19; FP: 3; FN: 2 <table><tr><td>Sensitivity (95%CI)*:</td><td>91 (72-97)</td></tr><tr><td>Specificity (95%CI)*:</td><td>86 (67-95)</td></tr></table> **3. Accuracy of CTA/PET (index tests 2 and 7) in detecting significant stenosis/hypoperfusion (per patient analysis)** TP: 20; TN: 22; FP: 0; FN: 2 <table><tr><td>Sensitivity (95%CI)*:</td><td>90.9 (72.2 to 97.5)</td></tr><tr><td>Specificity (95%CI)*:</td><td>100.0 (85.1 to 100.0)</td></tr></table> No adverse events were reported and no cardiac events occurred between tests.
Source of funding	Not reported
Comments	**Statistical methods** Accuracy measures calculated for each modality **Study limitations (as assessed using QUADAS-2)** 1a. UNCLEAR – consecutive recruitment not reported 1b. Patients recruited on basis of referral for coronary angiography HIGH 2a. LOW 2b. LOW 3a. LOW 3b. LOW 4. LOW

G.2 Review question 1 – supplementary test and treat randomised controlled trial review

<table>
<tr><td>Bibliographic reference</td><td>The SCOT-HEART investigators (2015) CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. The Lancet 385: 2383-2391</td></tr>
<tr><td>Study type</td><td>RCT, open-label, parallel-group (randomisation used minimisation to ensure balance between groups for certain characteristics)</td></tr>
<tr><td>Aim</td><td>To assess the effect of CTCA on the diagnosis, management and outcome of patients referred to the cardiology clinic with suspected angina</td></tr>
<tr><td>Patient characteristics</td><td>12 cardiology chest pain clinics across Scotland, November 2010 to September 2014

Inclusion;
- 18 to 85yrs, referred by a primary care physician to a cardiology chest pain clinic with stable suspected angina due to coronary heart disease
Exclusion;
- inability to undergo CT scanning, renal failure, major allergy to contrast media, pregnancy acute coronoary syndrome within 3months

Baseline;
<table>
<tr><td></td><td>Standard care and CTCA</td><td>Standard care</td></tr>
<tr><td>Male</td><td>1162 (56%)</td><td>1163 (56%)</td></tr>
<tr><td>Age</td><td>57.1±9.7</td><td>57.0±9.7</td></tr>
<tr><td>Previous CHD</td><td>186 (9%)</td><td>186 (9%)</td></tr>
<tr><td>Previous CVD</td><td>91 (4%)</td><td>48 (2%)</td></tr>
<tr><td>Previous PVD</td><td>36 (2%)</td><td>17 (1%)</td></tr>
<tr><td>Typical angina symptoms</td><td>737 (36%)</td><td>725 (35%)</td></tr>
<tr><td>Atypical angina symptoms</td><td>502 (24%)</td><td>486 (23%)</td></tr>
<tr><td>Non-anginal symptoms</td><td>833 (40%)</td><td>859 (41%)</td></tr>
<tr><td>Normal ECG</td><td>1757 (85%)</td><td>1735 (84%)</td></tr>
<tr><td>Abnormal ECG</td><td>292 (14%)</td><td>316 (15%)</td></tr>
<tr><td>Baseline diagnosis of CHD</td><td>982 (47%)</td><td>956 (46%)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**The SCOT-HEART investigators (2015) CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. The Lancet 385: 2383-2391**
	<table><tr><td>Baseline diagnosis of angina due to CHD</td><td>742 (36%)</td><td>743 (36%)</td></tr><tr><td>Predicted 10yr CHD risk</td><td>18±11%</td><td>17±12%</td></tr></table>
Number of Patients	N=4146
Intervention	N=2073 Standard care and CTCA; - 64 row detector scanner (Brilliance 64, Philips Medical Systems, Netherlands and Biograph mCT, Siemens, Germany) and 320 detector row scanner (Aquilion ONE, Toshiba Medical Systems, Japan) at 3 imaging sites - CT coronary angiograms assessed by ≥2 accredited assessors
Comparison	N=2073 Standard care
Length of follow up	6weeks for primary outcome
Location	UK
Outcomes measures and effect size	Obstructive coronary artery disease – defined as luminal stenosis >70% in ≥1 major epicardial vessel or >50% in the left main stem Luminal cross-sectional area stenosis; normal (<10%), mild non-obstructive (10-49%), moderate non-obstructive (50-70%), obstructive (>70%) Primary outcome; - Proportion of patients diagnosed with angina secondary to coronary heart disease at 6weeks Long term outcomes; - Death, myocardial infarction, coronary revascularisation procedures, admittance to hospital for chest pain episodes, cerebrovascular disease, peripheral vascular disease – identified with data from the Information and Statistics Division of the NHS Scotland and confirmed by health records Missing data; N=295/2073 defaulted or did not complete scan; - Less likely to have atypical angina; N=58 (23%) vs N=686 (39%), p<0.0001 - Less likely to have a diagnosis of angina; N=50 (20%) vs N=692 (38%), p<0.0001

Bibliographic reference	The SCOT-HEART investigators (2015) CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. The Lancet 385: 2383-2391
	CTCA findings; - Normal; N=654 (37%) - Evidence of CHD; N=1124 (63%), of these non-obstructive CHD; N=672 (38%), obstructive CHD; N=452 (25%) Opinion of clinicians reporting CTCA the CTCA finding of evidence of CHD increased the certainty (RR 3.76, 95%CI 3.61 to 3.89, p<0.0001) and reduced the frequency of (RR 0.78, 95%CI 0.70 to 0.86, p<0.0001) the diagnosis of angina due to coronary heart disease Reported by attending clinician; compared with standard care CTCA increased the certainty (RR 2.56, 95%CI 2.33 to 2.79, p<0.0001) and increased the frequency of (RR 1.09, 95%CI 1.02 to 1.17, p=0.0172) the diagnosis of angina due to coronary heart disease at 6weeks For the primary endpoint this was an increased certainty (RR 1.79, 95%CI 1.62 to 1.96, p<0.0001) and had no effect on frequency (RR 0.93, 95%CI 0.85 to 1.02, p=0.1289) of the diagnosis of angina due to coronary heart disease Overall 6week diagnosis of CHD changed in 27% of those having CTCA compared with 1% with standard care alone. (certainty of diagnosis was assessed by comparing yes/no with probable/unlikely) (frequency of diagnosis was compared between yes/probable and unlikely/no) Improvements in angina stability; - CTCA group (N=640); at 6weeks 44±28, baseline 62±24,p<0.001 - Standard care group (N=651); at 6weeks 44±28, baseline 62±21,p<0.001 Improvements in angina frequency; - CTCA group (N=655); at 6weeks 68±22, baseline 79±23,p<0.0001 - Standard care group (N=653); at 6weeks 68±22, baseline 80±23,p<0.0001 No differences in the improvements in angina stability and frequency between the groups Adverse events related to CTCA, N=31 (2%); - N=13 contrast reactions, N=7 contrast extravasations, N=4 vasovagal, N=4 headaches, N=3 other - All AEs were self-limiting with no cases of anaphylaxis or renal failure

Bibliographic reference	**The SCOT-HEART investigators (2015) CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. The Lancet 385: 2383-2391**
	Clinical outcomes (other outcomes reported, not extracted in this ET);

	Standard care and CTCA, N=2073	Standard care, N=2073	HR (95%CI)	P value
CHD death, MI and stroke	31 (1.5%)	48 (2.3%)	0.644 (0.410 to 1.012	0.0561
Non-fatal MI	22 (1.1%)	35 (1.7%)	0.627 (0.367 to 1.069)	0.0862
Non-fatal stroke	5 (0.1%)	7 (0.2%)	0.727 (0.228 to 2.315)	0.5900
Cardiovascular death	4 (0.2%)	7 (0.3%)	0.574 (0.167 to 1.971)	0.3776
Coronary revascularisation	233 (11.2%)	201 (9.7%)	1.198 (0.992 to 1.448)	0.0611
Hospitalisation for chest pain	247 (11.9%)	264 (12.7%)	0.928 (0.780 to 1.104)	0.3993

Source of funding	The Chief Scientist Office of the Scottish Government Health and Social Care Directorates, with supplementary awards from Edinburgh and Lothian's health Foundation Trust and the Heart Diseases Research Fund
Comments	For 80% power, 2-seided p of 0.05, aimed to recruit 2069 to detect an absolute change of 4% in the diagnosis of angina.

[1] <Insert Note here>

Bibliographic reference	**Douglas PS, Hoffmann U, Patel MR, et al. (2015) Outcomes of anatomical versus functional testing for coronary artery disease. NEJM 372: 1291-1300** **PROMISE study**
Study type	RCT (stratified by study site and according to the choice of the intended functional test if they were assigned to that study group)
Aim	To assess compare health outcomes in patients who presented with new symptoms suggestive of CAD who were assigned to anatomical testing with CTA or functional testing
Patient characteristics	193 sites in North America, July 2010 to September 2013

<table>
<tr><th>Bibliographic reference</th><td>Douglas PS, Hoffmann U, Patel MR, et al. (2015) Outcomes of anatomical versus functional testing for coronary artery disease. NEJM 372: 1291-1300
PROMISE study</td></tr>
<tr><td></td><td>Inclusion;
- symptomatic outpatients without diagnosed CAD whose physicians believed that nonurgent, noninvasive cardiovascular testing was necessary for evaluation of suspected CAD
- >54years (men), >64 years (female) or 45 to 54years (male) or 50 to 64years (female) with ≥1 cardiac risk factor (diabetes, peripheral artery disease, cerebrovascular disease, current/past tobacco use, hypertension, dyslipidaemia)
Exclusion;
- unstable haemodynamic status or arrthyhmias that required urgent evaluation for suspected acute coronary syndrome, a history of CAD or evaluation for CAD in the previous 12months, clinically significant congenital, valvular or cardiomyopathic heart disease

Baseline;
<table>
<tr><th></th><th>CTA, N=4996</th><th>Functional testing, N=5007</th></tr>
<tr><td>Mean age</td><td>60.7±8.3</td><td>60.9±8.3</td></tr>
<tr><td>Female</td><td>2595 (51.9%)</td><td>2675 (53.4%)</td></tr>
<tr><td>Primary presenting symptom – chest pain</td><td>3673/4992 (73.6%)</td><td>3599/5004 (71.9%)</td></tr>
<tr><td>Primary presenting symptom – dysnoea on exertion</td><td>712/4992 (46.3%)</td><td>778/5004 (15.5%)</td></tr>
<tr><td>Primary presenting symptom – other</td><td>607/4992 (45.2%)</td><td>627/5004 (12.5%)</td></tr>
<tr><td>Typical angina</td><td>590 (11.8%)</td><td>576 (11.5%)</td></tr>
<tr><td>Atypical angina</td><td>3873 (77.5%)</td><td>3900 (77.9%)</td></tr>
<tr><td>Nonanginal pain</td><td>533 (10.7%)</td><td>531 (10.6%)</td></tr>
</table></td></tr>
<tr><th>Number of Patients</th><td>N=10003</td></tr>
<tr><th>Intervention</th><td>N=4996
Anatomical testing;
- contrast enhanced CTRA, 64-slice or greater multidetector CT scanner</td></tr>
<tr><th>Comparison</th><td>N=5007
Functional testing;</td></tr>
</table>

Bibliographic reference	**Douglas PS, Hoffmann U, Patel MR, et al. (2015) Outcomes of anatomical versus functional testing for coronary artery disease. NEJM 372: 1291-1300** **PROMISE study**
	- Exercise ECG, exercise or pharmacologic nuclear stress testing and stress echocardiography
Number of Patients	N=10003
Intervention	N=4996 Anatomical testing and CTA; - N=4686, 93.8% had CTA as first test - N=4589, 97.9% had CTA - N=97, 2.1% had CAC scoring only - N=310, 6.2% did not have CTA as first test - N=154, 49.7% had other test as first test - N=9, 2.9% had catheterisation - N=104, 33.5% had nuclear stress imaging - N=27, 8.7% had stress echocardiography - N=14, 4.5% had exercise ECG - N=156, 50.3% did not have test
Comparison	N=5007 Functional testing strategy; - N=4692, 93.7% had functional test as first test - N=3159, 67.3% had nuclear stress imaging - N=1056, 22.5% had stress echocardiography - N=477, 10.2% had exercise ECG - N=315, 6.3% did not have functional test as a first test - N=67, 21.3% had other test as first test - N=20, 6.3% had catheterisation - N=47, 14.9% had CTA or CAC scoring - N=246, 78.1% did not have test - N=2, 0.6% had test before randomisation
Length of follow up	60days at study sites, 6month intervals via phone or mail for a minimum of 1year
Location	USA
Outcomes measures and	

<table>
<tr><td>Bibliographic reference</td><td>Douglas PS, Hoffmann U, Patel MR, et al. (2015) Outcomes of anatomical versus functional testing for coronary artery disease. NEJM 372: 1291-1300
PROMISE study</td></tr>
<tr><td>effect size</td><td>Primary endpoint;
- composite of major cardiovascular events (included death from any cause, MI, hospitalisation for unstable angina, and major complication of cardiovascular procedures or diagnostic testing (stroke, major bleeding, renal failure, or anaphylaxis))
Secondary endpoints;
- Composite of the primary endpoint or invasive catheterisation showing no obstructive CAD, other combinations of the components of the primary endpoint, invasive cardiac catheterisation showing no obstructive CAD, cumulative radiation exposure (latter 2 endpoints determined at 90 days)

Clinical end point;
<table>
<tr><td></td><td>CTA, N=4996</td><td>Functional testing, N=5007</td><td>Adjusted HR (95%CI)</td><td>P value</td></tr>
<tr><td>Primary composite end point</td><td>164</td><td>151</td><td>1.04 (0.83 to 1.29</td><td>0.75</td></tr>
<tr><td>Death from any cause</td><td>74</td><td>75</td><td></td><td></td></tr>
<tr><td>Nonfatal MI</td><td>30</td><td>40</td><td></td><td></td></tr>
<tr><td>Hospitalisation for unstable angina</td><td>61</td><td>41</td><td></td><td></td></tr>
<tr><td>Major procedural complication</td><td>4</td><td>5</td><td></td><td></td></tr>
<tr><td>Primary end point plus catheterisation, showing no obstructive CAD</td><td>332</td><td>353</td><td>0.91 (0.78 to 1.06)</td><td>0.22</td></tr>
<tr><td>Death or nonfatal MI</td><td>104</td><td>112</td><td>0.88 (0.67 to 1.15)</td><td>0.35</td></tr>
<tr><td>Death, nonfatal MI, or hospitalisation for unstable angina</td><td>162</td><td>148</td><td>1.04 (0.84 to 1.31)</td><td>0.70</td></tr>
</table>

During the first 12months of follow-up;
- Primary composite end point; N=88 (CTA group), N=91 (functional testing group), HR 0.94 (0.70 to 1.26), p=0.68</td></tr>
<tr><td>Source of funding</td><td>National Heart, Lung and Blood Institute</td></tr>
<tr><td>Comments</td><td>10000wold provide 90% power to detect a relative reduction of 20% in the primary endpoint, assuming event rate of 8% at 2.5years, significance of 0.05. ITT analysis</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>McKavanagh, P., Lusk, L. et al. (2015) 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 16: 441-448</td></tr>
<tr><td>Study type</td><td>Test and treat randomised controlled trial</td></tr>
<tr><td>Aim</td><td>To determine the symptomatic and prognostic differences resulting from a novel diagnostic pathway based on cardiac computerized tomography coronary angiography (CTCA) compared with the traditional exercise stress electrocardiography test (EST) in stable chest pain patients.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria
- Referred to rapid access clinics with symptoms of stable chest pain (defined as troponin negative without symptoms of unstable angina)
- Referred by primary care physicians or non-cardiologists.
Exclusion criteria
- Contraindications to exercise stress testing or CTCA.

Baseline characteristics
<table>
<tr><th></th><th>CTCA</th><th>EST</th></tr>
<tr><td>Age (mean, sd)</td><td>57.8 (10.0)</td><td>58.9 (10.2)</td></tr>
<tr><td>Number male</td><td>138/243</td><td>131/245</td></tr>
<tr><td>Pre-test probability of CAD (Diamond + Forrester: low/medium/high)</td><td>101/53/76</td><td>107/62/76</td></tr>
<tr><td>Character of chest pain (non angina/atypical/typical)</td><td>143/16/84</td><td>156/20/68</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>500 patients in total randomised

<table>
<tr><th></th><th>CTCA</th><th>EST</th></tr>
<tr><td>Randomised</td><td>250</td><td>250</td></tr>
<tr><td>Baseline measures</td><td>245</td><td>242</td></tr>
<tr><td>3 months follow up</td><td>226</td><td>224</td></tr>
<tr><td>12 months follow up</td><td>210</td><td>202</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>CTCA: Patients underwent calcium scoring and subsequent computerised tomography coronary angiogram on a 64-detector platform. Oral and intravenous beta-blockers were used pre-procedure to reduce heart rate. A coronary</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>McKavanagh, P., Lusk, L. et al. (2015) 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 16: 441-448</td></tr>
<tr><td></td><td>stenosis of >50% was considered significant.</td></tr>
<tr><td>Comparison</td><td>EST: Used standard Bruce protocol treadmill with continuous 12-lead ECG and manual blood pressure monitoring. Results were classified as negative, positive or inconclusive according to published criteria (Fox et al. 2006 Guidelines on management of stable angina pectoris: executive summary).</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Location</td><td>Rapid access chest clinics in Northern Ireland</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Diagnosis and management
<table>
<tr><td></td><td>CTCA</td><td>EST</td></tr>
<tr><td>Number of additional tests ordered before final diagnosis</td><td>72</td><td>128</td></tr>
<tr><td>Final diagnosis with significant CAD</td><td>70/243 (28.8%)</td><td>33/245 (13.5%)</td></tr>
<tr><td>Management: (CABG/PCI/medical/no intervention)</td><td>8/29/99/107</td><td>7/12/35/191</td></tr>
</table>
Hospital re-attendance (12 months follow up)
<table>
<tr><td></td><td>CTCA</td><td>EST</td></tr>
<tr><td>A&E visit leading to admission (0/1/2)</td><td>241/2/0</td><td>232/10/3</td></tr>
<tr><td>A&E visit total (0/1/2/3/4)</td><td>235/8/0/0/0</td><td>223/16/3/2/1</td></tr>
<tr><td>Cardiology outpatient visit (0/1/2/3)</td><td>217/24/2/0</td><td>199/38/6/2</td></tr>
</table>
Quality of life (Seattle angina questionnaire – disease specific quality of life)
<table>
<tr><td rowspan="2"></td><td colspan="2">Difference between CTCA and EST</td></tr>
<tr><td>Change from baseline to 3 months (mean, 95%CI, p value)</td><td>Change from baseline to 12 months (mean, 95%CI, p value)</td></tr>
<tr><td>Physical limitation</td><td>20.54 (24.3 to 3.3) 0.779</td><td>0.33 (24.3 to 5.0) 0.889</td></tr>
<tr><td>Angina stability</td><td>211.1 (217.4 to 24.8) 0.001</td><td>26.8 (212.8 to 20.7) 0.028</td></tr>
<tr><td>Angina frequency</td><td>22.7 (26.8 to 1.3) 0.184</td><td>21.9 (26.0 to 2.2) 0.365</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**McKavanagh, P., Lusk, L. et al. (2015) 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 16: 441-448**
	Treatment satisfaction: 22.1 (25.3 to 1.2) 0.213 / 21.4 (25.2 to 2.3) 0.446 Quality of life: 25.7 (210.3 to 21.2) 0.014 / 24.9 (29.6 to 20.19) 0.041
Source of funding	South Eastern Health and Social Care Trust and Northern Ireland Cardiovascular network
Comments	Inclusion of multiple types of chest pain limits applicability. Population was largely low risk of CAD at basline, according to diamond and forrester score. Exercise stress electrocardiography is not currently recommended as a diagnostic strategy for patients with suspected CAD, so relevance of comparator is questionable.

Bibliographic reference	**The SCOT-HEART investigators (2015) CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. The Lancet 385: 2383-2391**
Study type	RCT, open-label, parallel-group (randomisation used minimisation to ensure balance between groups for certain characteristics)
Aim	To assess the effect of CTCA on the diagnosis, management and outcome of patients referred to the cardiology clinic with suspected angina
Patient characteristics	12 cardiology chest pain clinics across Scotland, November 2010 to September 2014 Inclusion; - 18 to 85yrs, referred by a primary care physician to a cardiology chest pain clinic with stable suspected angina due to coronary heart disease Exclusion; - inability to undergo CT scanning, renal failure, major allergy to contrast media, pregnancy acute coronoary syndrome within 3months Baseline; Male: Standard care and CTCA 1162 (56%) / Standard care 1163 (56%)

Bibliographic reference	**The SCOT-HEART investigators (2015) CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. The Lancet 385: 2383-2391**
	<table><tr><td>Age</td><td>57.1±9.7</td><td>57.0±9.7</td></tr><tr><td>Previous CHD</td><td>186 (9%)</td><td>186 (9%)</td></tr><tr><td>Previous CVD</td><td>91 (4%)</td><td>48 (2%)</td></tr><tr><td>Previous PVD</td><td>36 (2%)</td><td>17 (1%)</td></tr><tr><td>Typical angina symptoms</td><td>737 (36%)</td><td>725 (35%)</td></tr><tr><td>Atypical angina symptoms</td><td>502 (24%)</td><td>486 (23%)</td></tr><tr><td>Non-anginal symptoms</td><td>833 (40%)</td><td>859 (41%)</td></tr><tr><td>Normal ECG</td><td>1757 (85%)</td><td>1735 (84%)</td></tr><tr><td>Abnormal ECG</td><td>292 (14%)</td><td>316 (15%)</td></tr><tr><td>Baseline diagnosis of CHD</td><td>982 (47%)</td><td>956 (46%)</td></tr><tr><td>Baseline diagnosis of angina due to CHD</td><td>742 (36%)</td><td>743 (36%)</td></tr><tr><td>Predicted 10yr CHD risk</td><td>18±11%</td><td>17±12%</td></tr></table>
Number of Patients	N=4146
Intervention	N=2073 Standard care and CTCA; - 64 row detector scanner (Brilliance 64, Philips Medical Systems, Netherlands and Biograph mCT, Siemens, Germany) and 320 detector row scanner (Aquilion ONE, Toshiba Medical Systems, Japan) at 3 imaging sites - CT coronary angiograms assessed by ≥2 accredited assessors
Comparison	N=2073 Standard care
Length of follow up	6weeks for primary outcome
Location	UK
Outcomes measures and effect size	Obstructive coronary artery disease – defined as luminal stenosis >70% in ≥1 major epicardial vessel or >50% in the left main stem Luminal cross-sectional area stenosis; normal (<10%), mild non-obstructive (10-49%), moderate non-obstructive (50-70%), obstructive (>70%)

Bibliographic reference	The SCOT-HEART investigators (2015) CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. The Lancet 385: 2383-2391
	Primary outcome; - Proportion of patients diagnosed with angina secondary to coronary heart disease at 6weeks Long term outcomes; - Death, myocardial infarction, coronary revascularisation procedures, admittance to hospital for chest pain episodes, cerebrovascular disease, peripheral vascular disease – identified with data from the Information and Statistics Division of the NHS Scotland and confirmed by health records Missing data; N=295/2073 defaulted or did not complete scan; - Less likely to have atypical angina; N=58 (23%) vs N=686 (39%), p<0.0001 - Less likely to have a diagnosis of angina; N=50 (20%) vs N=692 (38%), p<0.0001 CTCA findings; - Normal; N=654 (37%) - Evidence of CHD; N=1124 (63%), of these non-obstructive CHD; N=672 (38%), obstructive CHD; N=452 (25%) Opinion of clinicians reporting CTCA the CTCA finding of evidence of CHD increased the certainty (RR 3.76, 95%CI 3.61 to 3.89, p<0.0001) and reduced the frequency of (RR 0.78, 95%CI 0.70 to 0.86, p<0.0001) the diagnosis of angina due to coronary heart disease Reported by attending clinician; compared with standard care CTCA increased the certainty (RR 2.56, 95%CI 2.33 to 2.79, p<0.0001) and increased the frequency of (RR 1.09, 95%CI 1.02 to 1.17, p=0.0172) the diagnosis of angina due to coronary heart disease at 6weeks For the primary endpoint this was an increased certainty (RR 1.79, 95%CI 1.62 to 1.96, p<0.0001) and had no effect on frequency (RR 0.93, 95%CI 0.85 to 1.02, p=0.1289) of the diagnosis of angina due to coronary heart disease Overall 6week diagnosis of CHD changed in 27% of those having CTCA compared with 1% with standard care alone. (certainty of diagnosis was assessed by comparing yes/no with probable/unlikely) (frequency of diagnosis was compared between yes/probable and unlikely/no)

Bibliographic reference	**The SCOT-HEART investigators (2015) CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. The Lancet 385: 2383-2391**

Improvements in angina stability;

- CTCA group (N=640); at 6weeks 44±28, baseline 62±24,p<0.001
- Standard care group (N=651); at 6weeks 44±28, baseline 62±21,p<0.001

Improvements in angina frequency;

- CTCA group (N=655); at 6weeks 68±22, baseline 79±23,p<0.0001
- Standard care group (N=653); at 6weeks 68±22, baseline 80±23,p<0.0001

No differences in the improvements in angina stability and frequency between the groups

Adverse events related to CTCA, N=31 (2%);

- N=13 contrast reactions, N=7 contrast extravasations, N=4 vasovagal, N=4 headaches, N=3 other
- All AEs were self-limiting with no cases of anaphylaxis or renal failure

Clinical outcomes (other outcomes reported, not extracted in this ET);

	Standard care and CTCA, N=2073	Standard care, N=2073	HR (95%CI)	P value
CHD death, MI and stroke	31 (1.5%)	48 (2.3%)	0.644 (0.410 to 1.012	0.0561
Non-fatal MI	22 (1.1%)	35 (1.7%)	0.627 (0.367 to 1.069)	0.0862
Non-fatal stroke	5 (0.1%)	7 (0.2%)	0.727 (0.228 to 2.315)	0.5900
Cardiovascular death	4 (0.2%)	7 (0.3%)	0.574 (0.167 to 1.971)	0.3776
Coronary revascularisation	233 (11.2%)	201 (9.7%)	1.198 (0.992 to 1.448)	0.0611
Hospitalisation for chest pain	247 (11.9%)	264 (12.7%)	0.928 (0.780 to 1.104)	0.3993

Source of funding	The Chief Scientist Office of the Scottish Government Health and Social Care Directorates, with supplementary awards from Edinburgh and Lothian's health Foundation Trust and the Heart Diseases Research Fund
Comments	For 80% power, 2-seided p of 0.05, aimed to recruit 2069 to detect an absolute change of 4% in the diagnosis of angina.

Bibliographic reference	The SCOT-HEART investigators (2015) CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. The Lancet 385: 2383-2391

G.3 Review question 2

Bibliographic reference	Caselli C, et al. (2015a) HDL cholesterol, leptin and interlukin-6 predict high risk coronary anatomy assessed by CT angiography in patients with stable chest pain. Atherosclerosis 241: 55-61.
Study type	Cross-sectional
Aim	To determine whether specific bio-humoral markers of inflammation and metabolism are predictors of high risk coronary artery anatomy, as estimated by the CTA risk score, in patients with stable angina-like symptoms and intermediate pre-test probability of CAD enrolled in the EVINCI (Evaluation of INtegrated Cardiac Imaging for the detection and characterization of ischemic heart disease) study.
Patient characteristics	**Inclusion:** - Stable chest pain or equivalent symptoms - Intermediate probability of CAD **Exclusion:** - Acute coronary syndrome - Known CAD - Left ventricular ejection fraction <35% - Significant heart valve disease - Cardiomyopathy - Contradiction to stress imaging **Patient characteristics**:

	n=429
Demographics	
Age in years – mean (sd)	60.3 (8.3)
Male – n (%)	268 (62.5)

Bibliographic reference	Caselli C, et al. (2015a) HDL cholesterol, leptin and interlukin-6 predict high risk coronary anatomy assessed by CT angiography in patients with stable chest pain. Atherosclerosis 241: 55-61.

Cardiovascular risk factors – n (%)	
Family history of CAD	149 (34.7)
Diabetes mellitus	105 (24.5)
Hypertension	263 (61.3)
Hypercholesterolemia	250 (58.3)
Obesity	94 (21.9)
Smoking within the last year	108 (25.2)
Symptoms	
Typical angina	102 (23.8)
Atypical / non-anginal chest pain	327 (76.2)
Medication	
None	65 (15.2)
Beta-blockers	172 (40.1)
Calcium antagonists	50 (11.7)
ARBs/ACE Inhibitors	190 (44.3)
Diuretics	73 (17.0)
Nitrates	45 (10.5)
Anti-thrombotics	256 (59.7)
Oral antidiabetics/Insulin	82 19.1)
Statins	230 (53.6)

ARB = Angiotensin Receptor Blockers; ACE = Angiotensin Converting Enzyme

Distribution of CAD on CTCA – n (%)
Normal: 98 (23)
Non-obstructive CAD (<50% stenosis): 181 (42)
Obstructive CAD (50-70%): 90 (21)
Severe CAD (>70%): 60 (14)

Bibliographic reference	**Caselli C, et al. (2015a) HDL cholesterol, leptin and interlukin-6 predict high risk coronary anatomy assessed by CT angiography in patients with stable chest pain. Atherosclerosis 241: 55-61.**
	Diagnosis of CAD at invasive coronary angiography[1] – n (%): 133 (31.0)
Number of patients	N = 429 patients
Probability score / model	Assessed the comparative discrimination ability of 3 models to predict low and high CTA risk score (using 7 as a cut-off value): **1. Bio-humoral model** Derived from 17 biomarkers associated with inflammation and metabolism. Final model included three biomarkers which independently predicted CTA score in multivariate analyses: - HDL cholesterol - Leptin - Interleukin-6 (model adjusted for age, sex, presence of diabetes and hypertension) Median CTA risk score: 10.25 (0.0 – 20.01) **2. Framingham risk score** (no further description) Median Framingham Risk Score (25 – 75 percentiles): 10 (6.7 – 17) 3. Euro-SCORE – data not extracted Data from Euro-SCORE website shows model included following variables: Age; Gender; Diabetes; NYHA class; CCS class 4 angina; Renal impairment (creatinine clearance); LV function; Extracardiac arteriopathy ; Recent MI; Poor mobility; Pulmonary hypertension; Previous cardiac surgery; Chronic lung disease; Active endocarditis Median Euro-SCORE (25 – 75 percentiles): 2.5 (1.1 – 4.8)
Reference standard (or Gold standard)	<u>CTA risk score</u> Based on analysis of CTCA images. Score consists of three weight factors for each segment of the coronary tree: (i) a stenosis severity weight factor (ii) a stenosis location weight factor (iii) a weight factor for plaque composition.

<table>
<tr><td>Bibliographic reference</td><td>Caselli C, et al. (2015a) HDL cholesterol, leptin and interlukin-6 predict high risk coronary anatomy assessed by CT angiography in patients with stable chest pain. Atherosclerosis 241: 55-61.</td></tr>
<tr><td></td><td>All three weight factors are multiplied to calculate the segment score. The risk score for each patient is calculated by adding all segment scores.

CTA risk score correlated highly with Agatston CAC score computed according to standard methods.</td></tr>
<tr><td>Time between testing & treatment</td><td>Not stated.</td></tr>
<tr><td>Length of follow-up</td><td>Study period not specified.</td></tr>
<tr><td>Location</td><td>14 European centres</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Area under the ROC curve

Reference: CTA risk score using 7 as cut-off threshold for low vs high risk coronary anatomy
<table>
<tr><th></th><th>AUC (95% CIs)</th></tr>
<tr><td>Framingham Risk Score</td><td>0.63 (0.58 to 0.68)</td></tr>
<tr><td>Bio-humoral model</td><td>0.81 (0.77 to 0.85)</td></tr>
</table>
Sensitivity / specificity
No data provided</td></tr>
<tr><td>Source of funding</td><td>Supported by a grant from the European Union FP7-CP-FP506 2007 project (grant agreement no. 222315, EVINCI study)</td></tr>
<tr><td>Comments</td><td>Study limitations
Biohumoral model not validated in independent cohort from that used to develop the model so data were not extracted for evidence appraisal.
Euro-SCORE was developed to predict mortality from cardiac surgery and has not been validated to assess probability of CAD in populations with stable chest pain except in this study, so data were not extracted for evidence appraisal.
QUADAS-2</td></tr>
</table>

Bibliographic reference	Caselli C, et al. (2015a) HDL cholesterol, leptin and interlukin-6 predict high risk coronary anatomy assessed by CT angiography in patients with stable chest pain. Atherosclerosis 241: 55-61.
	1A - Not clear if analysis was prospective or patients were consecutively enrolled: UNCLEAR 1B – Patients were all 'intermediate probability of CAD' - HIGH 2A – LOW (FRS) 2B – LOW (FRS) 3A - Not clear if results were interpreted without knowledge of probability scores / patient clinical data: UNCLEAR 3B - LOW 4 - LOW

[2] *All patients enrolled in this study had CTCA and cardiac stress imaging; invasive CA undertaken only if at least one of these tests was positive.*

Bibliographic reference	Caselli et al. (2015b) A new integrated clinical-biohumoral model to predict functionally significant coronary artery disease in patients with chronic chest pain. Canadian Journal of Cardiology 31: 709-716.
Study type	Cross-sectional
Aim	To assess the incremental value of circulating biomarkers over the Genders model to predict functionally significant CAD in patients with chronic chest pain and intermediate pre-test probability of CAD enrolled in the EVINCI (Evaluation of INtegrated Cardiac Imaging for the detection and characterization of ischemic heart disease) study[1].
Patient characteristics	**Inclusion:** - Stable chest pain or equivalent symptoms - Intermediate probability of CAD - Adequate quality of blood samples for biomarker analysis **Exclusion:** - Acute coronary syndrome - Known CAD - Left ventricular ejection fraction <35%

<table>
<tr><td>Bibliographic reference</td><td>Caselli et al. (2015b) A new integrated clinical-biohumoral model to predict functionally significant coronary artery disease in patients with chronic chest pain. Canadian Journal of Cardiology 31: 709-716.</td></tr>
<tr><td></td><td>- Significant heart valve disease
- Cardiomyopathy
- Contradiction to stress imaging

Patient characteristics:
<table><tr><th></th><th>n=527</th></tr><tr><td>Demographics</td><td></td></tr><tr><td>Age in years – mean (sd)</td><td>60.4(8.9)</td></tr><tr><td>Male – n (%)</td><td>323 (61.3)</td></tr><tr><td>Cardiovascular risk factors – n (%)</td><td></td></tr><tr><td>Family history of CAD</td><td>186 (35.3)</td></tr><tr><td>Diabetes mellitus</td><td>138 (26.2)</td></tr><tr><td>Hypertension</td><td>332 (63.0)</td></tr><tr><td>Hypercholesterolemia</td><td>313 (59.4)</td></tr><tr><td>Obesity</td><td>123 (23.3)</td></tr><tr><td>Smoking within the last year</td><td>128 (24.3)</td></tr><tr><td>Symptoms</td><td></td></tr><tr><td>Typical angina</td><td>134 (25.4)</td></tr><tr><td>Atypical / non-anginal chest pain</td><td>393 (74.6)</td></tr></table>
Anatomic CAD(>50% stenosis) – n (%): 166 (32.7)</td></tr>
<tr><td>Number of patients</td><td>N=527 patients</td></tr>
<tr><td>Probability score / model</td><td>1. Updated D-F (Genders) model (updated Diamond and Forrester model validated by Genders et al. 2011)
Clinical model incorporating the following three clinical variables:
- Male sex
- Age
- Type of chest pain (typical / atypical/ non-anginal)</td></tr>
</table>

Bibliographic reference	Caselli et al. (2015b) A new integrated clinical-biohumoral model to predict functionally significant coronary artery disease in patients with chronic chest pain. Canadian Journal of Cardiology 31: 709-716.
	2. Bio-humoral model 2 (3 variables) Derived from various biohumoral variables; final model comprised three biohumoral variables which independently predicted functionally significant CAD in multivariate analyses: - HDL cholesterol - Aspartate aminotransferase (AST) - High-sensitivity C-reactive protein (hs-CRP) **3.EVINCI model (Integrated clinical & bio-humoral model 2)** Integrated model including the above three biohumoral variables and the three clinical variables: male sex, age and type of chest pain (typical / atypical/ non-anginal) EVINCI model was validated in a separate independent cohort (n=186 consecutive patients hospitalised for suspected CAD between Jan 2000 – Oct 2005). Data on patient characteristics for this sample were not retrieved.
Reference standard (or Gold standard)	Evidence of functionally significant CAD at stress imaging (plus invasive coronary angiography in subsample) Defined as 1 of the following 3 findings: 1. > 50% stenosis of the left main coronary artery or the proximal left anterior descending (LAD) artery, left circumflex (LCx) artery, or right coronary artery (RCA), associated with severe ischemia on stress imaging. Myocardial ischemia was considered severe if it involved >10% of the left ventricular myocardium, as documented by a summed difference score at stress MPI or by a segmental difference score at stress WMI. 2. > 50% stenosis of the left main coronary artery or proximal LAD artery(or both), LCx artery, or RCA, associated with a FFR < 0.80. 3. > 90% stenosis of the left main coronary artery or proximal LAD artery, or both.
Time between testing & treatment	Not stated.
Length of follow-up	Study period not specified.
Location	14 European centres

Bibliographic reference	**Caselli et al. (2015b) A new integrated clinical-biohumoral model to predict functionally significant coronary artery disease in patients with chronic chest pain. Canadian Journal of Cardiology 31: 709-716.**
Diagnostic accuracy measures (2 x 2 table)	**Area under the ROC curve** Reference: Functionally significant CAD (see definition in Reference Standard section above)

	AUC (95% CIs[2])
Updated D-F (Genders) model	0.58 (0.50 to 0.66)
Bio-humoral model 2	0.68 (0.62 to 0.74)
EVINCI model – development cohort	0.70 (0.64 to 0.76)
EVINCI model – validation cohort (n=186)	0.72 (0.64 to 0.80)

Sensitivity and specificity

1. 2x2 table Genders' model

Threshold = 15% probability of CAD

Updated D-F (Genders) model	**CAD+**	**CAD-**
≥15%	51	235
<15%	29	212

2. 2x2 table EVINCI (integrated clinical and biohumoral) model

Threshold = 15% probability of CAD

EVINCI model	**CAD+**	**CAD-**
≥15%	52	174
<15%	28	273

	Sensitivity (95% CIs[1])	**Specificity (95% CIs[1])**
Updated D-F (Genders) model	63.8% (82.8 to 73.4)	47.4% (42.8 to 52.1)
EVINCI model	65.0% (54.1 to 74.5)	61.1% (56.5 to 65.5)

Source of funding	Supported by a grant from the European Union FP7-CP-FP506 2007 project (grant agreement no. 222315, EVINCI study)

Bibliographic reference	**Caselli et al. (2015b) A new integrated clinical-biohumoral model to predict functionally significant coronary artery disease in patients with chronic chest pain. Canadian Journal of Cardiology 31: 709-716.**
Comments	**Study limitations** Biohumoral model 2 not validated in independent cohort from that used to develop the model so data were not extracted for evidence appraisal 1A - Not clear if analysis was prospective or patients were consecutively enrolled: UNCLEAR QUADAS-2 1B – Patients were all 'intermediate probability of CAD' - HIGH 2A - LOW 2B - Updated D-F (Genders) model**:** LOW 2B – EVINCI model**:** Requires information from blood assays that is unlikely to be available at a typical index clinic visit: HIGH 3A - Not clear if results were interpreted without knowledge of probability scores / patient clinical data: UNCLEAR 3B – Reference standard was functionally significant CAD (determined either by stress test or stress test *and* CA): UNCLEAR 4 – Some patients received stress test and not CA as reference standard: UNCLEAR

[1] *All patients enrolled in this study had cardiac stress imaging (and CTCA); invasive CA undertaken only if at least one of these tests was positive*
[2] *95% CIs calculated by reviewer from reported standard errors*

Bibliographic reference	**Cetin et al. (2014) Prediction of coronary artery disease severity using $CHADS_2$ and CHA_2DS_2-VASc scores and a newly defined CHA_2DS_2-VASc-HS score. American Journal of Cardiology 113: 950-956.**
Study type	Cross-sectional
Aim	To investigate whether three risk scores, $CHADS_2$, CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS, can be used to predict CAD severity.
Patient characteristics	Consecutive patients admitted for diagnostic coronary angiography (CA). **Inclusion:** - Referred from outpatients for CA for symptoms suggestive of CAD and/or abnormal exercise

Bibliographic reference	**Cetin et al. (2014) Prediction of coronary artery disease severity using $CHADS_2$ and CHA_2DS_2-VASc scores and a newly defined CHA_2DS_2-VASc-HS score. American Journal of Cardiology 113: 950-956.**

electrocardiographic testing or myocardial perfusion imaging test.

Exclusion:

- Acute coronary syndrome
- Acute heart failure
- Acute ischaemic stroke or transient ischaemic attack (TIA)
- Previous coronary artery bypass surgery
- Previous percutaneous coronary intervention

Patient Characteristics:

	n=407
Demographics	
Age in years – mean (sd)	61.0 (10.0)
Male – n (%)	294 (72.2)
Cardiovascular risk factors – n (%)	
Family history of CAD	90 (22.1)
Diabetes mellitus	119 (29.2)
Hypertension	247 (60.7)
Hyperlipidaemia	149 (36.6)
Smoker	119 (29.2)

Number of patients

N=407

Probability score / model

Note:
$CHADS_2$ was developed as a clinical predictor of the risk of stroke in patients with nonvalvular atrial fibrillation. Authors propose it can be used for predicting CAD severity as it includes similar risk factors.

1. $CHADS_2$

Calculated by assigning 1 point each for the presence of chronic heart failure, hypertension, age ≥75 years, and presence of diabetes mellitus, and assigning 2 points for history of stroke or TIA. Maximum total score = 6 points

2. CHA_2DS_2-VASc

Bibliographic reference	**Cetin et al. (2014) Prediction of coronary artery disease severity using $CHADS_2$ and CHA_2DS_2-VASc scores and a newly defined CHA_2DS_2-VASc-HS score. American Journal of Cardiology 113: 950-956.**
	A modification of the $CHADS_2$ score (provides better risk stratification of low-risk patients). Extends the latter by including additional common stroke risk factors including vascular disease (V), age 65 to 74 years (A), and female gender (as a sex category [Sc]). Maximum total score = 9 points **3. CHA_2DS_2-VASc-HS score** The CHA_2DS_2-VASc-HS score comprises hyperlipidaemia and smoking in addition to the components of the CHA_2DS_2-VASc score and male gender instead of female gender (see below). Maximum total score = 11 points C – Congestive heart failure – 1 point H – Hypertension – 1 point A_2 – Age >75 yrs – 2 points D – Diabetes mellitus – 1 point S_2 – Previous stroke or TIA – 2 points V – Vascular disease – 1 point A – Age 65-74 yrs – 1 point S_c – Sex category (male gender) – 1 point H – Hyperlipidaemia – 1 point S – Smoker – 1 point All scores calculated by two experienced cardiologists following CA, without knowledge of patients' CAD status.
Reference standard (or Gold standard)	Coronary Angiography (CA) Using Judkins technique. Angiograms were evaluated by 2 experienced cardiologists who assessed Gensini score, independent of risk factor scoring. CAD presence Significant CAD = ≥50% stenosis in at least 1 major epicardial artery Multi-vessel disease = ≥50% stenosis in at least 2 major epicardial coronary arteries.

<table>
<tr><td>Bibliographic reference</td><td>Cetin et al. (2014) Prediction of coronary artery disease severity using $CHADS_2$ and CHA_2DS_2-VASc scores and a newly defined CHA_2DS_2-VASc-HS score. American Journal of Cardiology 113: 950-956.</td></tr>
<tr><td></td><td>CAD severity
Determined by the number of significantly diseased coronary arteries. Gensini score was calculated for each patient from the coronary angiogram by assigning a severity score to each coronary stenosis as 1 for 1% to 25% narrowing, 2 for 26% to 50%, 4 for 51% to 75%, 8 for 76% to 90%, 16 for 91% to 99%, and 32 for a completely occluded artery. The score is then multiplied by a factor according to the importance of the coronary artery.</td></tr>
<tr><td>Time between testing & treatment</td><td>Not stated.</td></tr>
<tr><td>Length of follow-up</td><td>Study period not specified.</td></tr>
<tr><td>Location</td><td>Turkey (single centre)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Area under the ROC curve

Reference (i): Significant CAD = ≥50% stenosis in at least 1 vessel
<table>
<tr><th></th><th>AUC (95% CIs)</th></tr>
<tr><td>$CHADS_2$</td><td>0.69 (0.64 to 0.73)</td></tr>
<tr><td>CHA_2DS_2-VASc</td><td>0.65 (0.60 to 0.70)</td></tr>
<tr><td>CHA_2DS_2-VASc-HS score</td><td>0.76 (0.72 to 0.80)</td></tr>
</table>
Reference (ii): Multi-vessel disease = ≥50% stenosis in at least 2 major epicardial coronary arteries
<table>
<tr><th></th><th>AUC (95% CIs)</th></tr>
<tr><td>$CHADS_2$</td><td>0.72 (0.68 to 0.76)</td></tr>
<tr><td>CHA_2DS_2-VASc</td><td>0.68 (0.63 to 0.72)</td></tr>
<tr><td>CHA_2DS_2-VASc-HS score</td><td>0.80 (0.76 to 0.84)</td></tr>
</table>
Sensitivity and specificity
Data reported only for CAD severity (as measured by Gensini score) not CAD presence.</td></tr>
<tr><td>Source of funding</td><td>Not stated.</td></tr>
</table>

Bibliographic reference	**Cetin et al. (2014) Prediction of coronary artery disease severity using $CHADS_2$ and CHA_2DS_2-VASc scores and a newly defined CHA_2DS_2-VASc-HS score. American Journal of Cardiology 113: 950-956.**
Comments	**Study limitations** The models reported were developed and validated to predict stroke in patients with non-valvular AF. They have not been validated to predict CAD in populations with stable chest pain except this study, so data were not extracted for evidence appraisal.

Bibliographic reference	**Chen Z.W, et al. (2014) Validation of a novel clinical prediction score for severe coronary artery diseases before elective coronary angiography. PLoS ONE, 9: e94493-**
Study type	Cross-sectional
Aim	To develop a novel risk scoring system to guide early invasive coronary angiography in angina patients using analysis of clinical risk factors, electrocardiography (ECG), and echocardiography and compare the performance of this system with that of the Diamond-Forrester score for prediction of CAD and severe CAD.
Patient characteristics	Consecutive patients admitted for diagnostic coronary angiography (CA). **Inclusion:** - Patients with exertional chest tightness / chest pain referred for elective coronary angiography - Age 30-70 years (subsample selected for comparison with Diamond and Forrester score) - Providing a complete clinical history - Normal pre-procedural troponin T (below the 10% coefficient of variation value, <0.03 ng/mL) - Normal creatine kinase, <23 U/L **Exclusion:** - Previously undergone CA or CTCA - Acute coronary syndrome - Evidence of elevated cardiac troponin T (≥0.03 ng/mL) or creatine kinase (≥23 U/L) before CA - Evidence of heart failure - Cardiomyopathy - Congenital heart disease / heart valve disease - Recent surgery or trauma - Presence of active chronic inflammation, renal failure, dysfunction of haematological and immunological

Bibliographic reference	Chen Z.W, et al. (2014) Validation of a novel clinical prediction score for severe coronary artery diseases before elective coronary angiography. PLoS ONE, 9: e94493-

systems, carcinoma, or a condition treated with immunosuppressive agents.

Patient Characteristics:

	n=551
Demographics	
Age in years – mean (sd)	63.8 (9.7)
Male – n (%)	379 (68.8)
Cardiovascular risk factors – n (%)	
Hypertension	309 (70.8)
Diabetes	170 (30.9)
Hyperlipidaemia	169 (30.7)
Aortic valve calcification (AVC on echocardiography)	189 (34.3)
Symptoms – n (%)	
Typical angina	190 (50.4)
Atypical angina	132 (35.0)
Non-specific chest pain	55 (14.6)

Diagnosis of CAD – n (%): 440 (79.8)

Number of patients	N=551 (first consecutively enrolled patients comprised development cohort (n=347); subsequent consecutively enrolled patients comprised validation cohort (n=204)
Probability score / model	**1. Severe Predicting Score (SPS)** Derived from multivariate analysis incorporating risk factors, clinical variables and results of ECG and echocardiography testing. Blood biochemistry was analysed prior to coronary angiography. ECG undertaken on admission – abnormal ECG defined as Q waves in multiple leads, ST-T-wave inversions, left/right bundle-branch blockage, or left ventricular hypertrophy. Echocardiography performed using Philips IE33 instrument (Philips, Netherlands) with 2–3.5 MHz transducer (X3-1), and left ventricular EF and aortic valve calcification (AVC) were detected. Observers who made the diagnosis of AVC were blind to results of coronary angiography.

<table>
<tr><th>Bibliographic reference</th><th>Chen Z.W, et al. (2014) Validation of a novel clinical prediction score for severe coronary artery diseases before elective coronary angiography. PLoS ONE, 9: e94493-</th></tr>
<tr><td></td><td>SPS calculated as follows:
<table>
<tr><th>Risk factor</th><th>Range</th><th>Single score</th></tr>
<tr><td>Aortic valve calcification (AVC) - identified from echocardiography</td><td>Yes</td><td>3</td></tr>
<tr><td>Abnormal ECG</td><td>Yes</td><td>3</td></tr>
<tr><td>Diabetes</td><td>Yes</td><td>2</td></tr>
<tr><td>Male</td><td>Yes</td><td>2</td></tr>
<tr><td>Hyperlipidaemia</td><td>Yes</td><td>2</td></tr>
<tr><td>LDL-C (mmol/L)</td><td><1.8
1.8 to 2.2
≥2.2</td><td>0
1
2</td></tr>
<tr><td>HDL-C (mmol/L)</td><td>≥1.2
1.0 to 1.2
<1.0</td><td>0
1
2</td></tr>
<tr><td>Age (years)</td><td><65
≥65</td><td>0
2</td></tr>
<tr><td>Severe Predicting Score (SPS) – total maximum score</td><td></td><td>18</td></tr>
</table>
SPS score – mean (sd): 7.43 (3.33)

2. Diamond and Forrester model (n=377 patients 30-69yrs)
Based on age, sex and type of chest pain
Diamond and Forrester score – mean (sd): 68.3 (27.3)</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography (CA)
Significant CAD defined as ≥ 50% stenosis in at least one of the coronary arteries.

Severity of CAD evaluated by Gensini score - grades narrowing of the lumen as follows: 1, 1%-25% occlusion; 2, 26%-50% occlusion; 4, 51%-75% occlusion; 8,76%-90% occlusion; 16, 91%-99% occlusion; and 32, total occlusion. This score is multiplied by a factor accounting for the importance of the lesion position in the coronary</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Chen Z.W, et al. (2014) Validation of a novel clinical prediction score for severe coronary artery diseases before elective coronary angiography. PLoS ONE, 9: e94493-</td></tr>
<tr><td></td><td>arterial tree. Severe CAD defined as a Gensini score ≥20 (approximately equal to one stenosed lesion of 70% or more in the proximal left anterior descending artery).</td></tr>
<tr><td>Time between testing & treatment</td><td>Not clear</td></tr>
<tr><td>Length of follow-up</td><td>Study period: October 2011 to September 2012</td></tr>
<tr><td>Location</td><td>China (one centre)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Area under the ROC curve

Reference (i): Significant CAD = ≥50% stenosis in at least 1 vessel
<table>
<tr><th></th><th>AUC1</th></tr>
<tr><td>SPS score (validation cohort, n=204)</td><td>0.710</td></tr>
<tr><td>Diamond and Forrester score (n=377 patients aged 30-69yrs)</td><td>0.727</td></tr>
</table>
Reference (ii): Severe CAD = Gensini score ≥20 (approximately equal to ≥70% stenosis in the proximal left anterior descending artery).
<table>
<tr><th></th><th>AUC1</th></tr>
<tr><td>Diamond and Forrester score (n=377 patients aged 30-69yrs)</td><td>0.639</td></tr>
</table>
Sensitivity and specificity
Data reported only development cohort only.</td></tr>
<tr><td>Source of funding</td><td>Supported by the National Natural Science Foundation of China (Grant Nos: 81200146, 30901383 and 30671998), Zhongshan Hospital Youth Science Funding (Grant No: 2012ZSQN12), New Teacher Foundation of Ministry of Education (Grant No: 20120071120061), and Scientific Research for Young Teacher of Fudan University (Grant No: 20520133477).</td></tr>
</table>

Bibliographic reference	**Chen Z.W, et al. (2014) Validation of a novel clinical prediction score for severe coronary artery diseases before elective coronary angiography. PLoS ONE, 9: e94493-**
Comments	**Study limitations:** QUADAS-2 1A - LOW 1B – Patients were all referred for CA - HIGH 2A - LOW 2B - D-F model**:** LOW 2B – SPS model**:** Requires information from ECG and echocardiography that is unlikely to be available at a typical index clinic visit: HIGH 3A - Not clear if results were interpreted without knowledge of probability scores / patient clinical data: UNCLEAR 3B – LOW 4 - LOW

[1] *95% CIs for AUC (or p-value for comparison) not reported*

Bibliographic reference	**Dharampal A, et al. (2013) Restriction of the referral of patients with stable angina for CT coronary angiography by clinical evaluation and calcium score: impact on clinical decision-making. European Radiology 23: 2676-2686.**
Study type	Retrospective cross-sectional
Aim	To evaluate the additional value of the calcium score (CaSc) to clinical evaluation in symptomatically stable patients with suspected CAD in order to restrict referral for CT coronary angiography (CTCA) by reducing the number of patients with an intermediate probability of CAD.
Patient characteristics	Patients who had undergone diagnostic evaluation with unenhanced computed tomography (CT) and coronary angiography (CA), or CTCA in the absence of CA, between 2004-2011. **Inclusion:** - Symptomatically stable patients with suspected CAD - Referred by cardiologist for CTCA because of chest pain symptoms, or referred for CA and asked to participate in a CTCA study **Exclusion:** - Pregnancy - Iodine allergy

<table>
<tr><td>Bibliographic reference</td><td>Dharampal A, et al. (2013) Restriction of the referral of patients with stable angina for CT coronary angiography by clinical evaluation and calcium score: impact on clinical decision-making. European Radiology 23: 2676-2686.</td></tr>
<tr><td></td><td>- Impaired kidney function (serum creatinine >120 µmol/l)
- History of percutaneous coronary intervention, coronary artery bypass surgery, MI or non-diagnostic CTCA in the absence of CA

Patient Characteristics:
<table>
<tr><th></th><th>n=1,975</th></tr>
<tr><td>Demographics</td><td></td></tr>
<tr><td>Age in years – mean (sd)</td><td>59.0 (11.0)</td></tr>
<tr><td>Male – n (%)</td><td>1,155 (58.5)</td></tr>
<tr><td>Cardiovascular risk factors – n (%)</td><td></td></tr>
<tr><td>Family history of CVD (first- or second-degree relatives with premature CAD in men aged <55 years and in women aged <60 years old)</td><td>918 (46.5)</td></tr>
<tr><td>Diabetes mellitus (treatment with oral medication or insulin)</td><td>316 (16.0)</td></tr>
<tr><td>Hypertension (BP 140/90 mmHg or treatment for hypertension)</td><td>979 (49.6)</td></tr>
<tr><td>Hypercholesterolaemia (total cholesterol > 180 mg/dl or treatment for high cholesterol)</td><td>1081 (54.7)</td></tr>
<tr><td>Current smoker</td><td>525 (26.6)</td></tr>
<tr><td>BMI (kg/m^2) – mean (sd)</td><td>27 (4.5)</td></tr>
<tr><td>Chest pain typicality – n (%)</td><td></td></tr>
<tr><td>Typical angina</td><td>705 (35.7)</td></tr>
<tr><td>Atypical angina</td><td>810 (26.6)</td></tr>
<tr><td>Non-anginal chest pain</td><td>455 (23.0)</td></tr>
<tr><td>Clinical variables</td><td></td></tr>
<tr><td>ECG
- Pathalogical Q-waves – n (%)
- ST-T-wave changes – n (%)
- Calcium score – median [IQR]</td><td>
136 (6.9)
571 (28.9)
71 [0 - 383]</td></tr>
</table></td></tr>
<tr><td>Number of patients</td><td>N=1,975 patients</td></tr>
</table>

Bibliographic reference	**Dharampal A, et al. (2013) Restriction of the referral of patients with stable angina for CT coronary angiography by clinical evaluation and calcium score: impact on clinical decision-making. European Radiology 23: 2676-2686.**
Probability score / model	**1. Clinical evaluation (model 1)** Based on male gender, age, chest pain typicality, cardiac risk factors and ECG. **2. Clinical evaluation plus CT coronary calcium score (model 2)** Clinical evaluation score as above, combined with total calcium score calculated using the Agatston method by dedicated software (Syngo Calcium Scoring, Siemens) applied to CT imaging (64-slice single-source, 64-slice dual source, or 128-slice dual source CT system).
Reference standard (or Gold standard)	Coronary angiography (CA) *or* computed tomography coronary angiography (CTCA) CA Images were assessed by each coronary segment for presence of luminal stenosis in two orthogonal planes. Evaluated by one experienced cardiologist blinded to CT results. Where segments scored >20% stenosis on visual assessment these were quantified using a validated algorithm (CAASII, Maastricht, The Netherlands) by an experienced cardiologist. CTCA Underwent ECG-gated CTCA. Coronary segments analysed using modified 17-segment AHA classification. All CTs were interpreted by two radiologists with >3 years experience in cardiac imaging who were blinded to all other tests. Inter-observer disagreement resolved by consensus. Obstructive CAD = at least one lesion ≥50% diameter lumen reduction
Time between testing & treatment	Not clear
Length of follow-up	Retrospectively assessed records of patients who underwent clinical investigation between 2004 and 2011.
Location	The Netherlands (single centre)
Diagnostic accuracy measures (2 x 2 table)	**Area under the ROC curve** Reference: Obstructive CAD = at least one lesion ≥50% diameter lumen reduction **AUC (95%CIs)**

Bibliographic reference	**Dharampal A, et al. (2013) Restriction of the referral of patients with stable angina for CT coronary angiography by clinical evaluation and calcium score: impact on clinical decision-making. European Radiology 23: 2676-2686.**
	Clinical evaluation model 1 0.80 (0.78 to 0.82) **Clinical evaluation plus CT coronary calcium score model 2** 0.89 (0.87 to 0.90) **Sensitivity and specificity** Not reported.
Source of funding	Not reported
Comments	**Study limitations** The models reported were not validated in an independent cohort from that used to develop the models, so data were not extracted for evidence appraisal.

[1] *<Insert Note here>*

Bibliographic reference	**Gaibazzi, N. et al (2015) Differential incremental value of ultrasound carotid intima-media thickness, carotid plaque, and cardiac calcium to predict angiographic coronary artery. European Heart Journal – Cardiovascular Imaging Sep 10. pii: jev222. [E-pub ahead of print]**
Study type	Prospective cross-sectional
Aim	To assess the discrimination values of the Framingham Risk Score (FRS) and Diagnostic Imaging for Coronary Artery Disease (DICAD) score for presence of CAD, then test whether carotid intima-media thickness (cIMT), carotid plaques (cPL) and echocardiographic cardiac calcium score (eCS) have incremental discriminatory and reclassification predictive value for CAD in subjects undergoing coronary angiography, specifically depending on their low, intermediate, or high class of clinical risk.
Patient characteristics	Patients undergoing coronary angiography (CA) for suspected CAD between June 2012 and July 2013. **Inclusion:** - Any type of chest pain of recent onset in patients with risk factors and/or a positive (or inconclusive in a high-risk subject) stress test for ischaemia.

Bibliographic reference	Gaibazzi, N. et al (2015) Differential incremental value of ultrasound carotid intima-media thickness, carotid plaque, and cardiac calcium to predict angiographic coronary artery. European Heart Journal – Cardiovascular Imaging Sep 10. pii: jev222. [E-pub ahead of print]

Exclusion:

- Known CAD
- Previous acute coronary syndrome or coronary revascularisation
- Known cardiomyopathy or reduced (50%) left ventricular ejection fraction (LVEF)
- More than mild valvular disease
- Atrial fibrillation or other sustained arrhythmias
- Pregnancy/lactation
- Technically poor acoustic window.

Patient Characteristics:

	n=445
Demographics	
Age in years – mean (sd)	64.6 (11.0)
Male – n (%)	280 (62.9)
Cardiovascular risk factors – n (%)	
Family history of CVD	238 (53.4)
Diabetes mellitus	123 (27.6)
Hypertension	325 (73.0)
Current smoker	252 (56.6)
BMI (kg/m^2) – mean (sd)	26.3 (4.0)
LDL-cholesterol (mg/dL) – mean (sd)	114.3 (39.3)
HDL-cholesterol (mg/dL) – mean (sd)	43.4 (11.1)
Symptoms No breakdown reported	
Ultrasound assessments Carotid intima-media thickness (cIMT) (um) – mean (sd) Carotid plaques (cPL) (at least 1>1.5mm) – n (%) Echocardiographic calcium score (eCS) – median [IQR]	 744.8 (161.2) 253 (56.9) 2 [1-3]

Bibliographic reference	**Gaibazzi, N. et al (2015) Differential incremental value of ultrasound carotid intima-media thickness, carotid plaque, and cardiac calcium to predict angiographic coronary artery. European Heart Journal – Cardiovascular Imaging Sep 10. pii: jev222. [E-pub ahead of print]**
Number of patients	N=445
Probability score / model	**1. Framingham Risk Score (FRS)** Derived according to Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Pane lIII) – includes: age, gender, total cholesterol, HDL cholesterol, systolic blood pressure (and also whether the patient is treated or not for hypertension), smoking status. FRS <10 – n (%): 140 (31.5) FRS 10-20 – n (%): 148 (33.3) FRS >20 – n (%): 157 (35.3) **2. Diagnostic Imaging for Coronary Artery Disease (DICAD) score** DICAD score calculated according to the extended clinical prediction model by Genders et al (2012) Includes: age, gender, typicality of chest pain, diabetes, hypertension, dyslipidaemia, smoking, and CT-based coronary calcium score. DICAD <10.35 – n (%): 147 (33.0) DICAD 10.35-23.8 – n (%): 147 (33.0) DICAD >23.8 – N (%): 151 (33.9) Other non-validated models <u>FRS + transthoracic echocardiographic parameters</u> **3. FRS + Echocardiographic calcium score (eCS)** Standard transthoracic echocardiography was used for quantification of cardiac morphology and function in each patient. A final eCS was derived by consensus of two readers in each study site as the sum of all identified cardiac calcific deposits and was in the range from 0 (no calcium visible) to 8 (extensive cardiac and ascending aorta calcified deposits). <u>FRS + carotid ultrasound parameters</u> **4. FRS + Carotid intima-media thickness (cIMT)** Vascular examination was performed after the echocardiographic exam, switching to the 7.5-MHz linear probe and vascular pre-set. Carotid intima–media thickness (cIMT) was measured in both common carotid arteries. cIMT data were measured

<table>
<tr><td>Bibliographic reference</td><td>Gaibazzi, N. et al (2015) Differential incremental value of ultrasound carotid intima-media thickness, carotid plaque, and cardiac calcium to predict angiographic coronary artery. European Heart Journal – Cardiovascular Imaging Sep 10. pii: jev222. [E-pub ahead of print]</td></tr>
<tr><td></td><td>automatically at the far wall of the common carotid artery by radio frequency echo tracking software (QIMT, Esaote). Inter- and intra-operator reliability were assessed.

5. FRS + Carotid plaques (cPL)
To define the presence of cPL (both the common and in the internal carotid arteries were bilaterally scanned),at least two of the following criteria were required: a cIMTof >1.5 mm, change in the carotid wall surface contour, or focal change in the carotid wall echogenicity.</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography (CA)

Performed by the standard Judkins technique within 1 week of study enrolment (after ultrasound study was acquired).

Obstructive CAD was primarily defined as stenosis > 50% in any major epicardial coronary artery, although the alternative cut-off of >70% stenosis was also tested.
Angiograms were graded by visual of the physician performing the diagnostic procedure in each centre(on-site reading),who was blinded to all non-invasive data specific to the study.</td></tr>
<tr><td>Time between testing & treatment</td><td>Not specified.</td></tr>
<tr><td>Length of follow-up</td><td>Study period: June 2012 to July 2013.</td></tr>
<tr><td>Location</td><td>Italy (8 centres)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Area under the ROC curve
<u>Comparison: FRS vs DICAD</u>

Reference (i) CAD = >50% stenosis
<table>
<tr><th></th><th>AUC (95% CIs)</th></tr>
<tr><td>FRS</td><td>0.669 (0.618 to 0.720)</td></tr>
<tr><td>DICAD</td><td>0.673 (0.621 to 0.725)</td></tr>
</table>
Reference (ii) CAD = >70% stenosis</td></tr>
</table>

Bibliographic reference	Gaibazzi, N. et al (2015) Differential incremental value of ultrasound carotid intima-media thickness, carotid plaque, and cardiac calcium to predict angiographic coronary artery. European Heart Journal – Cardiovascular Imaging Sep 10. pii: jev222. [E-pub ahead of print]

	AUC (95% CIs)
FRS	0.653 (0.598 to 0.707)
DICAD	0.669 (0.615 to 0.723)

Sensitivity and specificity
No data reported.

Comparison: FRS vs FRS+cIMT

Reference: CAD = >50% stenosis

	AUC (95% CIs)
FRS	0.669 (0.618 to 0.720)
FRS+cIMT	0.680 (not reported)
p-value for comparison	p=0.33

Sensitivity and specificity
No data reported.

Comparison: FRS vs FRS+cPL

Reference: CAD = >50% stenosis

	AUC (95% CIs)
FRS	0.669 (0.618 to 0.720)
FRS+cPL	0.730 (0.681 to 0.780)
p-value for comparison	p=0.001

Sensitivity and specificity
No data reported.

Comparison: FRS vs FRS+eCS

Bibliographic reference	Gaibazzi, N. et al (2015) Differential incremental value of ultrasound carotid intima-media thickness, carotid plaque, and cardiac calcium to predict angiographic coronary artery. European Heart Journal – Cardiovascular Imaging Sep 10. pii: jev222. [E-pub ahead of print]

Reference: CAD = >50% stenosis

	AUC (95% CIs)
FRS	0.669 (0.618 to 0.720)
FRS+eCS	0.728 (0.681 to 0.776)
p-value for comparison	p=0.0005

Sensitivity and specificity
No data reported.

Comparison: FRS+cPL vs FRS+cPL+eCS

Reference: CAD = >50% stenosis

	AUC (95% CIs)
FRS+cPL	0.730 (0.681 to 0.780)
FRS+cPL+eCS	0.763 (0.717 to 0.809)
p-value for comparison	p=0.007

Comparison: FRS+eCS vs FRS+cPL+eCS

Reference: CAD = >50% stenosis

	AUC (95% CIs)
FRS+eCS	0.728 (0.681 to 0.776)
FRS+cPL+eCS	0.763 (0.717 to 0.809)
p-value for comparison	p=0.009

Sensitivity and specificity
No data reported.

Notes:

Bibliographic reference	**Gaibazzi, N. et al (2015) Differential incremental value of ultrasound carotid intima-media thickness, carotid plaque, and cardiac calcium to predict angiographic coronary artery. European Heart Journal – Cardiovascular Imaging Sep 10. pii: jev222. [E-pub ahead of print]**
	1. FRS was selected over DICAD for assessment of incremental discriminatory benefit of adding single ultrasound parameters due to non-significant difference in the discrimination yield of the two clinical scores and more widespread use of the FRS. 2. 50% stenosis level chosen as primary definition for CAD in comparisons between FRS and models including additional ultrasound parameters due to similar results between >50% and >70% thresholds when comparing FRS and DICAD.
Source of funding	Study not financially supported, but Esaote Spa (Florence-Italy) freely supported their ultrasound systems to participating centres for study duration.
Comments	**Study limitations** Models combining FRS with added echocardiographic and ultrasound parameters were not validated in a separate patient sample, so these data were not extracted for evidence appraisal. QUADAS-2: 1A – Unclear if patients were consecutively enrolled: UNCLEAR 1B – All patients were referred for CA; some had abnormal prior stress test: HIGH 2A - LOW 2B – FRS: LOW 2B – DICAD requires information from CT calcium score which is not applicable to pre-test probability assessment at an index clinic visit: HIGH 3A - LOW 3B – LOW 4 - LOW

[1] *<Insert Note here>*

Bibliographic reference	**Genders, T. et al. (2010) Incremental value of the CT coronary calcium score for the prediction of coronary artery disease. European Radiology, 20: 2331-2340.**
Study type	Cross-sectional
Aim	To validate 5 previously published clinical prediction models and determine the incremental value of CT calcium

Bibliographic reference	**Genders, T. et al. (2010) Incremental value of the CT coronary calcium score for the prediction of coronary artery disease. European Radiology, 20: 2331-2340.**
	score for the prediction of prevalent obstructive CAD in patients with new onset stable typical or atypical angina.
Patient characteristics	Study population was derived from a larger study evaluating CTCA. All patients were referred for conventional coronary angiography (CA) based on their presentation or functional testing, and underwent CTCA within a week before CA. **Inclusion:** - Patients with chest pain suggestive of stable angina and suspected of having CAD - Sinus heart rhythm and ability to hold breath for 15 seconds **Exclusion:** - Acute coronary syndrome or history of myocardial infarction - History of percutaneous coronary intervention or coronary bypass surgery - Impaired renal function (serum creatinine >120 µmol/L) - Known iodine intolerance **Patient Characteristics:**

	n=254
Demographics	
Age in years – mean (sd)	59 (11)
Male – n (%)	171 (67)
Cardiovascular risk factors – n (%)	
Family history	126 (50)
Diabetes (plasma glucose ≥126 mg/dL or 7.0 mmol)	32 (13)
Hypertension	140 (55)
Past or current smoker	63 (25)
BMI (kg/m^2) – mean (sd)	27 (4)
Dyslipidaemia (serum cholesterol >200 mg/dL or 5.18 mmol/L	136 (54)
Symptoms – n (%) Typical chest pain	 118 (46)
Clinical assessments Calcium score (measured according to Agatston) – mean (sd)	 346 (572)

Bibliographic reference	**Genders, T. et al. (2010) Incremental value of the CT coronary calcium score for the prediction of coronary artery disease. European Radiology, 20: 2331-2340.**
	Median calcium score: 138 CAD on coronary angiography – n (%): 123 (48)
Number of patients	N=254
Probability score / model	CT calcium scoring Metoprolol (100 mg, Selokeen, AstraZeneca, London, UK) was administered orally 1 h before CT in patients with heart rates >65 beats per minute. A 64-slice single source CT system (Sensation 64; Siemens, Germany) was used to acquire standard spiral low-dose and ECG gated coronary calcium CT images. One observer (with more than 3 years' experience), blinded to the CA and clinical data, measured the coronary calcium by the Agatston method using dedicated software (syngo Calcium Scoring VE31H, Siemens, Germany). Five prediction models were identified from the literature and validated using the dataset: **1. Diamond and Forrester 1979 (+CTCS)** Includes age, sex and type of chest pain. **2. Pryor et al. 1993 [aka Duke Clinical Score] (+CTCS)** Includes age, sex, type of chest pain, smoking, dyslipidaemia, diabetes and the interaction between age and smoking, age and dyslipidaemia, sex and smoking, and age and sex. **3. Morise et al. 1994 (+CTCS)** Includes age, sex and type of chest pain, dyslipidaemia and diabetes. **4. Morise et al. 1997 (+CTCS)** Includes age, sex, type of chest pain, smoking, dyslipidaemia, diabetes, oestrogen status, hypertension, family history, obesity, BMI and the interaction between dyslipidaemia and family history. 5. Shaw et al. 1998 (+CTCS) – data not extracted. The original paper shows this is a combined model incorporating age, sex, typical chest pain, smoking, dyslipidaemia and diabetes with data from exercise stress testing (which is outside the remit of this review) so data were not extracted. .

<table>
<tr><td>Bibliographic reference</td><td>Genders, T. et al. (2010) Incremental value of the CT coronary calcium score for the prediction of coronary artery disease. European Radiology, 20: 2331-2340.</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography (CA)
Coronary segments were assessed on CA following a 17-segment modified American Heart Association (AHA) classification model by a single observer (with more than 10 years' experience), who was blinded to the CT and clinical data.
Significant CAD defined as mean luminal narrowing ≥50%.
Validated quantitative coronary angiography software (CAAS II, Pie Medical, Maastricht, the Netherlands) was used.</td></tr>
<tr><td>Time between testing & treatment</td><td>Not clear</td></tr>
<tr><td>Length of follow-up</td><td>Main study enrolled patients over 24-month period.</td></tr>
<tr><td>Location</td><td>The Netherlands (single centre)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Area under the ROC curve

Reference: Significant CAD = ≥50% stenosis in at least 1 vessel (present/absent) on CA
<table>
<tr><th></th><th>AUC (95% CIs)</th><th>p-value for comparison</th></tr>
<tr><td>Diamond and Forrester
Diamond and Forrester + CTCS</td><td>0.798 (0.742 to 0.854)
0.890 (0.851 to 0.930)</td><td>
p<0.001</td></tr>
<tr><td>Pryor et al. 1993
Pryor et al. 1993 + CTCS</td><td>0.838 (0.789 to 0.887)
0.901 (0.863 to 0.938)</td><td>
p<0.001</td></tr>
<tr><td>Morise et al. 1994
Morise et al. 1994 + CTCS</td><td>0.831 (0.780 to 0.881)
0.899 (0.861 to 0.937)</td><td>
p<0.01</td></tr>
<tr><td>Morise et al. 1997
Morise et al. 1997 + CTCS</td><td>0.840 (0.792 to 0.889)
0.898 (0.859 to 0.936)</td><td>
p<0.001</td></tr>
</table>
Sensitivity and specificity
Data not reported.</td></tr>
<tr><td>Source of funding</td><td>Funded by the Health Care Efficiency Research grant (number 945–04–263) from the Netherlands Organisation for Health Research and Development, and by internal funding through a Health Care Efficiency grant from the Erasmus University Medical Center, Rotterdam.</td></tr>
</table>

Bibliographic reference	**Genders, T. et al. (2010) Incremental value of the CT coronary calcium score for the prediction of coronary artery disease. European Radiology, 20: 2331-2340.**
Comments	**Study limitations:** Prediction models that included CTCS were not validated in a separate patient sample, so these data were not extracted for evidence appraisal. QUADAS-2: 1A – Not clear if patients were consecutively enrolled: UNCLEAR 1B – All patients were referred for CA; some had prior abnormal functional test: HIGH 2A - D-F, Duke Clinical Score, Morise 1994, Morise 1997: all LOW 2B – D-F, Duke Clinical Score, Morise 1994, Morise 1997: all LOW 3A - LOW 3B – LOW 4 - LOW

[1] *<Insert Note here>*

Bibliographic reference	**Genders,T. et al. [The CAD consortium] (2011) A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. European Heart Journal 32: 1316-1330.**
Study type	Prospective cross-sectional
Aim	To study the validity of the Diamond and Forrester model for estimating the probability of CAD, to update the model using recently collected data, and extend the model for patients beyond 70 years, using data from contemporary cohorts.
Patient characteristics	**Inclusion:** - Patients with chest pain suggestive of stable angina - Underwent coronary angiography **Exclusion:** - acute coronary syndrome or unstable chest pain - history of myocardial infarction or previous revascularisation (percutaneous coronary intervention or coronary artery bypass graft surgery) **Patient Characteristics:**

	n=2,272[1]

Bibliographic reference	**Genders,T. et al. [The CAD consortium] (2011) A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. European Heart Journal 32: 1316-1330.**
	<table><tr><td>**Demographics**</td><td></td></tr><tr><td>Age in years – mean (sd)</td><td>62.3 (10.4)</td></tr><tr><td>Male – n (%)</td><td>1,527 (67.2)</td></tr><tr><td>**Symptoms – n (%)** Typical chest pain Atypical chest pain Non-specific chest pain</td><td> 1,204 (53.0) 607 (26.7) 461 (20.3)</td></tr><tr><td>**Clinical assessments** CAD on coronary angiography</td><td> 1,325 (58.3)</td></tr></table> Note: Typical chest pain defined as having (i) substernal chest pain or discomfort, that is (ii) provoked by exertion or emotional stress and (iii) relieved by rest and/or nitroglycerine. Atypical chest pain defined as having two of the before-mentioned criteria. If one or none of the criteria was present, the patient was classified as having non-specific chest pain.
Number of patients	N=2,260
Probability score / model	**1. Diamond-Forrester model** Includes: age, sex and type of chest pain Originally developed to be applicable only in patients aged 30-69 years, so validation was restricted to a subsample of patients aged 30-69 (n=1683; 68.9% male, 55.7% with obstructive CAD on CA). **2. Updated and extended Diamond-Forrester model** Updated D-F model, including patients below 30 and above 69 years of age. Updated model was extended to include a random effect intercept allowing for likely variation in CAD prevalence at the different hospitals, and a random effect around the coefficient for type of chest pain to allow for differences in clinical diagnosis across hospitals. Validation of the updated model was done in an independent registry dataset of unselected outpatients (n=454) who all subsequently underwent CTCA (all) or CA (subset).
Reference standard (or Gold standard)	Coronary angiography (CA) Performed at each hospital according to local protocols; interpretation of CA was allowed by both visual and

<table>
<tr><td>Bibliographic reference</td><td>Genders,T. et al. [The CAD consortium] (2011) A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. European Heart Journal 32: 1316-1330.</td></tr>
<tr><td></td><td>quantitative assessment.
Statistical analyses adjusted for hospital.

Obstructive CAD = ≥50% stenosis in one or more vessels</td></tr>
<tr><td>Time between testing & treatment</td><td>Not clear.</td></tr>
<tr><td>Length of follow-up</td><td>Duration of study not reported.</td></tr>
<tr><td>Location</td><td>10 countries (14 hospitals) across Europe and North America</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Area under the ROC curve

Reference: Obstructive CAD = ≥50% stenosis in one or more vessels
<table>
<tr><th></th><th>AUC (95% CIs)</th></tr>
<tr><td>Diamond-Forrester (validation sample n=1,683[2])
- adjusting for hospital</td><td>0.78 (0.76 to 0.81)
0.81 (0.79 to 0.83)</td></tr>
<tr><td>Updated Diamond-Forrester (n=2,660 development cohort – data not extracted)
- extended to allow for heterogeneity in CAD prevalence and classification of chest pain across hospitals</td><td>0.79 (0.77 to 0.81)

0.82 (0.80 to 0.84)</td></tr>
<tr><td>Updated D-F (n=454, external validation sample)</td><td>0.76 (0.71 to 0.81)</td></tr>
</table>
Sensitivity and specificity
Data not reported for 2x2 table</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>QUADAS-2:
1A – Not clear if consecutive patients were assessed: UNCLEAR
1B – D-F: Patients were all referred for CA: HIGH
1B – Updated D-F (validation cohort): LOW
2A - LOW
2B – D-F: LOW; Updated D-F: LOW
3A – D-F: Not clear if results were interpreted without knowledge of probability scores: UNCLEAR</td></tr>
</table>

Bibliographic reference	Genders,T. et al. [The CAD consortium] (2011) A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. European Heart Journal 32: 1316-1330.
	3A - Updated D-F (validation cohort): Not clear if results were interpreted without knowledge of probability scores / patient clinical data: UNCLEAR 3B – LOW 4 - LOW

[1] *Sample (n=2,272) includes 12 patients excluded from analyses due to missing data. This sample was used to validate the original D-F model (restricted to those aged 30-69yrs) and develop updated D-F model. Validation of the updated model was done in an independent registry dataset of unselected outpatients (n=454 who subsequently underwent CTCA or CA)*

Bibliographic reference	Genders,T. et al. [The CAD Consortium] (2012) Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ 344: e3485-
Study type	Cross-sectional
Aim	To develop prediction models that better estimate the pre-test probability of CAD in low prevalence populations and to determine the incremental diagnostic value of exercise electrocardiography and the coronary calcium score.
Patient characteristics	**Inclusion:** - Patients presenting with stable chest pain - Referred for catheter based or CT based coronary angiography **Exclusion:** - Acute coronary syndrome or unstable chest pain - History of myocardial infarction or previous revascularisation (percutaneous coronary intervention or coronary artery bypass graft surgery) **Patient Characteristics:**

	n=4,426[1]
Demographics	
Age in years – mean (sd)	57.2 (12)
Male – n (%)	2406 (54)
Cardiovascular risk factors – n (%)	
Family history of CAD (in 1st degree male relative <55yrs or female <65yrs)	1720 (44)

Bibliographic reference	Genders,T. et al. [The CAD Consortium] (2012) Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ 344: e3485-	
	Previous cerebrovascular disease (carotid artery disease, stroke or TIA)	78 (3)
	Previous renal artery disease	43 (1)
	Previous peripheral artery disease	79 (2)
	Diabetes (plasma glucose ≥7.0 mmol or treatment with diet / medication)	622 (15)
	Hypertension (BP ≥140/90 mmHg or use of hypertensive treatment)	2475 (58)
	Past or current smoker	1231 (29)
	BMI (kg/m2) – mean (median)	28 (27)
	Dyslipidaemia (serum cholesterol >200 mg/dL or 5.18 mmol/L	2194 (52)
	Symptoms – n (%) - Typical chest pain - Atypical chest pain - Non-specific chest pain	 759 (17) 2699 (61) 966 (22)
	Clinical assessments Exercise ECG (n=1612) – n (%) - Normal - Abnormal - Non-diagnostic Coronary calcium (Agatston) scores (n=4009) – n (%) 0 0 to <10 10 to <100 100 to <400 ≥400 CTCA results (n=4287) – n (%) No obstructive CAD Moderate CAD (50-70% stenosis) Severe CAD (≥70% stenosis, or ≥50% left main stenosis)	 671 (42) 443 (27) 498 (31) 1777 (44) 402 (10) 749 (19) 606 (15) 475 (12) 3232 (75) 505 (12) 550 (13)

Bibliographic reference	**Genders,T. et al. [The CAD Consortium] (2012) Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ 344: e3485-**
	Coronary angiography results (n=848) – n (%) 406 (48) No obstructive CAD 177 (21) Moderate CAD (50-70% stenosis) 265 (31) Severe CAD (≥70% stenosis, or ≥50% left main stenosis)
Number of patients	N=4,426 (subsample of patients in low prevalence setting (=10 hospitals) used for validating prediction models)
Probability score / model	**1. Duke clinical score** Based on age, sex, smoking, diabetes, history of MI, symptoms of angina pectoris, hypercholesterolemia, and ECG changes to calculate pre-test probability of at least one coronary artery stenosis ≥75% lumen diameter reduction at CA. <u>New prediction models:</u> All clinical variables are known to be associated with coronary artery disease so were entered simultaneously in a multivariable, random effects, logistic regression model that included hospital as a random effect to account for clustering of patients within hospitals. Non-significant predictors with small effects (that is, odds ratio <1.01) were omitted. **2. Basic model (updated Diamond and Forrester, Genders et al. 2011)** Includes: age, sex, symptoms, and setting **3. Clinical model** As above, with additional risk factor variables: diabetes, hypertension, dyslipidaemia, smoking, and body mass index **3. Extended model (DICAD)** Includes all variables in the clinical model with the addition of coronary calcium score. Note that exercise ECG was included in the multivariate analysis to derive the model but as it was not a significant independent predictor it was excluded from the final model. <u>Note:</u>

<table>
<tr><th>Bibliographic reference</th><th>Genders,T. et al. [The CAD Consortium] (2012) Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ 344: e3485-</th></tr>
<tr><td></td><td>For model development, a dummy ‘setting’ variable was included to account for differences in patient selection based on referrals to catheter based coronary angiography versus CT based coronary angiography. Coded ‘0’ (low prevalence setting) if a patient came from a database created by selecting patients who underwent CTCA (of whom only a proportion went on to undergo catheter based CA); coded ‘1’ (high prevalence setting) if the patient came from a database that was created selecting patients who underwent catheter based CA (of whom a proportion also underwent the CT based procedure).

Models were tested in ‘low prevalence’ populations (data from 10 hospitals) for whom best diagnostic management should be determined based on an estimated pre-test probability (by contrast, all patients in high prevalence setting had a clinical indication for catheter based CA so pre-test probability not relevant).</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography (CA) or imputed data from computed tomography coronary angiography (CTCA) and other predictors.

<u>Note</u>: Only a minority of patients underwent catheter based CA so data were imputed using data from CTCA and other predictor variables (n=3615 (64%) values imputed for catheter based CA) Correlation between results of CA and CTCA in 1609 patients who underwent both was good; r = 0.72).

Significant obstructive coronary artery disease = at least one vessel with at least 50% diameter stenosis found on catheter based coronary angiography.</td></tr>
<tr><td>Time between testing & treatment</td><td>Not clear (retrospective analysis)</td></tr>
<tr><td>Length of follow-up</td><td>Study duration not reported.</td></tr>
<tr><td>Location</td><td>11 countries (18 centres)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Area under ROC curve
Reference: obstructive coronary artery disease = at least one vessel with at least 50% diameter stenosis found on catheter based coronary angiography
<table>
<tr><td>N=4,426 patients in low prevalence datasets (10 hospitals)</td><td>AUC (95% CIs)</td></tr>
<tr><td>Duke clinical score</td><td>0.78 (0.76 to 0.81)</td></tr>
<tr><td>Basic model (updated Diamond and Forrester) – mean of cross-validation procedures</td><td>0.77</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Genders,T. et al. [The CAD Consortium] (2012) Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ 344: e3485-**
	<table><tr><td>**Clinical model** – mean of cross-validation procedures</td><td>0.79</td></tr><tr><td>**Extended model (DICAD)** – mean of cross-validation procedures</td><td>0.88</td></tr></table> **Sensitivity and specificity** Not reported.
Source of funding	Not reported.
Comments	**Study limitations:** QUADAS-2: 1A – Not clear if patients were consecutively enrolled: UNCLEAR 1B – Patients all referred for CTCA (not developed for 'high prevalence' patients referred for CA): UNCLEAR 2A - LOW 2B – Duke Clinical Score: LOW 2B – Updated D-F: LOW 2B – Clinical model: LOW 2B – DICAD requires information from CT calcium score which is not applicable to pre-test probability assessment at an index clinic visit: HIGH 3A - Not clear if results were interpreted without knowledge of probability scores / patient clinical data: UNCLEAR 3B – LOW 4 - LOW

[1] *Number of patients with available data varies*

Bibliographic reference	**Hong,S. et al. (2012) Assessing coronary disease in symptomatic women by the Morise score. Journal of Women's Health 21: 843-850.**
Study type	Retrospective cross-sectional
Aim	To evaluate the predictive value of the Morise score for the diagnosis pf CAD, as determined by computed tomography coronary angiography (CTCA), in symptomatic women without a history of CAD, comparing the results with the Diamond-Forrester risk assessment.
Patient characteristics	**Inclusion:**

Bibliographic reference	Hong,S. et al. (2012) Assessing coronary disease in symptomatic women by the Morise score. Journal of Women's Health 21: 843-850.

- Consecutive women who underwent CTCA examination for chest pain

Exclusion:

- Prior history of CAD
- Cardiac catheterisation (with or without percutaneous intervention), or coronary artery bypass graft surgery (CABG)
- High calcium scores in proximal arteries precluding CTCA (Agatston > 400)

Patient Characteristics:

	n=140
Demographics	
Age in years – mean (sd)	64 (11)
Male – n (%)	0
Cardiovascular risk factors – n (%)	
Hypertension	71 (51)
Diabetes	23 (16)
Hyperlipidaemia	90 (64)
Past or current smoker	21 (15)
Positive family history	59 (42)
Oestrogen status[1] - Positive (premenopausal) - Negative (postmenopausal) - Unknown	 6 (4) 124 (89) 10 (7)
Symptoms – n (%) - Atypical - Typical - Non-cardiac	 102 (73) 29 (21) 9 (6)
Clinical assessments CT calcium score – median [IQR]	 5 [0-77]

<table>
<tr><td>Bibliographic reference</td><td>Hong,S. et al. (2012) Assessing coronary disease in symptomatic women by the Morise score. Journal of Women's Health 21: 843-850.</td></tr>
<tr><td></td><td>No CAD (on CTCA) – n (%): 45 (32)
Non-obstructive CAD: 73 (52)
Obstructive CAD: 22 (16)</td></tr>
<tr><td>Number of patients</td><td>N=140 (n=100 for Diamond and Forrester analysis)</td></tr>
<tr><td>Probability score / model</td><td>1. Morise et al. 1997 score

Calculated as follows:
<table>
<tr><td>Age</td><td>>65 years
9 points</td><td>50-65 years
6 points</td><td><50 years
3 points</td></tr>
<tr><td>Symptoms</td><td>Typical angina
5 points</td><td>Atypical angina
3 points</td><td>Non-anginal
1 point</td></tr>
<tr><td>Oestrogen status</td><td>Positive
-3 points</td><td>Negative
+3 points</td><td>Unknown
0 point</td></tr>
<tr><td>Diabetes</td><td>Yes
2 points</td><td>No
0 Points</td><td></td></tr>
<tr><td colspan="2">Hypertension, family history, obesity (BMI >27), hyperlipidaemia, smoking (any history)</td><td colspan="2">1 point (each)</td></tr>
</table>
Risk factor stratification: Low = 0-8 points; Intermediate = 9-15 points; High = 16-24 points.

2. Diamond and Forrester
Classified as follows:
<table>
<tr><th>Age</th><th>Gender</th><th>Typical / definite angina</th><th>Atypical / definite angina</th><th>Non-anginal chest pain</th><th>Asymptomatic</th></tr>
<tr><td>30-39</td><td>Women</td><td>Intermediate</td><td>Very low</td><td>Very low</td><td>Very low</td></tr>
<tr><td>40-49</td><td>Women</td><td>Intermediate</td><td>Low</td><td>Very low</td><td>Very low</td></tr>
<tr><td>50-59</td><td>Women</td><td>Intermediate</td><td>Intermediate</td><td>Low</td><td>Very low</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Hong,S. et al. (2012) Assessing coronary disease in symptomatic women by the Morise score. Journal of Women's Health 21: 843-850.**
	<table><tr><td>60-69</td><td>Women</td><td>High</td><td>Intermediate</td><td>Intermediate</td><td>Low</td></tr></table> Note: 40/140 patients were not included for Diamond and Forrester risk stratification as they were >69 years.
Reference standard (or Gold standard)	Computed tomography coronary angiography (CTCA) Performed using a dual-source 64-slice system (Somatom Definition, Siemens Medical Systems, Germany). ECG monitoring was continuous throughout. A gated, non-contrast CT scan was initially performed to evaluate coronary artery calcification, and an Agatston calcium score calculated using a threshold value of 130 Hounsfield units to delineate calcification. Images analysed by different interpreting physicians. Women with calcium scores >0 were classed as having evidence of CAD. The coronary artery tree was divided into 16 segments based on a modified AHA classification. Segments were evaluated for presence of atherosclerosis and associated degree of stenosis. Each CTAC study was classified into one of three groups: - No CAD = 0 calcium score and no evidence of atherosclerosis - Non-obtrusive CAD = calcified, mixed or non-calcified plaque with <50% luminal narrowing - Obstructive CAD = calcified, mixed or non-calcified plaque with ≥50% narrowing in one segment.
Time between testing & treatment	Not clear (retrospective study)
Length of follow-up	Patients underwent CTCA during study period: January 2007 to September 2008.
Location	USA (single centre)
Diagnostic accuracy measures (2 x 2 table)	**Area under the ROC curve** Reference: Obstructive CAD = calcified, mixed or non-calcified plaque with ≥50% narrowing in one segment. <table><tr><th></th><th>AUC[2]</th></tr><tr><td>Morise</td><td>0.771</td></tr><tr><td>Diamond and Forrester</td><td>0.61</td></tr><tr><td>p-value for comparison</td><td>p<0.001</td></tr></table>

<table>
<tr><td>Bibliographic reference</td><td>Hong,S. et al. (2012) Assessing coronary disease in symptomatic women by the Morise score. Journal of Women's Health 21: 843-850.</td></tr>
<tr><td></td><td>
Sensitivity and specificity³

(i) Morise: ‘Positive’ for obstructive CAD (≥50% stenosis) = high / intermediate probability score; negative for CAD = low probability score

<table>
<tr><th></th><th>CAD on CTCA</th><th>No CAD on CTCA</th></tr>
<tr><td>Morise +ve</td><td>95 (TP)</td><td>38 (FP)</td></tr>
<tr><td>Morise –ve</td><td>0 (FN)</td><td>7 (TN)</td></tr>
</table>
Sensitivity: 100 (95%CIs 96.1 to 100.0); Specificity: 15.6 (95%CIs 7.7 to 28.8)

(ii) Diamond and Forrester: : ‘Positive’ for obstructive CAD (≥50% stenosis) = high / intermediate probability score; negative for CAD = low/ very low probability score

<table>
<tr><th></th><th>CAD on CTCA</th><th>No CAD on CTCA</th></tr>
<tr><td>Diamond and Forrester +ve</td><td>59 (TP)</td><td>34 (FP)</td></tr>
<tr><td>Diamond and Forrester –ve</td><td>2 (FN)</td><td>5 (TN)</td></tr>
</table>
Sensitivity: 96.7 (95%CIs 88.8 to 99.1); Specificity: 12.8 (95%CIs 5.6 to 26.7)
</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Study limitations:
QUADAS-2:
1A – LOW
1B – Restricted study population (women only) who were referred for CTCA: HIGH
2A - LOW
2B – D-F: LOW
2B – MORISE 1997: LOW
3A - Not clear if results were interpreted without knowledge of probability scores / patient clinical data: UNCLEAR
3B – LOW
4 - LOW</td></tr>
</table>

[1] *Menopausal status not routinely documented on intake forms: in women without documented date of last period, status was based on age (≥51yrs classified as postmenopausal, <45yrs classified as premenopausal; 45-50yrs classified as unknown oestrogen status)*
[2] *95%CIs not reported for AUCs*
[3] *Calculated from reported data by reviewer*

Bibliographic reference	**Hwang,Y. (2010) Coronary heart disease risk assessment and characterization of coronary artery disease using coronary CT angiography: comparison of asymptomatic and symptomatic groups. Clinical Radiology 65: 601-608.**
Study type	Cross-sectional
Aim	To evaluate the presence of coronary artery disease (CAD) in relation to risk of coronary heart disease (CHD) and assess plaque characteristics from coronary computed tomography (CT) angiography in asymptomatic and symptomatic patients.
Patient characteristics	Inclusion: - patients who underwent CTCA for general health evaluation, or for atypical or non-anginal chest pain Exclusion: - incomplete medical record required for the assessment of CHD risk - non-diagnostic image quality obtained from CTCA - presence of typical anginal chest pain - a history of CHD Note: Data are extracted for symptomatic subgroup with atypical or non-anginal chest pain only, not those patients who were asymptomatic and underwent CTCA for general health evaluation. Atypical chest pain was defined as having two of the following three features and non-anginal chest pain was defined as having only one of these characteristics: (i) typical substernal chest pain (ii) exacerbation by physical or emotional stress (iii) relieved by nitrates and /or resting less than10min. **Patient characteristics**

	n=252
Demographics	
Age in years – mean (sd)	59.1 (11.7)
Male – n (%)	145 (58)

Bibliographic reference	**Hwang,Y. (2010) Coronary heart disease risk assessment and characterization of coronary artery disease using coronary CT angiography: comparison of asymptomatic and symptomatic groups. Clinical Radiology 65: 601-608.**
	Cardiovascular risk factors – n (%) |
	Hypertension | 84 (33)
	Diabetes | 77 (31)
	Smoking | 96 (38)
	Positive family history | 16 (6)
	Cholesterol (mg/dl) – mean (sd) | 185.5 (43.5)
	LDL (mg/dl) – mean (sd) | 102.4 (34.7)
	HDL (mg/dl) – mean (sd) | 50 (13.7)
	Triglycerides (mg/dl) – median [IQR] | 111 [75.5 - 158.5]
Number of patients	N=252 (symptomatic subgroup)
Probability score / model	**Framingham Risk Score** Includes: age, gender, total cholesterol, HDL cholesterol, systolic blood pressure (and also whether the patient is treated or not for hypertension), smoking status. Applied retrospectively based on patient records. High risk (CHD risk equivalents or a 10-year risk >20%) – n (%): 87 (35) Moderate risk (> 2 risk factors and a 10-year risk ≤20%) – n (%): 90 (36) Low risk (0-1 risk factor) – n (%): 75 (30)
Reference standard (or Gold standard)	CTCA Performed using a 64-section MDCT (SOMATOM Sensation64 Siemens Medical Solutions, Germany). Images analysed by two experienced radiologists using dedicated coronary software (Leonardo, Siemens Medical System, Germany). Coronary arterial segments were investigated for the presence and characteristics of coronary plaques. Participants classified into three subgroups: (1) non-calcified: participants with only non-calcified plaques (2) mixed; participants with mixed plaques (3) calcified; participants with only calcified plaques.

<table>
<tr><td>Bibliographic reference</td><td>Hwang,Y. (2010) Coronary heart disease risk assessment and characterization of coronary artery disease using coronary CT angiography: comparison of asymptomatic and symptomatic groups. Clinical Radiology 65: 601-608.</td></tr>
<tr><td></td><td>Plaque densities > 130 HU were classified as calcified and the coronary calcium score (CCS) was calculated according to the Agatston scoring system.

Degree of stenosis was classified as significant if the patient had >70% area of the cross-sectional image affected or more than 50% of the diameter of the longitudinal image affected.
The segment with the worst stenosis was evaluated in patients with multiple lesions.</td></tr>
<tr><td>Time between testing & treatment</td><td>Not clear (retrospective analysis).</td></tr>
<tr><td>Length of follow-up</td><td>Patients underwent CTCA between January 2006 and July 2008.</td></tr>
<tr><td>Location</td><td>Korea (single centre)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Area under ROC curve

Reference: Significant CAD = stenosis of >70% area of the cross-sectional image or >50% diameter of the longitudinal image
<table>
<tr><th>Framingham Risk Score</th><th>AUC (95% CIs)[1]</th></tr>
<tr><td>All symptomatic patients (n=252)</td><td>0.708</td></tr>
<tr><td>Men (n=145)
- ≥45 years (n=127)
- <45 years (n=18)</td><td>0.692
0.598
0.453</td></tr>
<tr><td>Women (n=39)
- ≥55 years (n=23)
- <55 years (n=16)</td><td>0.805
0.758
- [2]</td></tr>
<tr><td>Risk groups
- High risk (n=87)
- Medium risk (n=90)
- Low risk (n=75)</td><td>
0.646
0.613
0.715</td></tr>
</table>
Sensitivity and specificity</td></tr>
</table>

Bibliographic reference	**Hwang,Y. (2010) Coronary heart disease risk assessment and characterization of coronary artery disease using coronary CT angiography: comparison of asymptomatic and symptomatic groups. Clinical Radiology 65: 601-608.**
	CAD presence (symptomatic patients) = FRS cut-off value 11.50 Sensitivity 82.6%; specificity 47.4%
Source of funding	Not reported.
Comments	**Study limitations:** QUADAS-2: 1A – Not clear if consecutive patients were assessed; patients with typical angina chest pain were excluded: HIGH 1B – Patients were all referred for CTCA; those with typical angina chest pain were excluded: HIGH 2A - LOW 2B - LOW 3A - Not clear if results were interpreted without knowledge of probability scores / patient clinical data: UNCLEAR 3B – LOW 4 - LOW

[1] *95%CIs not reported for AUCs*
[2] *ROC curve could not be analysed because of absence of CAD in this subgroup.*

Bibliographic reference	**Jensen J, et al. (2012) Risk stratification of patients suspected of coronary artery disease: comparison of five different models. Atherosclerosis 220: 557-562.**
Study type	Cross-sectional
Aim	To compare the performance of five risk models (Diamond–Forrester, the updated Diamond–Forrester, Morise, Duke, and a new model designated COronary Risk SCORE (CORSCORE) in predicting significant coronary artery disease (CAD) in patients with chest pain suggestive of stable angina pectoris.
Patient characteristics	**Inclusion:** - Consecutive patients with chest pain indicative of CAD referred for CA **Exclusion:** - Unstable angina - Previous percutaneous coronary intervention or coronary artery bypass grafting

Bibliographic reference	Jensen J, et al. (2012) Risk stratification of patients suspected of coronary artery disease: comparison of five different models. Atherosclerosis 220: 557-562.

Patient characteristics

	n=633
Demographics	
Age in years – mean (sd)	63.1 (11.4)
Male – n (%)	336 (53.1)
Cardiovascular risk factors – n (%)	
Medically treated hypertension	382 (60.3)
Diabetes	107 (16.9)
Smoking	410 (64.8)
Positive family history	317 (50.1)
History of myocardial infarction	26 (4.1)
Medically treated hypercholesterolaemia	363 (57.3)
Negative oestrogen status (women only)	221 (34.9)
Body mass index (kg/m^2) – mean (sd)	27.3 (4.4)
Symptoms – n (%)	
CCS Angina class	1.6 (0.9)
Clinical assessments – n (%)	
ST-depression on ECG	9 (1.4)
Q-wave on ECG	35 (5.5)

Note: CCS angina - as classified by the Canadian Cardiovascular Society:
(1) only angina on considerable exertion
(2) daily activities are only slightly hampered by angina
(3) daily activities are considerably hampered by angina
(4) no activities performed without angina.

Significant CAD on CA – n (%): 216 (34.1)

Bibliographic reference	**Jensen J, et al. (2012) Risk stratification of patients suspected of coronary artery disease: comparison of five different models. Atherosclerosis 220: 557-562.**
Number of patients	N=633 (= cohort II sample in which the 5 models were compared)[1]
Probability score / model	**1. Diamond and Forrester** Uses age, sex, and typicality of chest pain symptoms to calculate likelihood of significant coronary artery stenosis >50% in patients 30-69 (but applied to wider age range in present study) **2. Updated Diamond and Forrester** Updated risk model (as modified by Genders et al. 2011) extended to include patients >69 years. **3. Duke clinical score** Based on age, sex, smoking, diabetes, history of MI, symptoms of angina pectoris, hypercholesterolemia, and ECG changes to calculate pre-test probability of at least one coronary artery stenosis ≥75% lumen diameter reduction at CA. **4. Morise 1997 score** Based on sex, age, smoking, diabetes, symptoms of angina pectoris, hypercholesterolemia, hypertension, family history of CAD, BMI, obesity (defined as BMI >27), and oestrogen status. Calculates the pre-test probability of stenosis at CAG >50% in one or more coronary arteries. **5. CORSCORE** Model derived from multivariate regression analyses of data from cohort I. Comprised information on age, sex, smoking, history of myocardial infarction, angina class, medically treated hypercholesterolemia,and medically treated hypertension. The model calculates the probability of at least one coronary artery stenosis >50% at CAG. Model was validated in cohort II and compared with the other prediction models detailed above.
Reference standard (or Gold standard)	Coronary angiography Performed with Philips Allura Xper FD10 or Philips Integris Allura (Philips Healthcare, the Netherlands) using standard technique. A minimum of 5 projections of the left coronary artery and at least 2 projections of the right coronary artery were used. The coronary angiograms were read by two cardiologists not blinded to clinical data. Significant CAD was defined as stenosis (lumen area diameter reduction ≥50%) in one or more coronary arteries using eye-balling or automatic quantitative standard technique.

<table>
<tr><td>Bibliographic reference</td><td>Jensen J, et al. (2012) Risk stratification of patients suspected of coronary artery disease: comparison of five different models. Atherosclerosis 220: 557-562.</td></tr>
<tr><td>Time between testing & treatment</td><td>Not clear.</td></tr>
<tr><td>Length of follow-up</td><td>Analysed data for patients referred for CA between July 2004 and April 2010.</td></tr>
<tr><td>Location</td><td>Denmark (single centre)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Area under ROC curve

Reference: Significant CAD = stenosis ≥50% in one or more coronary arteries on CA.
<table>
<tr><td></td><td>AUC[2]</td><td colspan="5">p-value for comparison</td></tr>
<tr><td></td><td></td><td>D-F</td><td>U D-F</td><td>DU</td><td>MO</td><td>CO</td></tr>
<tr><td>Diamond-Forrester (D-F)</td><td>0.642</td><td></td><td>p<0.001</td><td>p<0.001</td><td>p=0.049</td><td>p=0.001</td></tr>
<tr><td>Updated Diamond Forrester (U D-F)</td><td>0.714</td><td></td><td></td><td>p=0.680</td><td>p=0.36</td><td>p=0.480</td></tr>
<tr><td>Duke (DU)</td><td>0.718</td><td></td><td></td><td></td><td>p=0.320</td><td>p=0.560</td></tr>
<tr><td>Morise (MO)</td><td>0.681</td><td></td><td></td><td></td><td></td><td>p=0.024</td></tr>
<tr><td>CORSCORE (CO)</td><td>0.727</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Sensitivity and specificity
Not reported.</td></tr>
<tr><td>Source of funding</td><td>None</td></tr>
<tr><td>Comments</td><td>Study limitations:
QUADAS-2:
1A – LOW
1B – All patients had been referred for CA - HIGH
2A – all models: LOW
2B – all models: LOW
3A – States that angiograms were interpreted by cardiologists not blinded to patients’ clinical data - HIGH
3B – LOW
4 - LOW</td></tr>
</table>

[1] *Data for Cohort I (retrospective sample of n=4,781 patients used to develop the CORESCORE model) were not extracted.*
[2] *95%CIs not reported for AUCs*

<table>
<tr><td>Bibliographic reference</td><td>Kotecha D, et al. (2010) Contemporary predictors of coronary artery disease in patients referred for angiography. European Journal of Cardiovascular Prevention & Rehabilitation. 17: 280-288.</td></tr>
<tr><td>Study type</td><td>Cross-sectional</td></tr>
<tr><td>Aim</td><td>To assess the ability of risk scores, conventional risk factors, high-sensitivity C-reactive protein (hs-CRP) and B-type natriuretic peptide (BNP) to predict the presence, extent and severity of angiographic coronary disease.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion:
Consecutive patients attending elective diagnostic coronary angiography

Exclusion:
Precipitating coronary event (acute coronary syndrome or MI)
Heart transplantation

Patient characteristics:

<table>
<tr><th></th><th>N=539</th></tr>
<tr><td>Demographics</td><td></td></tr>
<tr><td>Age in years – mean (sd)</td><td>64.7 (10.9)</td></tr>
<tr><td>Male – n (%)</td><td>363 (67.4)</td></tr>
<tr><td>Cardiovascular risk factors – n (%)</td><td></td></tr>
<tr><td>Family history of premature CVD</td><td>187 (34.7)</td></tr>
<tr><td>Diabetes</td><td>118 (21.9)</td></tr>
<tr><td>Current smoker</td><td>88 (16.3)</td></tr>
<tr><td>Regular exercise</td><td>207 (38.4)</td></tr>
<tr><td>Prior CVD</td><td>302 (56.0)</td></tr>
<tr><td>Prior revascularisation</td><td>113 (21.0)</td></tr>
<tr><td>Peripheral vascular disease</td><td>52 (9.7)</td></tr>
<tr><td>Body mass index (kg/m^2) – mean (sd)</td><td>28.7 (5.2)</td></tr>
<tr><td>Symptoms – n (%)</td><td></td></tr>
<tr><td>Chest pain</td><td>410 (76.1)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Kotecha D, et al. (2010) Contemporary predictors of coronary artery disease in patients referred for angiography. European Journal of Cardiovascular Prevention & Rehabilitation. 17: 280-288.**

Dyspnoea	342 (63.5)
Clinical assessments – mean (sd)	
Systolic BP (mmHg)	143.9 (20.8)
Diastolic BP (mmHg)	79.5 (10.3)
Pulse pressure (mmHg)	64.5 (18.1)
Total cholesterol (mmol/l)	4.60 (1.12)
HDL-cholesterol (mmol/l)	1.22 (0.34)
Glomerular filtration rate (GFR) (ml/min per 1.73 m^2)	83.4 (23.2)
BNP (pg/ml)	40 (73)
High sensitivity CRP – n (%)	267 (49.6)
Medication – n (%)	
Aspirin	384 (71.2)
Clopidogrel	81 (15.0)
Beta-blockers	243 (45.1)
Calcium channel blockers	122 (22.6)
Nitrates	89 (16.5)
Statins	334 (62.0)

Obstructive CAD on CA – n (%): 328 (60.9)

Number of patients	N=539
Probability score / model	**1. Framingham risk score** Includes: age, gender, total cholesterol, HDL cholesterol, systolic blood pressure, whether the patient is treated or not for hypertension, smoking status. Gives an estimate of 10-year absolute event risk of total coronary disease, including angina, recognized and unrecognized MI and coronary deaths. Mean 10-year risk (sd): 14.0 (9.1) **2. SCORE** Includes: age, gender, total cholesterol, systolic blood pressure, smoking status. High-risk formula used based on total cholesterol; multiplication factor of two for diabetic men and four for diabetic women.

<table>
<tr><td>Bibliographic reference</td><td>Kotecha D, et al. (2010) Contemporary predictors of coronary artery disease in patients referred for angiography. European Journal of Cardiovascular Prevention & Rehabilitation. 17: 280-288.</td></tr>
<tr><td></td><td>Developed to predict 10-year fatal CVD risk
Mean 10-year risk (sd): 13.2 (15.1).

3. Conventional risk factors model
Multivariate model included the following pre-specified variables:
Age, sex, diabetes, chest pain, prior CVD, BMI, pulse pressure, glomerular filtration rate (GFR), total cholesterol, LV impairment.

4. Conventional risk factors + hs-CRP and BNP model
As above, but with the addition of the biomarkers high-sensitivity C-reactive protein (hs-CRP) and B-type natriuretic peptide (BNP).

Note: multivariate analyses adjusted for medication usage.</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary angiography (CA)

All participants underwent routine coronary angiography as per local guidelines. Random sample of10% of angiograms at each centre were reviewed by two experienced, blinded operators to evaluate consistency.
Obstructive CAD defined as one or more stenosis of >50% in a native major epicardial artery or main tributary.</td></tr>
<tr><td>Time between testing & treatment</td><td>Not clear (prospective analysis)</td></tr>
<tr><td>Length of follow-up</td><td>Eligible patients were recruited from 2006 to 2008.</td></tr>
<tr><td>Location</td><td>Australia (3 centres)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Area under ROC curve

Reference: Obstructive CAD = >50% stenosis in a native major epicardial artery or main tributary
<table>
<tr><th></th><th>AUC[1]</th><th colspan="4">p-value for comparison</th></tr>
<tr><th></th><th></th><th>FRS</th><th>SCORE</th><th>Risk</th><th>Risk +</th></tr>
<tr><td>Framingham risk score (FRS)</td><td>0.739</td><td></td><td>p=0.185</td><td>p<0.001</td><td>p<0.001</td></tr>
<tr><td>SCORE – high risk formula</td><td>0.754</td><td></td><td></td><td>p<0.001</td><td>p<0.001</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Kotecha D, et al. (2010) Contemporary predictors of coronary artery disease in patients referred for angiography. European Journal of Cardiovascular Prevention & Rehabilitation. 17: 280-288.**
	<table><tr><td>**Conventional risk factors model (Risk)**</td><td>0.826</td><td></td><td></td><td></td><td>p=0.286</td></tr><tr><td>**Conventional risk factors + hs-CRP and BNP (Risk +)**</td><td>0.829</td><td></td><td></td><td></td><td></td></tr></table> **Sensitivity and specificity** Comparative data are reported but with insufficient information regarding what threshold levels were used to assess each model's sensitivity and specificity.
Source of funding	Supported by the Monash Centre of Cardiovascular Research and Education in Therapeutics, Monash University, Melbourne, the Royal Brompton and Harefield NHS Trust Clinical Trials and Evaluation Unit, London and an unrestricted research grant from IM Medical Ltd., Melbourne (a supplier of cardiovascular diagnostic devices).
Comments	**Study limitations:** Model based on conventional risk factors (with or without addition of biomarkers) was not validated in a separate sample of patients to that used to derive the models, so data these data were not extracted for evidence appraisal. QUADAS-2: 1A – LOW 1B – All patients had been referred for CA: HIGH 2A – all models: LOW 2B – all models: LOW 3A – Not clear if results were interpreted without knowledge of probability scores / patient clinical data: UNCLEAR 3B – LOW 4 - LOW

[1] *95%CIs not reported for AUCs*

Bibliographic reference	**Kumamaru K, et al. (2014) Overestimation of pretest probability of coronary artery disease by Duke clinical score in patients undergoing coronary CT angiography in a Japanese population. Journal of Cardiovascular Computed Tomography 8: 198-204.**
Study type	Cross-sectional
Aim	To test the hypothesis that the Duke Clinical Score (DCS) overestimates the CAD probability when applied to patients evaluated with CT coronary angiography (CTCA) and compute an adjustment of the calculated DCS to

<table>
<tr><td>Bibliographic reference</td><td>Kumamaru K, et al. (2014) Overestimation of pretest probability of coronary artery disease by Duke clinical score in patients undergoing coronary CT angiography in a Japanese population. Journal of Cardiovascular Computed Tomography 8: 198-204.</td></tr>
<tr><td></td><td>apply to this population.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion:
- Consecutive, symptomatic patients with no known CAD, suspected of having CAD, who underwent CTCA
- Complete information to enable calculation of Duke Clinical Score

Exclusion:
- Inadequate CTCA study
- Incomplete information to enable calculation of Duke Clinical Score

Patient characteristics:
<table>
<tr><th></th><th>N=3,996</th></tr>
<tr><td>Demographics</td><td></td></tr>
<tr><td>Age in years – mean (sd)</td><td>66.4 (11.6)</td></tr>
<tr><td>Male – n (%)</td><td>1986 (49.7)</td></tr>
<tr><td>Cardiovascular risk factors – n (%)</td><td></td></tr>
<tr><td>Family history of premature CVD</td><td>1083 (27.1)</td></tr>
<tr><td>Diabetes</td><td>699 (17.5)</td></tr>
<tr><td>Smoking</td><td>699 (17.5)</td></tr>
<tr><td>Body mass index (kg/m^2) – mean (sd)</td><td>23.7 (3.5)</td></tr>
<tr><td>Dyslipidaemia</td><td>2853 (71.4)</td></tr>
<tr><td>Hypertension</td><td>2350 (58.8)</td></tr>
<tr><td>History of cerebral infarction</td><td>220 (5.5)</td></tr>
<tr><td>Symptoms – n (%)</td><td></td></tr>
<tr><td>- Typical chest pain
- Atypical chest pain
- Non-anginal chest pain</td><td>1343 (33.6)
2406 (60.2)
248 (6.2)</td></tr>
<tr><td>Clinical assessments</td><td></td></tr>
<tr><td>Total calcium score – mean (sd)</td><td>188.1 (501.6)</td></tr>
<tr><td>CAD on CTCA – n (%)</td><td>931 (23.3)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Kumamaru K, et al. (2014) Overestimation of pretest probability of coronary artery disease by Duke clinical score in patients undergoing coronary CT angiography in a Japanese population. Journal of Cardiovascular Computed Tomography 8: 198-204.**
	<table><tr><td>CAD on CA</td><td>707 (17.7)</td></tr></table> Note: baseline patients who were excluded from assessment sample due to having incomplete information in patient record to enable calculation of Duke Clinical Score were younger and had a lower incidence of typical chest pain.
Number of patients	N=3996 with complete information for Duke Clinical Score calculation (randomly divided into training cohort, n=2789 and validation cohort, n=1207)
Probability score / model	**Duke Clinical score** Calculated using original DCS (Pryor et al. 1983, 1993). Based on age, sex, type of chest pain, smoking status, cholesterol, diabetes, hypertension
Reference standard (or Gold standard)	Computed tomography coronary angiography CTCA *or* Coronary angiography (CA) (1) Computed tomography coronary angiography (CTCA) – all patients Performed using either a 64-detector or 320-detector row CT scanner. Coronary calcium scoring: Coronary artery calcium scoring performed using the Agatston method. A calcified lesion was defined as >3 contiguous voxels with attenuation of at least 130 Hounsfield units. (2) Coronary angiography (CA), n=994 (21.1%) Performed based on CTCA finding and clinical assessment. Undertaken within 2 weeks of CTCA. Coronoary stenosis was evaluated by 2 imagers (blinded to clinical information) by consensus reading. CTCA and CA images were interpreted separately without knowledge of the other exam. Coronary system divided into AHA 16 segment models. Significant CAD = >50% stenosis in the diameter of at least 1 segment.
Time between testing & treatment	Not clear (retrospective analysis)

<table>
<tr><td>Bibliographic reference</td><td>Kumamaru K, et al. (2014) Overestimation of pretest probability of coronary artery disease by Duke clinical score in patients undergoing coronary CT angiography in a Japanese population. Journal of Cardiovascular Computed Tomography 8: 198-204.</td></tr>
<tr><td>Length of follow-up</td><td>Consecutive patients referred for CTCA were recruited between Feb 2009 and April 2013.</td></tr>
<tr><td>Location</td><td>Japan (single centre)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>(i) CTCA

Reference: significant CAD on CTCA = at least 1 segment had >50% stenosis in the diameter
<table>
<tr><th></th><th>AUC[2]</th></tr>
<tr><td>Duke clinical score (training cohort, n=2,879)</td><td>0.705</td></tr>
<tr><td>Duke clinical score (validation cohort, n=1,207)</td><td>0.706</td></tr>
</table>
(ii) CA (n=929 patient subgroup with at least 1 significant stenosis on CTCA images and full data for calculating DCS)

Reference: significant CAD on CA = at least 1 segment had >50% stenosis in the diameter
<table>
<tr><th></th><th>AUC[2]</th></tr>
<tr><td>Duke clinical score</td><td>0.586</td></tr>
</table>
Sensitivity and specificity
Data not reported.</td></tr>
<tr><td>Source of funding</td><td>Not reported.</td></tr>
<tr><td>Comments</td><td>Study Limitations
QUADAS-2:
1A – excluded patients who had incomplete information to enable calculation of Duke Clinical Score were younger and had a lower incidence of typical chest pain: HIGH
1B – All patients had been referred for CTCA: UNCLEAR
2A - LOW
2B – LOW
3A - Not clear if results were interpreted without knowledge of probability scores / patient clinical data: UNCLEAR
3B – LOW</td></tr>
</table>

Bibliographic reference	Kumamaru K, et al. (2014) Overestimation of pretest probability of coronary artery disease by Duke clinical score in patients undergoing coronary CT angiography in a Japanese population. Journal of Cardiovascular Computed Tomography 8: 198-204.
	4 - LOW

[1] *<Insert Note here>*

<table>
<tr><td>Bibliographic reference</td><td>Park et al. (2011) Clinical significance of framingham risk score, flow-mediated dilation and pulse wave velocity in patients with stable angina, Circulation Journal, 75, 1177-1183</td></tr>
<tr><td>Study type</td><td>Cross-sectional</td></tr>
<tr><td>Aim</td><td>To evaluate the age-adjusted Framingham risk score (AFRS), flow-mediated dilation (FMD) and brachial-ankle pulse wave velocity (baPWV) for the prediction of the coronary heart disease (CHD) in patients with stable angina.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion:
Consecutive patients aged >30 and <75 years, had stable angina pectoris by history taking or stress test, and were scheduled to undergo coronary angiography (CAG)

Exclusion:
History of acute coronary syndrome, significant valvular heart disease (more than moderate degree), left ventricular dysfunction (left ventricular ejection fraction <55%), ankle-brachial index (ABI) <0.9, atrial fibrillation, chronic kidney disease, or an inability to follow the protocol.

Patient characteristics:

<table>
<tr><td></td><td>N = 138</td></tr>
<tr><td>Age (yrs)</td><td>59±7</td></tr>
<tr><td>Sex</td><td>72/138 male</td></tr>
<tr><td>Diabetes</td><td>42 (30%)</td></tr>
<tr><td>Hypertension</td><td>89 (64%</td></tr>
<tr><td>Current smoking</td><td>43 (31%)</td></tr>
<tr><td>Family history of coronary heart disease</td><td>19 (14%)</td></tr>
<tr><td>Body mass index (kg/m2)</td><td>25.0±3.4</td></tr>
<tr><td>Systolic blood pressure (mmHg)</td><td>130±15</td></tr>
<tr><td>Diastolic blood pressure (mmHg)</td><td>76±9</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Park et al. (2011) Clinical significance of framingham risk score, flow-mediated dilation and pulse wave velocity in patients with stable angina, Circulation Journal, 75, 1177-1183**
	Total cholesterol (mg/dl): 202±42 Coronary heart disease*: 71 (51%) Flow-mediated dilation (%): 9.9±4.4 Aspirin: 102 (74%) Statin: 36 (26%) β-blocker: 70 (51%) ACEI/ARB: 53 (38%) Nitrate: 15 (11%) Calcium channel blocker: 34 (25%) ** Defined as a lumen diameter stenosis >50% in >–1 major coronaryartery*
Number of patients	N = 138
Probability score / model	**Age- adjusted Framingham risk score (AFRS):** divides the participant's Framingham risk score by the estimated average risk of the same age group, thus providing the relative risk of the 10-year CHD. In patients who had been treated for dyslipidemia prior to the study, previous data was used (total cholesterol and HDL cholesterol) before initiation of dyslipidemia therapy. **Brachial-ankle pulse wave velocity (baPWV):** The baPWV was measured using a volume-plethysmographic apparatus. Cuffs were connected to both plethysmographic and oscillometric sensors, with placement around both arms and ankles while the participant remained in the supine position. The distance between sampling points of baPWV was calculated automatically according to the height of the patient. In this study, the left side baPWV was used for the analyses. **Flow-mediated dilation (FMD):** An experienced vascular sonographer who was blinded to the patients' information performed an ultrasound examination using a Vivid 7 ultrasound system with a 12-MHz linear array transducer. A landmark 10 cm above the proximal wrist crease of the left radial artery (RA) was used for the ultrasound measurement location. The baseline diameter of the RA was measured from 2-dimensional gray scale longitudinal images. Subsequently, a blood pressure cuff was inflated at the forearm up to 220 mmHg for 5 min. After cuff release, the RA diameter was measured at 1, 2 and 3 min. Measurements were taken at 7 points, and the maximal and minimal values were discarded. The mean value from these 5 measurements was used for further analysis.

Bibliographic reference	Park et al. (2011) Clinical significance of framingham risk score, flow-mediated dilation and pulse wave velocity in patients with stable angina, Circulation Journal, 75, 1177-1183
	Least squares linear regression was used to evaluate the association between the AFRS and FMD with baPWV. Multivariate logistic regression analysis was performed to assess independent risk predictors for significant CHD.
Reference standard (or Gold standard)	Coronary angiography (CAG). CHD was defined as lumen diameter stenosis >50% in 1 ≥ major coronary artery as determined by CAG. The CAG was interpreted by 1 cardiologist who was blinded to patients' clinical data.
Time between testing & treatment	Not reported
Length of follow-up	Not reported.
Location	Korea (single centre)
Diagnostic accuracy measures (2 x 2 table)	The area under the ROC curves for the prediction of CHD: AFRS = 0.863 (95%CI 0.800–0.927) FMD = 0.726 (95%CI 0.643–0.809), baPWV = 0.694 (95%CI 0.605–0.784) The area under the ROC curves for: AFRS plus iFMD = 0.864 (95%CI 0.801–0.927) AFRS plus baPWV = 0.863 (95%CI 0.801–0.926) AFRS plus iFMD plus baPWV = 0.863 (95%CI 0.798–0.925)
Source of funding	Not reported.
Comments	**Study limitations:** Brachial-ankle pulse wave velocity (baPWV) and flow-mediated dilation (FMD) are single tests and not multivariate models, so data were not extracted for quality appraisal. Models combining AFRS with either or both these test parameters were not validated in a separate patients sample, so data were not extracted for quality appraisal. QUADAS-2: 1A – LOW 1B – Restricted age population (30-75yrs), all patients were referred for CA: HIGH 2A – AFRS: LOW 2B - LOW 3A - LOW 3B - LOW 4 - LOW

[3] *<Insert Note here>*

<table>
<tr><td>Bibliographic reference</td><td>Pickett et al. (2013) Accuracy of traditional age, gender and symptom based pre-test estimation of angiographically significant coronary artery disease in patients referred for coronary computed tomographic angiography, American Journal of Cardiology, 112, 208-211.</td></tr>
<tr><td>Study type</td><td>Cross-sectional</td></tr>
<tr><td>Aim</td><td>To compare the expected prevalence of angiographically significant CAD predicted by DF classification with the observed prevalence of angiographically significant CAD inpatients clinically referred for 64 CCTA.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
Consecutive patients referred for CTCA. Atypical angina was most common symptom prompting referral (63%)
Angina was symptoms of chest pain were classified as non-anginal, atypical angina or typical angina. Typical angina was defined as:
1) Substernal location
2) Occurs with exertion or emotional stress
3) Is consistently relieved with rest or nitroglycerin.
Atypical angina was defined by having 2 of the aforementioned criteria, and chest pain possessing <2 of the criteria was defined as nonanginal.

Exclusion criteria:
None reported.

Patient characteristics:

<table>
<tr><td></td><td>N = 1027</td></tr>
<tr><td>Age (yrs)</td><td>50±12</td></tr>
<tr><td>Sex</td><td>606 male</td></tr>
<tr><td>Diabetes mellitus</td><td>112 (10%)</td></tr>
<tr><td>Hyperlipidaemia (patient identified or treated)</td><td>562 (51%)</td></tr>
<tr><td>Smokers</td><td>135 (12%)</td></tr>
<tr><td>Family history of premature coronary heart disease</td><td>290 (26%)</td></tr>
<tr><td>Body mass index (kg/m2)</td><td>29±5</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Pickett et al. (2013) Accuracy of traditional age, gender and symptom based pre-test estimation of angiographically significant coronary artery disease in patients referred for coronary computed tomographic angiography, American Journal of Cardiology, 112, 208-211.**
	Hypertension: 562 (51%) Total cholesterol (mg/dl): 190±38 Low-density lipoprotein cholesterol (mg/dl): 116 ± 33 High-density lipoprotein cholesterol (mg/dl): 53±21
Number of patients	N = 1027
Probability score / model	**Diamond and Forrester** (DF) classification. **Morise score (1997)**: incorporates age, risk factors and DF criteria symptoms.
Reference standard (or Gold standard)	64-slice CCTA. Each CCTA examination was performed on the same 64-slice scanner All scans were jointly interpreted by a cardiologist and radiologist who reached consensus. Maximal epicardial vessel luminal stenosis was visually estimated, waucith patients categorized as having (1) normal coronary arteries, (2) nonobstructive CAD (<50% stenosis), or (3) 50% visual luminal stenosis in > 1 epicardial coronary artery segment > 1.5 mm in diameter (angiographically significant CAD).
Time between testing & treatment	Not reported.
Length of follow-up	Patients were referred for CTCA between July 2006 – December 2010
Location	USA (one centre).
Diagnostic accuracy measures (2 x 2 table)	For the prediction of any angiographically significant CAD, DF classification had an area under the curve of 0.72 (95% CI 0.66 to 0.78) on receiver-operating characteristic curve analysis Incorporating standard cardiovascular risk factors using the Morise score for the prediction of angiographically significant CAD, the area under the curve was 0.68 (95% CI 0.63 to 0.74), whereas age alone had an area under the curve of 0.69 (95% confidence interval 0.63 to 0.75).
Source of funding	Not reported.
Comments	**Study limitations:** QUADAS-2 1A - LOW 1B – All patients were referred for CTCA: UNCLEAR 2A – all models: LOW 2B – all models: LOW

Bibliographic reference	**Pickett et al. (2013) Accuracy of traditional age, gender and symptom based pre-test estimation of angiographically significant coronary artery disease in patients referred for coronary computed tomographic angiography, American Journal of Cardiology, 112, 208-211.**
	3A - Not clear if results were interpreted without knowledge of probability scores / patient clinical data: UNCLEAR 3B - LOW 4 - LOW

Bibliographic reference	**Rademaker et al. (2014) Comparison of different cardiac risk scores for coronary artery disease in symptomatic women: do female-specific risk factors matter?, European Journal of Preventive Cardiology, 21, 1443-1450**
Study type	Cross-sectional
Aim	To compare the accuracy of several widely used cardiac risk assessment scores in predicting the likelihood of obstructive coronary artery disease (CAD) on CT coronary angiography (CTCA) in symptomatic women and to explore which female-specific risk factors were independent predictors of obstructive CAD on CTCA and whether adding these risk factors to pre-test probability scores would improve their predictive value.
Patient characteristics	**Inclusion criteria** Consecutive female patients referred for CTCA for evaluation for presence of significant CAD. **Exclusion criteria** - Prior history of CAD (e.g previous myocardial infarction) - Had absolute or relative contraindications for CCTA such as: o Significant severe arrhythmia o Pregnancy o Renal insufficiency o Known allergy to iodinated contrast material. Patient characteristics:

	N = 178
Age (yrs)	59 ± 9 (29 ≤ 50 yrs)
BMI (kg/m^2)	26 ± 4
Risk factors for CAD	

Bibliographic reference	Rademaker et al. (2014) Comparison of different cardiac risk scores for coronary artery disease in symptomatic women: do female-specific risk factors matter?, European Journal of Preventive Cardiology, 21, 1443-1450
	Diabetes mellitus type 2: 23 (13%) Hypercholesterolaemia: 63 (35%) Hypertension: 76 (43%) Obesity (BMI > 27 kg/m^2): 56 (32%) Current or former smoker: 76 (43%) Family history of CAD: 102 (57%) **Symptoms** Typical chest pain: 34 (20%) Atypical chest pain: 70 (39%) Non-specific chest pain: 70 (39%) Asymptomatic: 4 (2%) **Female-related factors** Number of pregnancies: 2.2 ± 1.4 Number of children: 1.8 ± 1.2 Pregnancy-related hypertension: 32 (18%) Gestational diabetes: 8 (4.5%) Pre-eclampsia: 13 (7.3%) Oophorectomy: 28 (15.7%) Hysterectomy: 53 (29.8%) Hormone replacement therapy: 34 (19.1%) Oestrogen positive: 50 (28.1%) Oestrogen negative: 128 (71.9%)
Number of patients	N = 178
Probability score / model	□ Diamond and Forrester (DF) – based on age, sex and symptoms of angina pectoris □ Updated Diamond and Forrester – by Genders et al 2011, extended the predictive effects of age, sex and type of chest pain based on a contemporary cohort and using modern statistical methods. Low risk < 30%, intermediate 30 – 70%.

Bibliographic reference	**Rademaker et al. (2014) Comparison of different cardiac risk scores for coronary artery disease in symptomatic women: do female-specific risk factors matter?, European Journal of Preventive Cardiology, 21, 1443-1450**
	Morise score – sex, age, tobacco use, diabetes mellitus, symptoms of angina pectoris, hypertension, family history, hyperlipidaemia, obesity and oestrogen status. Duke clinical score – sex, age, tobacco use, diabetes mellitus, history of myocardial infarction, symptoms of angina pectoris, cholesterol concentration and ECG changes.
Reference standard (or Gold standard)	CT scan with determination of calcium scoring followed by CCTA on a 64-slice CT scanner. Oral and/or intravenous metoprolol was administered as needed to achieve a stable heart rate of 65 bpm. A standard scanning protocol was applied. Images were interpreted and scored on a four point scale: - Normal (no stenosis) - Non-obstructive CAD (0 to < 50% diameter stenosis) - Obstructive CAD (≥ 50% luminal narrowing) - Non-diagnostic (severe artefacts that impaired adequate grading of all coronary vessels).
Time between testing & treatment	Not reported.
Length of follow-up	June 2006 – October 2010
Location	Netherlands
Diagnostic accuracy measures (2 x 2 table)	**Area under the ROC curve:** **Updated Diamond and Forrester + gestational diabetes mellitus (GDM) + Oestrogen status:** 0.71 (95% CI: 0.63 – 0.77) Compared to DF p<0.001 Compared to Duke score p<0.01. **Morise score**: 0.67 (95% CI: 0.60 – 0.74) Compared to DF p<0.02 **Updated Diamond and Forrester (Genders et al 2011):** 0.61 (95% CI: 0.53 – 0.68) **Duke clinical score:** 0.59 (95% CI: 0.51 – 0.66) **D-F:** 0.56 (95% CI: 0.49 – 0.64)

Bibliographic reference	**Rademaker et al. (2014) Comparison of different cardiac risk scores for coronary artery disease in symptomatic women: do female-specific risk factors matter?, European Journal of Preventive Cardiology, 21, 1443-1450**
Source of funding	No funding received for research.
Comments	**Study limitations:** Model developed by combining Updated D-F score with additional female-specific risk factors was not validated in a separate patient sample, so these data were not extracted for evidence appraisal. QUADAS-2 1A - LOW 1B – Restricted study population (women only) who were referred for CTCA: HIGH 2A – all models: LOW 2B – all models: LOW 3A - Not clear if results were interpreted without knowledge of probability scores / patient clinical data: UNCLEAR 3B - LOW 4 - LOW

Bibliographic reference	**Rosenberg et al., PREDICT (Personalized Risk Evaluation and Diagnosis in the Coronary Tree) Investigators (2010) Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. Annals of Internal Medicine, 153, 425-434**
Study type	Cross-sectional
Aim	To validate a previously developed 23-gene expression-based classifier for diagnosis of obstructive CAD in non-diabetic patients.
Patient characteristics	**Inclusion criteria:** Subjects referred for diagnostic coronary angiography were eligible with a history of chest pain, suspected anginal-equivalent symptoms, or a high risk of CAD, and no known prior myocardial infarction (MI), revascularization, or obstructive CAD. **Exclusion criteria:** Diabetes If at catheterization, they had acute MI, high risk unstable angina, severe non-coronary heart disease (congestive heart failure, cardiomyopathy or valve disease), systemic infectious or inflammatory conditions, or were taking immunosuppressive or chemotherapeutic agents.

Bibliographic reference	**Rosenberg et al., PREDICT (Personalized Risk Evaluation and Diagnosis in the Coronary Tree) Investigators (2010) Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. Annals of Internal Medicine, 153, 425-434**
	Patient characteristics: N = 526 (validation cohort only; data for development cohort not extracted n=640)
Number of patients	N = 1343 divided into independent algorithm development (694) and validation (649) cohorts.
Probability score / model	An algorithm specifically relating non-diabetic patient CAD status to expression levels consisting of 23 genes, grouped in the 6 terms, 4 sex-independent and 2 sex-specific age functions. Gene expression algorithm: Prior to coronary angiography, venous blood samples were collected. Automated RNA purification from whole blood samples using the Agencourt RNAdvance system, cDNA synthesis, and RT-PCR were performed. All PCR reactions were run in triplicate and median values used for analysis. The gene expression algorithm was developed with obstructive CAD defined by QCA as ≥50% stenosis in >1 major coronary artery, corresponding approximately to 65–70% stenosis based on clinical angiographic read. The algorithm was locked prior to the validation study. Raw algorithm scores were computed from median expression values for the 23 algorithm genes, age and sex as described (Appendix 3) and used in all statistical analyses; scores were linearly transformed to a 0–40 scale for ease of reporting. The Diamond-Forrester (D–F) risk score comprised of age, sex, and chest pain type, was prospectively chosen to evaluate the added value of the gene expression score to clinical factors. D–F classifications of chest pain type (typical angina, atypical angina and nonanginal chest pain) were assigned based on subject interviews and D-F scores assigned.
Reference standard (or Gold standard)	Coronary angiograms were analysed by computer-assisted QCA. Trained technicians, blinded to clinical and gene expression data, visually identified all lesions >10% diameter stenosis (DS) in vessels with diameter >1.5mm. Technicians traced the vessel lumen across the lesion between the nearest proximal and distal non-diseased locations. The minimal lumen diameter (MLD), reference lumen diameter (RLD = average diameter of normal segments proximal and distal of lesion) and %DS (%DS = (1 - MLD/RLD) x 100) were then calculated. Patients with CAD = ≥ 50% stenosis
Time between testing & treatment	Not reported
Length of follow-up	Patient enrolled between July 2007 - April 2009

Bibliographic reference	**Rosenberg et al., PREDICT (Personalized Risk Evaluation and Diagnosis in the Coronary Tree) Investigators (2010) Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. Annals of Internal Medicine, 153, 425-434**
Location	USA (39 centres; part of PREDICT study)
Diagnostic accuracy measures (2 x 2 table)	**Area under the curve (standard error)** The prospectively defined primary endpoint was the ROC curve area for algorithm score prediction of disease status. Data were available for 525 of the validation cohort patients. ROC curves were estimated for the: a) D–F risk score: AUC 0.66 (95% CI: 061 to 0.71[1]) b) a combined model of algorithm score and D–F risk score (validation cohort): AUC 0.72 (95% CI: 0.68 to 0.76) **Sensitivity, specificity:** Sensitivity and specificity were calculated for a score threshold of 14.75, corresponding to a disease likelihood of 20% from the validation set data. At this threshold, sensitivity = 85% and specificity = 43%.
Source of funding	CardioDx, Inc
Comments	**Study limitations:** QUADAS-2: 1A – Not clear if patients were consecutively enrolled: UNCLEAR 1B - Restricted study population (patients with diabetes were excluded) who were referred for CA: HIGH 2A – all models: LOW 2B – D-F: LOW 2B – D-F + gene expression algorithm: Requires information from genetic testing of blood sample that would not be available at a typical index clinic visit: HIGH 3A - LOW 3B - LOW 4 - LOW

[1] *95% CIs calculated by the reviewer from standard error*

<table>
<tr><td>Bibliographic reference</td><td>Shmilovich et al. (2014) Incremental value of diagonal earlobe crease to the Diamond-Forrester classification in estimating the probability of significant coronary artery disease determined by computed tomographic angiography, American Journal of Cardiology, 114, 1670-1675.</td></tr>
<tr><td>Study type</td><td>Cross-sectional</td></tr>
<tr><td>Aim</td><td>To evaluate whether the addition of a diagonal earlobe crease (DELC) enhances the predictive ability of D-F to detect coronary artery disease >50 % stenosis (CAD50) by coronary computed tomographic angiography (CTA).</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria
Consecutive patients who underwent coronary CTA at hospital.
After a clinical history, patients were dichotomously divided into those having chest pain or not. For those with chest pain, typical angina pectoris was rigidly defined as: (1) substernal, jaw, or arm pressure-like pain, (2) induced by exertion, and (3) resolved with rest or use of nitroglycerin.
Only data for patients with chest pain are extracted, as per review protocol.

Exclusion criteria
A history of CAD (myocardial infarction, coronary stenting, and previous bypass surgery) and if an expert reader did not consider the coronary CTA image quality to be good or excellent.

Patient characteristics
<table>
<tr><td></td><td>Chest pain cohort(N = 199)</td></tr>
<tr><td>DELC</td><td>143 (72%)</td></tr>
<tr><td>Age (yrs)</td><td>61±14</td></tr>
<tr><td>Sex</td><td>105 (53%)</td></tr>
<tr><td>Diabetes mellitus</td><td>38 (19%)</td></tr>
<tr><td>Hypertension</td><td>114 (57%)</td></tr>
<tr><td>Smokers</td><td>74 (37%)</td></tr>
<tr><td>CAD family history</td><td>60 (30%)</td></tr>
<tr><td>Total cholesterol (mg/dL)</td><td>168 ± 40</td></tr>
<tr><td>Glucose (mg/dL)</td><td>95 ± 30</td></tr>
</table>
CAD: coronary artery disease; DELC: diagonal ear lobe crease;</td></tr>
<tr><td>Number of patients</td><td>N = 199 patients with chest pain (of 430 who underwent CTCA)</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Shmilovich et al. (2014) Incremental value of diagonal earlobe crease to the Diamond-Forrester classification in estimating the probability of significant coronary artery disease determined by computed tomographic angiography, American Journal of Cardiology, 114, 1670-1675.</td></tr>
<tr><td>Probability score / model</td><td>Diamond Forrester (DF):
The pre-test probability of CAD50 was calculated using the original DF table of probabilities (generating a “DF probability”) and treated as a categorical variable. Patients with “intermediate” or “high” DF probability were considered suspected of having CAD50.

Diagonal ear lobe crease (DELC):
The presence of a DELC was determined by consensus by 2 trained observers before coronary CTA. A DELC was defined as a wrinkle-like line extending diagonally from the tragus across the lobule to the rear edge of the auricle of the ear, not related to sleeping position or wearing earrings.</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>Coronary CTA:
Performed on all patients using SOMATOM Definition dual-source scanner (Siemens Medical Systems, Germany). Image interpretation was performed by 2 American Heart Association level-3 expert readers, blinded to presence or absence of DELC, using the modified AHA 15 segment coronary artery tree model. Discrepancies resolved by consensus.</td></tr>
<tr><td>Time between testing & treatment</td><td>Not reported.</td></tr>
<tr><td>Length of follow-up</td><td>Consecutive patients attending CTCA over 9 month period were enrolled.</td></tr>
<tr><td>Location</td><td>USA (single centre)</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>
<table>
<tr><th></th><th>DF</th><th>DF+DELC</th></tr>
<tr><td></td><td>Patients with chest pain (n = 199)</td><td>Patients with chest pain (n = 199)</td></tr>
<tr><td>Sensitivity</td><td>97%</td><td>91%</td></tr>
<tr><td>Specificity</td><td>20%</td><td>41%</td></tr>
<tr><td>Positive likelihood ratio</td><td>1.21</td><td>1.54</td></tr>
<tr><td>Negative likelihood ratio</td><td>0.15</td><td>0.22</td></tr>
<tr><td>Area under the curve</td><td>0.59</td><td>0.66</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Shmilovich et al. (2014) Incremental value of diagonal earlobe crease to the Diamond-Forrester classification in estimating the probability of significant coronary artery disease determined by computed tomographic angiography, American Journal of Cardiology, 114, 1670-1675.</td></tr>
<tr><td></td><td>Sensitivity and specificity 2X2 table
Patients with chest pain n = 199
Diamond-Forrester – Reference CAD= ≥50% stenosis
<table>
<tr><th>D-F model</th><th>CAD+</th><th>CAD-</th></tr>
<tr><td>Intermediate / high probability</td><td>33</td><td>132</td></tr>
<tr><td>Low probability</td><td>1</td><td>33</td></tr>
</table>
Sensitivity: 97.1 (95% CI 85.1 to 99.5)
Specificity: 20.0 (95% CI: 14.6 to 26.8)</td></tr>
<tr><td>Source of funding</td><td>Fellowship from American Physicians Fellowship for Medicine in Israel, Boston, MA.</td></tr>
<tr><td>Comments</td><td>Study limitations:
Model developed by combining D-F score and diagonal earlobe crease was not validated in a separate cohort, so those data were not extracted for evidence appraisal.
<u>QUADAS-2</u>
1A - LOW
1B – Patients had all been referred for CTCA: UNCLEAR
2A – D-F: LOW
2B – D-F: LOW
3A - Not clear if results were interpreted without knowledge of probability scores / patient clinical data: UNCLEAR
3B - LOW
4 - LOW</td></tr>
</table>

[2] *<Insert Note here>*

Bibliographic reference	**Versteylen et al. (2011) Comparison of Framingham, PROCAM, SCORE, and Diamond Forrester to predict coronary atherosclerosis and cardiovascular events, Journal of Nuclear Cardiology, 18, 904-911.**
Study type	Cross-sectional
Aim	To study the most commonly used risk profiling algorithms in their ability to predict for (1) CAD on CCTA, and (2)

Bibliographic reference	**Versteylen et al. (2011) Comparison of Framingham, PROCAM, SCORE, and Diamond Forrester to predict coronary atherosclerosis and cardiovascular events, Journal of Nuclear Cardiology, 18, 904-911.**
	for major adverse cardiovascular events, in patients presenting with chest pain at the cardiology outpatient clinic.
Patient characteristics	Patients presenting with chest pain in one outpatient clinic. **Inclusion criteria** A recent history of cardiac (a) typical chest pain; a diagnostic CCTA scan (with seven or more interpretable coronary segments). **Exclusion criteria** Unstable angina, previous myocardial infarction, previous revascularization, hemodynamic instability, contrast allergy, pregnancy, and renal failure. **Patient characteristics**

	N = 1296
Age (yrs)	56 ±11
Sex	606 female (46.8%)
BMI (kg/m^2)	27 ± 5
Active smokers	316 (24.4)
Diabetes mellitus	102 (7.9)
Positive family history	522 (40.3)
Systolic blood pressure (mmHg)	142 ± 19
Typical chest pain	169 (13)
Glucose (mg/dL)	104 ± 24
Creatinin (mg/dL)	1.1 ± 0.2
Total cholesterol (mg/dL)	209 ± 46
Clinical risk scores	
Framingham	21 ± 16
PROCAM	12 ± 13
SCORE	4 ± 4

Bibliographic reference	**Versteylen et al. (2011) Comparison of Framingham, PROCAM, SCORE, and Diamond Forrester to predict coronary atherosclerosis and cardiovascular events, Journal of Nuclear Cardiology, 18, 904-911.**
	Diamond Forrester: 42 ± 26 **CAD on CCTA** No CAD: 490 (37.8) Insignificant CAD (< 50% stenosis): 489 (37.7) Significant CAD (≥ C50% stenosis): 317 (24.5)
Number of patients	N = 1296
Probability score / model	**Diamond Forrester score:** The probability of having significant CAD was calculated using the Diamond Forrester model. This model takes into account age, sex, and type of chest pain, which was classified as typical, atypical or non-anginal. The commonly used classification cut-offs of 30% and 70% were used. A score below 30% was considered low, 30%-70% intermediate and > 70% high risk of having significant CAD. **Framingham risk score:** 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. **PROCAM risk score:** PROCAM participants were followed up for acute coronary events (myocardial infarction, sudden cardiac death) for 10 years. The calibrated risk score included; age, LDL cholesterol, smoking, HDL cholesterol, systolic blood pressure, family history of premature myocardial infarction, diabetes mellitus, and triglycerides. A score below 10% is considered low, 10%-20% intermediate, and >20% high 10-year risk of coronary events. **SCORE risk score:** The SCORE predicts 10-year risk on fatal cardiovascular disease resulted in a model which included gender, age, systolic blood pressure, total cholesterol, and smoking. A score of 0%-4% was considered low, 5%-9% intermediate, and C10% high risk of cardiovascular death in 10 years.
Reference standard (or Gold standard)	CCTA was performed using a 64-slice CT scanner. All CCTA scans were independently analysed by two experienced cardiologists, both blinded for patient details. Disagreements discussed and agreed by consensus. AHA 16-segment coronary artery tree classification used, assessing images using Cardiac Comprehensive

Bibliographic reference	**Versteylen et al. (2011) Comparison of Framingham, PROCAM, SCORE, and Diamond Forrester to predict coronary atherosclerosis and cardiovascular events, Journal of Nuclear Cardiology, 18, 904-911.**
	Analysis software (Philips Healthcare). Degree of stenosis was evaluated visually and classified as insignificant (no lesions, or one or more lesions with luminal stenosis of <50%), or significant (one or more lesions with luminal stenosis of ≥50%).
Time between testing & treatment	Not reported.
Length of follow-up	Mean 19 ± 9 months between December 2007 and June 2010,
Location	The Netherlands (one centre)
Diagnostic accuracy measures (2 x 2 table)	<u>AUC for prediction of any coronary lesion:</u> **FRS**: 0.74 (95% CI: 0.72 - 0.77) **SCORE**: 0.72 (95% CI: 0.70 - 0.75) (both FRS and SCORE significantly higher than PROCAM, p ≤ 0.03) **PROCAM**: 0.70 (95% CI: 0.67 - 0.73) (significantly higher than D-F, p < 0.01) **Diamond Forrester:** 0.65 (95% CI: 0.62 - 0.68). <u>AUC for prediction of significant CAD stenosis (≥50% lesion)</u> **FRS**: 0.68 (95% CI: 0.64 - 0.72) **SCORE**: 0.69 (95% CI: 0.65 - 0.72) (both FRS and SCORE significantly higher than PROCAM, p ≤ 0.001) **PROCAM:** 0.64 (95% CI: 0.61 - 0.68) (marginally higher than D-F, p < 0.05) **Diamond Forrester:** 0.65 (95% CI: 0.61 - 0.68)
Source of funding	None reported
Comments	**Study limitations:** <u>QUADAS-2:</u> 1A – Not clear if consecutive patients were enrolled: UNCLEAR 1B - Patients had all been referred for CTCA: UNCLEAR 2A – all models: LOW 2B – all models: LOW 3A - LOW 3B - LOW 4 - LOW

Bibliographic reference	Versteylen et al. (2011) Comparison of Framingham, PROCAM, SCORE, and Diamond Forrester to predict coronary atherosclerosis and cardiovascular events, Journal of Nuclear Cardiology, 18, 904-911.

[2] *<Insert Note here>*

Bibliographic reference	Wasfy et al. (2012) Comparison of the Diamond-Forrester method and Duke Clinical Score to predict obstructive coronary artery disease by computed tomographic angiography, American Journal of Cardiology, 109, 998-1004.
Study type	Cross-sectional
Aim	To evaluate the ability of the Diamond and Forrester method (DFM) and the Duke Clinical Score (DCS) to predict obstructive coronary artery disease (CAD) on coronary computed tomographic angiography (CCTA) and the effect of these different risk scores on the appropriateness level using the 2010 Appropriate Use Criteria.
Patient characteristics	**Inclusion criteria** Consecutive symptomatic patients who presented for CCTA for evaluation of CAD. **Exclusion criteria** None reported **Patient characteristics**

	N = 114
Age (yrs)	56.3 ±13
Sex	59 men (52%)
Diabetes mellitus	17 (15%)
Hypertension	65 (57%)
Current smokers	14 (12%)
Previous myocardial infarction	5 (4%)
Patient symptoms	
Nonanginal chest pain	42 (37%)
Atypical angina	46 (37%)
Typical angina	26 (23%)

Bibliographic reference	**Wasfy et al. (2012) Comparison of the Diamond-Forrester method and Duke Clinical Score to predict obstructive coronary artery disease by computed tomographic angiography, American Journal of Cardiology, 109, 998-1004.**
Number of patients	N = 114
Probability score / model	**Diamond and Forrester:** Established in a combination of symptomatic patients referred for invasive angiography and autopsy studies; includes: age, sex, chest pain type. Developed to predict ≥50% stenosis. Patients categorised as having low (10%), intermediate (10% to 90%),or high (>90%) risk of obstructive CAD (defined as > 50% luminal stenosis). **Duke Clinical Score (DCS)** Established and validated in symptomatic patients referred for invasive angiography, includes: chest pain type; age; sex; previous MI (with or without Q waves); smoking; hyperlipidaemia; diabetes; ST-T wave changes (ECG). Developed to predict ≥75% stenosis. <u>Note</u>: ECG information was not available for all patients so information regarding Q waves and ST-segment deviation was not included in the calculation of the DCS. Patients classified using the DCS as having low (< 30%), intermediate (30% - 70%) or high (> 70%) risk of obstructive CAD (defines as > 70% luminal stenosis).
Reference standard (or Gold standard)	Coronary computed tomographic angiography (CCTA) performed on the Definition dual-source 62-slice CT scanner. The overall disease severity was determined by the greatest stenosis identified among all evaluable segments: Normal – absence of plaque and no luminal stenosis Mild to moderate (non-obstructive) CAD – estimated stenosis ,70% Mild disease defines as stenosis estimated as < 40% Moderate disease defined as stenosis estimated as ≥ 40% but ≤ 70% Significant (obstructive) CAD – estimated stenosis ≥ 70%. Primary indication for each CCTA was determined by several sources: - Patient questionnaire - Radiology order entry system

Bibliographic reference	**Wasfy et al. (2012) Comparison of the Diamond-Forrester method and Duke Clinical Score to predict obstructive coronary artery disease by computed tomographic angiography, American Journal of Cardiology, 109, 998-1004.**
	- Electronic medical records Two physicians who were unaware of CCTA results assigned each examinations primary indication and each study was categorized as appropriate, inappropriate or uncertain using the 2010 Appropriate Use Criteria.
Time between testing & treatment	Not reported.
Length of follow-up	Patients referred for CTCA between March 2008 – July 2008
Location	USA (one centre)
Diagnostic accuracy measures (2 x 2 table)	Diagnostic accuracy (area under the ROC curve) for identifying obstructive CAD: **DFM:** 0.69 **DCS** = 0.80
Source of funding	None reported.
Comments	**Study limitations:** QUADAS-2 1A - LOW 1B – All patients had been referred for CTCA: UNCLEAR 2A – both models: LOW 2B – both models: LOW 3A – Patient clinical data and medical history were available to those performing and interpreting scans: HIGH 3B - LOW 4 - LOW

[1] *<Insert Note here>*

Bibliographic reference	**Winther et al. (2016) Diagnosing coronary artery disease by sound analysis from coronary stenosis induced turbulent blood flow: diagnostic performance in patients with stable angina pectoris. International Journal of Cardiovascular Imaging, -, 2015**
Study type	Cross-sectional

Bibliographic reference	**Winther et al. (2016) Diagnosing coronary artery disease by sound analysis from coronary stenosis induced turbulent blood flow: diagnostic performance in patients with stable angina pectoris. International Journal of Cardiovascular Imaging, -, 2015**
Aim	To evaluate the diagnostic accuracy of an acoustic test (CADscore) to detect CAD and compare it to clinical risk stratification and coronary artery calcium score (CACS).
Patient characteristics	**Inclusion criteria** Patients referred for CCTA or invasive coronary angiography (ICA) as part of their evaluation of suspected obstructive CAD. Inclusions: symptoms suggestive of angina pectoris and age > 18 yrs. **Exclusion criteria** Unstable angina pectoris or acute coronary syndrome, arrhythmia including atrial fibrillation and tachycardia higher than 85 bpm, known diastolic cardiac murmur, left ventricle ejection fraction <50 %, previous thoracic and cardiac surgery, severe chronic obstructive lung disease or asthma with inability to perform a breath hold for 8 s, active treatment for cancer or organ transplantation, and pregnancy. **Patient characteristics** 109 (48 %) patients were referred to CCTA and 119 (52 %) to ICA. Based on the results of the CCTA and ICA, the patients were grouped into non-CAD (n = 124), non-obstructive CAD (n = 41), and obstructive CAD (n = 63) Of those who had obstructive CAD: 11 (70%) had 1-vessel disease, 12 (22%) had 2-vessel disease and 5 (8%) had 3-vessel disease or left main.

	Non CAD (N = 124),	Non-obstructive CAD (N = 41)	Obstructive CAD (N = 63)
Age	58.9 ± 11.1	64.5 ± 9.4	65.3 ± 9.2
Gender (Male)	51 (41 %)	22 (54 %)	48 (76 %)
BMI	27.4 ± 4.5	25.2 ± 2.8	26.6 ± 4.0
Systolic blood pressure	137 ± 19	145 ± 20	143 ± 18
Diastolic	81 ± 10	82 ± 12	82 ± 11
Smoking			
Actively	28 (23 %)	8 (20 %)	11 (17 %)
Previous	41 (33 %)	13 (32 %)	37 (59 %)
None	54 (44 %)	19 (46 %)	15 (24 %)

Bibliographic reference	Winther et al. (2016) Diagnosing coronary artery disease by sound analysis from coronary stenosis induced turbulent blood flow: diagnostic performance in patients with stable angina pectoris. International Journal of Cardiovascular Imaging, -, 2015			
	Total cholesterol	5.1 ± 1.1	5.1 ± 1.2	5.0 ± 1.1
	Diabetes	8 (6 %)	4 (10 %)	9 (14 %)
	Previous percutaneous coronary intervention	1 (1 %)	5 (12 %)	17 (27 %)
	Diamond–Forrester score, mean	25 ± 17	34 ± 21	51 ± 22
	Diamond–Forrester risk categories			
	Very low,<10 %	27 (22 %)	1 (2 %)	1 (2 %)
	Low, ≥ 10 to < 30 %	56 (45 %)	20 (49 %)	14 (22 %)
	Moderate, ≥ 30 to <60 %	34 (27 %)	13 (32 %)	21 (33 %)
	High, ≥ 60 %	7 (6 %)	7 (17 %)	27 (43 %)
	Cardiac imaging characteristics			
	Left ventricle ejection fraction by echo	61 ±4	60 ±4	60 ± 3
	Coronary artery calcium score, mean	64 ± 147	414 ± 465	1130 ± 1293
	Coronary artery calcium score groups = 0	70 (57 %)	2 (5 %)	2 (3 %)
	Coronary artery calcium score groups > 0 and < 400	47 (38 %)	22 (54 %)	23 (38 %)
	Coronary artery calcium score groups ≥ 400	6 (5 %)	17 (42 %)	36 (59 %)
Number of patients	N = 228, N = 109 referred to CCTA and N = 119 referred to ICA			
Probability score / model	**CAD-score recording and algorithm:** An acoustic sensor with an optimized computerized algorithm and recording principle. The acoustic sensor system recording site is the fourth left intercostal space. The automatic algorithm identifies acoustic properties of the diastolic heart sound statistically related to CAD.			

Bibliographic reference	**Winther et al. (2016) Diagnosing coronary artery disease by sound analysis from coronary stenosis induced turbulent blood flow: diagnostic performance in patients with stable angina pectoris. International Journal of Cardiovascular Imaging, -, 2015**
	Updated Diamond-Forrester score (no detail provided, Genders 2011 cited.) **Coronary artery calcium score (CACS)** (no detail provided)
Reference standard (or Gold standard)	**Coronary computed tomography (CCTA)** Computed tomography scans were acquired using a dual source multidetector scanner. All included patients underwent a non-enhanced scan from which CACS were calculated with the Agatston method. Patients referred for CCTA subsequently underwent a contrast-enhanced scan with prospective electrocardiogram gating and dose modulation in the systolic or diastolic phases depending on heart rate. All coronary segments were analysed according to standard clinical practice with the use of commercially available software. The stenosis severity was obtained in the following manner: no stenosis: 0 % diameter reduction; mild to moderate stenosis: 1–49 % diameter reduction; and severe stenosis: 50–100 % diameter reduction. Abnormal CCTA results were defined as a segment with a diameter greater than 2 mm and a more than 50 % reduction in luminal diameter. **Invasive coronary angiography** ICA was performed using standard techniques in a clinical setting. Coronary segments with a reference diameter larger than 2 mm and more than 30 % diameter stenosis were categorized as having CAD (non-obstructive or obstructive).
Time between testing & treatment	Not reported.
Length of follow-up	Not reported.
Location	Denmark
Diagnostic accuracy measures (2 x 2 table)	Diagnostic accuracy of obstructive CAD vs non-obstructive CAD. **CAD-score** = 0.72 (CI 0.65 – 0.79) **Updated Diamond- Forrester** = 0.79 (CI 0.72 – 0.86 %) **CAD-score + Diamond-Forrester** = 0.82 (CI 0.76 – 0.88) higher compared to both standalone CAD-score ($p<0.01$) and the Diamond-Forrester score ($p<0.05$) and no difference compared to CACS alone ($p = 0.28$)

Bibliographic reference	**Winther et al. (2016) Diagnosing coronary artery disease by sound analysis from coronary stenosis induced turbulent blood flow: diagnostic performance in patients with stable angina pectoris. International Journal of Cardiovascular Imaging, -, 2015**
	CAD-score + Diamond-Forrester with CACS = AUC: 0.87 (CI 0.82 – 0.92)
Source of funding	Danish National Business Innovation Fund and Acarix A/S.
Comments	**Study limitations:** Single tests (e.g. acoustic CAD-score) were outside the remit of this review of clinical prediction models. The models developed to combine this test variable (and coronary artery calcium score) with the Diamond –Forrester prediction score were not validated in a separate cohort, so data were not extracted for evidence appraisal. QUADAS-2: 1A - LOW 1B – All patients were scheduled for CTCA (and Ca scoring, plus CA if prior tests were abnormal): UNCLEAR 2A - LOW 2B - LOW 3A – Not clear if reference standard was interpreted without knowledge of patients' probability scores / clinical data: UNCLEAR 3B - LOW 4 - LOW

[1] *<Insert Note here>*

Bibliographic reference	**Yalcin et al. (2012) Cardiovascular risk scores for coronary atherosclerosis, Acta Cardiologica, 67, 557-563.**
Study type	Cross-sectional
Aim	To compare frequently used cardiovascular risk scores in predicting the presence of coronary artery disease (CAD) and 3-vessel disease.
Patient characteristics	**Inclusion criteria** Patients who had diagnostic coronary angiography. **Exclusion criteria** Previous coronary bypass surgery, previous percutaneous coronary intervention, acute coronary syndrome, left

Bibliographic reference	Yalcin et al. (2012) Cardiovascular risk scores for coronary atherosclerosis, Acta Cardiologica, 67, 557-563.
	main coronary artery disease, valvular heart disease, cardiomyopathy, peripheral artery disease or other vascular diseases such as vasculitis, aortic aneurysm and arrhythmia. **Patient characteristics** Men (N = 218) / Women (N = 132) Age (yrs): 58±14 / 62 ± 10 BMI (kg/m^2): 26 ± 4 / 27 ± 5 Systolic blood pressure (mm Hg): 143 ± 25 / 148 ± 23 Diastolic blood pressure (mm Hg): 80 ± 9 / 81 ± 10 Smoking: 101 (46%) / 12 (9%) Family history: 51 (23%) / 30 (23%) Hypertension: 123 (56%) / 96 (73%) Diabetes mellitus: 43 (20%) / 51 (39%) Total cholesterol (mmol/L): 4.9 ± 1.2 / 5.1 ± 1.0
Number of patients	N = 350
Probability score / model	Framingham risk score (**FRS**) and **PROCAM**: categorised into 3 groups based on risk percentages (low, < 10%; intermediate 10% - 20% and high > 20%). Modified FRS (**MFRS**): the diabetic patients were evaluated in the high risk group differently than the FRS. **SCORE**: 2 different scales were developed based on the total cholesterol (low and high-risk regions). In this tool, patients were categorised to 3 different risk groups according to risk levels (low < 5%, intermediate 5 – 8%, high > 8%.
Reference standard (or Gold standard)	Coronary angiography was performed using standard methods. Studies were examined independently by 2 experienced invasive cardiologists. The patients without any angiographic evidence of coronary atherosclerosis with normal contrast filling and clearance were grouped as normal coronary artery group. The coronary artery disease (CAD) group included patients with angiographic evidence of atherosclerotic lesions that were clearly seen, regardless of degree of stenosis. Major CAD included disease with > 50% stenosis in any epicardial artery or any side branch of > 2.5 mm that supplied a large portion of the myocardium and all other atherosclerotic

<table>
<tr><td>Bibliographic reference</td><td>Yalcin et al. (2012) Cardiovascular risk scores for coronary atherosclerosis, Acta Cardiologica, 67, 557-563.</td></tr>
<tr><td></td><td>lesions were accepted as not clinically relevant. The severity of CAD was assessed by the number of diseased vessels in the major CAD group. Results for prediction of CAD refer to all patients with CAD, both clinically important and not relevant.</td></tr>
<tr><td>Time between testing & treatment</td><td>Not reported</td></tr>
<tr><td>Length of follow-up</td><td>Patients who had CA between January 2006 – January 2007</td></tr>
<tr><td>Location</td><td>Turkey</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>Area under the ROC curve:

<u>CAD</u>

FRS: 0.76 (95% CI: 0.69 – 0.82)
MFRS: 0.73 (95% CI: 0.67 – 0.79)
PROCAM score: 0.69 (95% CI: 0.62 – 0.75)
SCORE (High risk regions): 0.65 (95% CI: 0.59 – 0.72)
SCORE (low risk regions): 0.58 (95% CI: 0.51 – 0.66)

<u>3-vessel disease</u>

FRS: 0.74 (95% CI: 0.60 – 0.77)
MFRS: 0.65 (95% CI: 0.56 – 0.74)
PROCAM score: 0.68 (95% CI: 0.60 – 0.77)
SCORE (High risk regions): 0.70 (95% CI: 0.61 – 0.79)
SCORE (low risk regions): 0.61 (95% CI: 0.51 – 0.71)

Sensitivity and specificity

The threshold for all probability scores was CAD = ‘high risk’ category (vs. ‘intermediate/low risk’ = no CAD)

<table>
<tr><th></th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr>
<tr><td><u>CAD</u></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Yalcin et al. (2012) Cardiovascular risk scores for coronary atherosclerosis, Acta Cardiologica, 67, 557-563.**		
	FRS	42 (41 – 43)	91 (90 – 92)
	MFRS	46 (45 – 47)	74 (73 – 75)
	PROCAM	29 (28 – 30)	95 (94 – 96)
	SCORE (High risk regions)	19 (18 – 20)	97 (96 – 98)
	SCORE (low risk regions):	3 (1 – 5)	100 (98 – 100)
	3-vessel disease		
	FRS	58 (57– 59)	74 (73 – 75)
	MFRS	53 (52 – 54)	63 (62 – 64)
	PROCAM	35 (34 – 36)	91 (89 – 91)
	SCORE (High risk regions)	31 (30 – 32)	90 (89 – 91)
	SCORE (low risk regions):	8 (7 – 9)	99 (98 – 100)
Source of funding	None reported.		
Comments	**Study limitations:** QUADAS-2: 1A - LOW 1B – Chest pain not reported; all patients had been referred for diagnostic CA: HIGH 2A –all models: LOW 2B – all models: LOW 3A - Not clear if reference standard was interpreted without knowledge of patients' probability scores / clinical data: UNCLEAR 3B - LOW 4 - LOW		

[1] *<Insert Note here>*

Bibliographic reference	**Yang et al. (2015) A Clinical model to identify patients with high-risk coronary artery disease, JACC: Cardiovascular Imaging 8: 427-434.**
Study type	Cross-sectional

Bibliographic reference	**Yang et al. (2015) A Clinical model to identify patients with high-risk coronary artery disease, JACC: Cardiovascular Imaging 8: 427-434.**
Aim	To develop a clinical model that identifies patients with and without high risk coronary artery disease (CAD).
Patient characteristics	**Inclusion criteria**: Consecutive patients referred to coronary CTA for suspected CAD were included in the study. **Exclusion criteria:** Patients with documented CAD or a history of myocardial infarction, coronary revascularisation, cardiac transplantation and congenital heart disease were excluded from the analysis. **Patient characteristics** (see reference standard for definition of high-risk)
Number of patients	N = 7,333 (validation cohort)

Validation cohort (N=7,333)	**High-risk CAD (N = 349)**	**Non High-risk CAD (N = 6984)**
Mean age, yrs	63 ± 10.3	57 ± 11.7
Mean BMI, kg/m^2	27 ± 4.9	28.8 ± 7.0
Male	242 (69.3)	3671 (52.6)
Hypertension	241 (69.1)	3799 (54.4)
Diabetes	136 (39.0)	1393 (20.0)
Hyperlipidemia	199 (57.0)	3591 (51.4)
Current smoking	86 (24.6)	1313 (18.8)
PVD history	14 (4.0)	217 (3.1)
Symptoms		
Asymptomatic	103 (29.5)	2316 (33.2)
Atypical	155 (44.4)	3509 (50.2)
Typical	91 (26.1)	1159 (16.6)
Family history of CAD	98 (28.1)	2752 (39.4)

Bibliographic reference	**Yang et al. (2015) A Clinical model to identify patients with high-risk coronary artery disease, JACC: Cardiovascular Imaging 8: 427-434.**
Probability score / model	**HRA score (novel clinical prediction model)** Derived from multivariable logistic regression in derivation cohort (n=24,251), applying a scoring system developed by assigning points for each variable demonstrated by the FRS. Model includes age, sex, diabetes, hyperlipidaemia, hypertension, current smoking, chest pain symptoms, family histpry of CAD, peripheral vascular disease. Validated in separate cohort (n=7,333). 3 risk categories: Low (≤7 points), intermediate (8 to 17points),and high (≥18 points). **Updated D-F (Genders)** Applied to derivation cohort (n=24,251) for the purpose of comparison with the new HRA model.
Reference standard (or Gold standard)	**CCTA**: single or dual-source 64-slice CT scanners. Coronary artery diameter stenosis was graded using a 4-point score (normal or mild, 50%; moderate 50% - 69% or severe ≥ 70%). Patients were further categorised according to presence and absence of high-risk CAD, defined as left main coronary artery stenosis (≥50%), 3-vessel disease (≥70%) or 2-vessel disease (≥70%) involving the proximal left anterior descending artery.
Time between testing & treatment	Not reported.
Length of follow-up	Patients referred for CTCA between 2005– 2009 were enrolled.
Location	Data from CONFIRM registry (12 sites across 6 countries: US, Canada, Austria, Germany, Italy, Switzerland, Korea)
Diagnostic accuracy measures (2 x 2 table)	**Area under the curve**: Reference: presence of high-risk CAD = as left main coronary artery stenosis (≥50%), 3-vessel disease (≥70%) or 2-vessel disease (≥70%) involving the proximal left anterior descending artery 1. HRA model: 0.71 (95% CI: 0.69 – 0.74) (validation cohort) 2. Updated D-F (Genders) model: 0.64 (95% CI 062 to 0.67) (derivation cohort)
Source of funding	None reported
Comments	**Study limitations:** 1A – Not clear if patients were consecutively enrolled: UNCLEAR

Bibliographic reference	Yang et al. (2015) A Clinical model to identify patients with high-risk coronary artery disease, JACC: Cardiovascular Imaging 8: 427-434.
	1B – All patients had been referred for CTCA: UNCLEAR 2A – all models: LOW 2B – all models: LOW 3A - 3A - Not clear if reference standard was interpreted without knowledge of patients' probability scores / clinical data: UNCLEAR 3B - LOW 4 - LOW

Appendix H: QUADAS-2 Quality Assessment Summary

H.1 Review question 1

Table 79: QUADAS-2 Quality assessment ratings for risk of bias and applicability with corresponding GRADE quality ratings.

		Risk of bias					Applicability concerns			
		QUADAS 2				Overall	QUADAS 2			Overall
Study	Index test(s)	Patient selection 1a	Index test 2a	Reference standard 3a	Flow and timing 4		Patient selection 1b	Index test 2b	Reference standard 3b	
Arnold et al 2010	4a, 4b, 4a+4b	UNCLEAR	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Bettencourt et al 2011	2,9, 2+9	LOW	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Budoff et al 1998	7	LOW	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Budoff et al 2007	7	UNCLEAR	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Budoff et al 2008	2	UNCLEAR	LOW	LOW	UNCLEAR	**S**	HIGH	LOW	LOW	**S**
Budoff et al 2013	2, 3	HIGH	UNCLEAR	LOW	LOW	**S**	HIGH	LOW	LOW	**S**
Cadimartiri et al 2007	2	LOW	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Cadimartiri et al 2008	2	UNCLEAR	UNCLEAR	HIGH	LOW	**VS**	UNCLEAR	LOW	LOW	**NS**
Carrascosa et al 2010	2	LOW	LOW	LOW	LOW	**NS**	LOW	HIGH	LOW	**S**
Chen et al 2011	2	LOW	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Cramer et al 1997	7	LOW	HIGH	HIGH	LOW	**VS**	HIGH	LOW	LOW	**S**
Di Bello et al 1996a	4b,7	LOW	HIGH	LOW	LOW	**S**	UNCLEAR	LOW	LOW	**NS**
Di Bello et al 1996b	4b,7	LOW	LOW	LOW	LOW	**NS**	UNCLEAR	LOW	LOW	**NS**
Donati et al 2010	2	UNCLEAR	LOW	LOW	UNCLEAR	**S**	HIGH	LOW	LOW	**S**
Fleming et al 1992	7	HIGH	LOW	HIGH	LOW	**VS**	HIGH	UNCLEAR	LOW	**S**
Fujitaka et al 2009	2, 2+7	LOW	LOW	LOW	LOW	**NS**	UNCLEAR	LOW	LOW	**NS**
Hennessy et al 1998	4b	UNCLEAR	LOW	LOW	LOW	**NS**	LOW	HIGH*	LOW	**S**
Herzog et al 2007	2	LOW	LOW	LOW	UNCLEAR	**NS**	UNCLEAR	LOW	LOW	**NS**

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		Risk of bias					Applicability concerns			
		QUADAS 2				Overall	QUADAS 2			Overall
Herzog et al 2008	2	LOW	LOW	LOW	UNCLEAR	NS	HIGH	LOW	LOW	S
Herzog et al 2009	2	LOW	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Hoffmann et al 1993	4b	HIGH	HIGH	LOW	LOW	VS	HIGH	LOW	LOW	S
Javadrashid et al 2009	3	LOW	UNCLEAR	UNCLEAR	LOW	S	HIGH	LOW	LOW	S
Kaminek et al 2015	7	UNCLEAR	HIGH	HIGH	LOW	VS	HIGH	LOW	UNCLEAR	S
Kawase et al 2004	6	LOW	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Klein et at 2008	6	LOW	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Klem et al 2006	6	LOW	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Krittayaphong et al 2009	6	UNCLEAR	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Marangelli et al 1994	4b	LOW	LOW	HIGH	LOW	S	HIGH	LOW	LOW	S
Marwick et al 1993	4b,7	UNCLEAR	HIGH	LOW	LOW	S	HIGH	LOW	LOW	S
Mazeika et al 1991	4b	UNCLEAR	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Meng et al 2009	2	UNCLEAR	LOW	LOW	LOW	NS	UNCLEAR	LOW	LOW	NS
Miszalaski-Jamka et al 2012	4a	LOW	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Muhlenbruch et al 2007	2	HIGH	LOW	LOW	UNCLEAR	S	HIGH	LOW	LOW	S
Nagel et al 1999	4b, 5	LOW	LOW	LOW	LOW	NS	UNCLEAR	LOW	LOW	NS
Nazeri et al 2009	2	LOW	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Nieman et al 2009	2	HIGH	LOW	LOW	UNCLEAR	S	HIGH	LOW	LOW	S
Nixdorff et al 2008	4b	LOW	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Onishi et al 2010	4a	LOW	LOW	UNCLEAR	LOW	NS	UNCLEAR	LOW	LOW	NS
Overhus et al 2010	2	UNCLEAR	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Parodi et al 1999	4b	UNCLEAR	UNCLEAR	LOW	LOW	S	UNCLEAR	LOW	LOW	NS
Piers et al 2008	2	HIGH	LOW	LOW	LOW	S	HIGH	LOW	LOW	S
Pontone et al 2014	2	HIGH	LOW	LOW	LOW	S	HIGH	LOW	LOW	S
Pugliese et al 2008	2	HIGH	LOW	LOW	LOW	S	HIGH	LOW	LOW	S
Raff et al 2005	2	LOW	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Ropers et al 2006	2	UNCLEAR	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Rixe et al 2009	2	LOW	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S

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		Risk of bias					Applicability concerns			
		QUADAS 2				Overall	QUADAS 2			Overall
San Roman et al 1996	4b	LOW	LOW	LOW	LOW	**NS**	UNCLEAR	LOW	LOW	**NS**
San Roman et al 1998	4b,7	LOW	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Santoro et al 1998	4b, 7	UNCLEAR	LOW	UNCLEAR	LOW	**S**	LOW	LOW	LOW	**NS**
Schepis et al 2007	7, 3+7	UNCLEAR	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Senior et al 2004	4b, 7	UNCLEAR	LOW	UNCLEAR	LOW	**S**	HIGH	LOW	LOW	**S**
Severi et al 1993	4b	HIGH	LOW	LOW	LOW	**S**	HIGH	LOW	LOW	**S**
Shaikh et al 2014	4b	HIGH	LOW	LOW	LOW	**S**	HIGH	LOW	LOW	**S**
Sheikh et al 2009	2	LOW	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Stolzmann et al 2011	6, 3+6	LOW	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Swailam et al 2010	2	UNCLEAR	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Thomassen et al 2013	2,7,2+7	UNCLEAR	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Van Werkhoven et al 2010	2	UNCLEAR	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Von Ziegler 2014	3	LOW	LOW	LOW	LOW	**NS**	HIGH	LOW	LOW	**S**
Yao et al 2004	7	LOW	LOW	LOW	UNCLEAR	**NS**	HIGH	LOW	LOW	**S**

H.2 Review question 2

Study	Model	Risk of bias				GRADE	Applicability concerns			GRADE
		Patient selection 1a	Index test 2a	Reference standard 3a	Flow and timing 4a	Risk of bias	Patient selection 1b	Index test 2b	Reference standard 3b	Indirectness
Caselli 2015a	FRS	UNCLEAR	LOW	UNCLEAR	LOW	**S**	HIGH	LOW	LOW	**S**
Caselli 2015b	Updated D-F (Genders)	UNCLEAR	LOW	UNCLEAR	UNCLEAR	**VS**	HIGH	LOW	UNCLEAR	**S**
	EVINCI	UNCLEAR	LOW	UNCLEAR	UNCLEAR	**VS**	HIGH	HIGH	UNCLEAR	**VS**
Chen 2014	D-F	LOW	LOW	UNCLEAR	LOW	**NS**	HIGH	LOW	LOW	**S**
	SPS	LOW	LOW	UNCLEAR	LOW	**NS**	HIGH	HIGH	LOW	**VS**

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Study	Model	Risk of bias				GRADE	Applicability concerns			GRADE
Gaibazzi 2015	FRS	UNCLEAR	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
	DICAD	UNCLEAR	LOW	LOW	LOW	NS	HIGH	HIGH	LOW	VS
Genders 2010	D-F	UNCLEAR	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
	Duke Clinical Score	UNCLEAR	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
	Morise 1994	UNCLEAR	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
	Morise 1997	UNCLEAR	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Genders 2011	D-F	UNCLEAR	LOW	UNCLEAR	LOW	S	HIGH	LOW	LOW	S
	Updated D-F (Genders)	UNCLEAR	LOW	UNCLEAR	LOW	S	LOW	LOW	LOW	NS
Genders 2012	Duke Clinical Score	UNCLEAR	LOW	UNCLEAR	LOW	S	UNCLEAR	LOW	LOW	NS
	Updated D-F (Genders)	UNCLEAR	LOW	UNCLEAR	LOW	S	UNCLEAR	LOW	LOW	NS
	Clinical model (Genders + risk factors)	UNCLEAR	LOW	UNCLEAR	LOW	S	UNCLEAR	LOW	LOW	NS
	DICAD	UNCLEAR	LOW	UNCLEAR	LOW	S	UNCLEAR	HIGH	LOW	VS
Hong 2012	Morise 1997	LOW	LOW	UNCLEAR	LOW	NS	HIGH	LOW	LOW	S
	D-F	LOW	LOW	UNCLEAR	LOW	NS	HIGH	LOW	LOW	S
Hwang 2010	FRS	HIGH	LOW	UNCLEAR	LOW	S	HIGH	LOW	LOW	S
Jensen 2012	D-F	LOW	LOW	HIGH	LOW	S	HIGH	LOW	LOW	S
	Updated D-F (Genders)	LOW	LOW	HIGH	LOW	S	HIGH	LOW	LOW	S
	Duke Clinical Score	LOW	LOW	HIGH	LOW	S	HIGH	LOW	LOW	S
	Morise 1997	LOW	LOW	HIGH	LOW	S	HIGH	LOW	LOW	S
	CORSCORE	LOW	LOW	HIGH	LOW	S	HIGH	LOW	LOW	S
Kotecha 2010	FRS	LOW	LOW	UNCLEAR	LOW	NS	HIGH	LOW	LOW	S

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Study	Model	Risk of bias				GRADE	Applicability concerns			GRADE
	SCORE- high risk	LOW	LOW	UNCLEAR	LOW	NS	HIGH	LOW	LOW	S
Kumamaru 2014	Duke Clinical Score	HIGH	LOW	UNCLEAR	LOW	S	UNCLEAR	LOW	LOW	NS
Park 2011	Age-adjusted FRS (AFRS)	LOW	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
Pickett 2013	D-F	LOW	LOW	UNCLEAR	LOW	NS	UNCLEAR	LOW	LOW	NS
	Morise 1997	LOW	LOW	UNCLEAR	LOW	NS	UNCLEAR	LOW	LOW	NS
Rademaker 2014	D-F	LOW	LOW	UNCLEAR	LOW	NS	HIGH	LOW	LOW	S
	Duke Clinical Score	LOW	LOW	UNCLEAR	LOW	NS	HIGH	LOW	LOW	S
	Updated D-F (Genders)	LOW	LOW	UNCLEAR	LOW	NS	HIGH	LOW	LOW	S
	Morise 1997	LOW	LOW	UNCLEAR	LOW	NS	HIGH	LOW	LOW	S
Rosenberg 2010	D-F	UNCLEAR	LOW	LOW	LOW	NS	HIGH	LOW	LOW	S
	Combined D-F + gene expression algorithm	UNCELAR	LOW	LOW	LOW	NS	HIGH	HIGH	LOW	VS
Shmilovich 2014	D-F	LOW	LOW	UNCLEAR	LOW	NS	UNCLEAR	LOW	LOW	NS
Versteylen 2011	D-F	UNCLEAR	LOW	LOW	LOW	NS	UNCLEAR	LOW	LOW	NS
	FRS	UNCLEAR	LOW	LOW	LOW	NS	UNCLEAR	LOW	LOW	NS
	PROCAM	UNCLEAR	LOW	LOW	LOW	NS	UNCLEAR	LOW	LOW	NS
	SCORE	UNCLEAR	LOW	LOW	LOW	NS	UNCLEAR	LOW	LOW	NS
Wasfy 2012	D-F	LOW	LOW	HIGH	LOW	S	UNCLEAR	LOW	LOW	NS
	Duke Clinical Score	LOW	LOW	HIGH	LOW	S	UNCLEAR	LOW	LOW	NS
Winther 2016	Update D-F (Genders)	LOW	LOW	UNCLEAR	LOW	NS	UNCLEAR	LOW	LOW	NS
Yalcin 2012	FRS	LOW	LOW	UNCLEAR	LOW	NS	HIGH	LOW	LOW	S
	Modified FRS (mFRS)	LOW	LOW	UNCLEAR	LOW	NS	HIGH	LOW	LOW	S
	PROCAM	LOW	LOW	UNCLEAR	LOW	NS	HIGH	LOW	LOW	S
	SCORE- high risk	LOW	LOW	UNCLEAR	LOW	NS	HIGH	LOW	LOW	S

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Study	Model	Risk of bias				GRADE	Applicability concerns			GRADE
	SCORE- low risk	LOW	LOW	UNCLEAR	LOW	**NS**	HIGH	LOW	LOW	**S**
Yang 2015	Update D-F (Genders)	UNCLEAR	LOW	UNCLEAR	LOW	**S**	UNCELAR	LOW	LOW	**NS**
	HRA score	UNCLEAR	LOW	UNCLEAR	LOW	**S**	UNCELAR	LOW	LOW	**NS**

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Appendix I: GRADE profiles

I.1 Review question 1

Number of studies	Number of participants	Risk of bias	Indirectness	Inconsistency	Imprecision	TP	FP	FN	TN	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	GRADE quality
Index test 2: CTCA – 50% stenosis												
25[1]	2058	NS	S[2]	VS[3]	NS	1072	208	26	752	0.96 (0.94 to 0.97)	0.79 (0.72 to 0.84)	VERY LOW
Index test 2: CTCA – 70% stenosis												
3[4]	371	S[5]	S[6]	VS[7]	S[8]	112	54	3	202	0.96 (0.88 to 0.99)	0.72 (0.55 to 0.85)	VERY LOW
Index test 3: Calcium scoring – 50% stenosis, Threshold: 0 Hounsfield units												
2[9]	8504	NS	S[10]	VS[11]	S[12]	2124	2848	22	3510	0.99 (0.97 to 0.99)	0.49 (0.36 to 0.63)	VERY LOW
Index test 3: Calcium scoring – 50% stenosis, Threshold: 400 Hounsfield units												
2[13]	8504	NS	S[14]	NS	NS	1168	788	978	5570	0.54 (0.52 to 0.57)	0.88 (0.87 to 0.88)	MODERATE
Index test 3: Calcium scoring – 70% stenosis, Threshold: 0 Hounsfield units												
1[15]	8274	NS	S[16]	N/A	NS	723	4357	9	3185	0.99 (0.98 to 0.99)	0.42 (0.41 to 0.43)	MODERATE
Index test 3: Calcium scoring – 70% stenosis, Threshold: 400 Hounsfield units												
1[17]	8274	NS	S[18]	N/A	NS	618	1226	114	6316	0.84 (0.82 to 0.87)	0.84 (0.83 to 0.85)	MODERATE
Index test 4a: Stress echocardiography, perfusion – 50% stenosis												
3[19]	182	NS	S[20]	NS	NS	99	13	20	50	0.84 (0.76 to 0.90)	0.79 (0.69 to 0.86)	MODERATE

Number of studies	Number of participants	Risk of bias	Indirectness	Inconsistency	Imprecision	TP	FP	FN	TN	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	GRADE quality
Index test 4a: Stress echocardiography, perfusion – 70% stenosis												
1[21]	62	NS	S[22]	N/A	S[23]	26	9	3	24	0.90 (0.73 to 0.98)	0.73 (0.54 to 0.87)	LOW
Index test 4b: Stress echocardiography, wall motion – 50% stenosis, Stress method: vasoldilatation												
5[24]	422	NS	S[25]	VS[26]	S[27]	226	16	67	113	0.77 (0.69 to 0.83)	0.86 (0.68 to 0.95)	VERY LOW
Index test 4b: Stress echocardiography, wall motion – 50% stenosis, Stress method: heart rate modification												
8[28]	899	NS	NS	S[29]	NS	458	61	145	235	0.76 (0.72 to 0.79)	0.81 (0.71 to 0.88)	MODERATE
Index test 4b: Stress echocardiography, wall motion – 70% stenosis, Stress method: vasodilatation												
7[30]	767	S[31]	NS	VS[32]	S[33]	306	32	144	285	0.64 (0.49 to 0.76)	0.90 (0.86 to 0.93)	VERY LOW
Index test 4b: Stress echocardiography, wall motion – 70% stenosis, Stress method: heart rate modification												
4[34]	257	S[35]	S[36]	S[37]	S[38]	114	12	37	94	0.75 (0.62 to 0.85)	0.88 (0.79 to 0.93)	VERY LOW
Index test 5: Cardiac magnetic resonance, wall motion – 50% stenosis												
1[39]	172	NS	NS	N/A	NS	94	9	15	54	0.86 (0.78 to 0.92)	0.86 (0.75 to 0.93)	HIGH
Index test 6: Cardiac magnetic resonance, perfusion – 50% stenosis												
5[40]	331	NS	S[41]	NS	NS	155	22	29	125	0.84 (0.76 to 0.90)	0.85 (0.77 to 0.90)	MODERATE
Index test 6: Cardiac magnetic resonance, perfusion – 70% stenosis												
3[42]	204	NS	S[43]	VS[44]	S[45]	92	21	7	84	0.93 (0.84 to 0.97)	0.81 (0.56 to 0.93)	VERY LOW
Index test 7a: Myocardial Perfusion Scintigraphy, SPECT – 50% stenosis												
11[46]	923	S[47]	S[48]	VS[49]	NS	503	68	123	229	0.81 (0.74 to 0.86)	0.78 (0.70 to 0.85)	VERY LOW

Number of studies	Number of participants	Risk of bias	Indirectness	Inconsistency	Imprecision	TP	FP	FN	TN	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	GRADE quality
Index test 7a: Myocardial Perfusion Scintigraphy, SPECT – 70% stenosis												
3[50]	145	S[51]	S[52]	VS[53]	VS[54]	68	11	29	37	0.76 (0.44 to 0.93)	0.76 (0.58 to 0.88)	VERY LOW
Index test 7b: Myocardial Perfusion Scintigraphy, PET – 70% stenosis												
1[55]	44	NS	S[56]	N/A	S[57]	20	3	2	19	0.91 (0.71 to 0.99)	0.86 (0.65 to 0.97)	LOW
Index test 9: CT Perfusion – 50% stenosis												
1[58]	90	NS	S[59]	N/A	S[60]	26	0	22	42	0.54 (0.39 to 0.69)	1.00 (0.92 to 1.00)	LOW
Index test 9: CT Perfusion – 70% stenosis												
1[61]	90	NS	S[62]	N/A	S[63]	25	1	13	51	0.66 (0.49 to 0.80)	0.98 (0.90 to 1.00)	LOW

1. *Bettencourt 2011, Budoff 2008, Cademartiri 2007, Cademartiri 2008, Carrascosa 2010, Chen et al 201, Donati 2007, Fujitaka 2009, Herzog 2007, Herzog 2008, Herzog 2009, Meng 2009, Nazeri 2009, Nieman 2009, Overhus 2010, Piers 2008, Pontone 2014, Pugliese 2008, Raff 2005, Rixe 2009, Ropers 2006, Sheikh 2009, Swailam 2010, Thomassen 2013 , van Werkhoven 2010*
2. *21/25 of contributing trials had serious applicability issues according to QUADAS-2 checklist (see Table 79)*
3. *I^2 value for specificity (80%) indicates very substantial unexplained heterogeneity*
4. *Bettencourt 2011, Budoff 2008, Muhlenbruch 2007*
5. *2/3 of contributing trials had serious risk of bias issues according to QUADAS-2 checklist (see Table 79)*
6. *3/3 of contributing trials had serious applicability issues according to QUADAS-2 checklist (see Table 79)*
7. *I^2 value for specificity (79.2%) indicates very substantial unexplained heterogeneity*
8. *Confidence intervals for specificity exceed 20% range*
9. *Budoff 2013, von Zeigler 2014*
10. *2/2 contributing trials had serious applicability issues according to QUADAS-2 checklist (see Table 79)*
11. *I^2 value for specificity (92.1%) indicates very substantial unexplained heterogeneity*
12. *Confidence intervals for specificity exceed 20% range*
13. *Budoff 2013, von Zeigler 2014*
14. *2/2 contributing trials had serious applicability issues according to QUADAS-2 checklist (see Table 79)*
15. *von Zeigler 2014*
16. *Contributing trial had serious applicability issues according to QUADAS-2 checklist (see Table 79)*
17. *von Zeigler 2014*
18. *Contributing trial had serious applicability issues according to QUADAS-2 checklist (see Table 79)*

19. Arnold 2010, Miszalski-Jamka 2012, Onishi 2010
20. 3/3 contributing trials had serious applicability issues according to QUADAS-2 checklist (see Table 79)
21. Arnold 2010
22. Contributing trial had serious applicability issues according to QUADAS-2 checklist (see Table 79)
23. Confidence intervals for sensitivity and specificity exceed 20% range
24. Arnold 2010, Parodi 1999, San Roman 1996, San Roman 1998, Senior 2004
25. 3/5 contributing trials had serious applicability issues according to QUADAS-2 checklist (see Table 79)
26. I^2 value for specificity (76.6%) indicates very substantial unexplained heterogeneity
27. Confidence intervals for sensitivity and specificity exceed 20% range
28. Di Bello 1996a, Di Bello 1996b, Hennessy 1998, Marwick 1993, Nagel 1999, Onishi 2010, San Roman 1998, San Roman 1996
29. I^2 value for specificity (64.6%) indicates substantial unexplained heterogeneity
30. Arnold 2010, Marangelli 1994, Mazeika 1991, Santoro 1998, Senior 2004, Severi 1993, Shaikh 2013
31. 5/7 contributing trials had serious risk of bias issues according to QUADAS-2 checklist (see Table 79)
32. I^2 value for sensitivity (84.6%) indicates very substantial unexplained heterogeneity
33. Confidence intervals for sensitivity exceeds 20% range
34. Marangelli 1994, Nixdorff 2007, Santoro 1998,Hoffman 1993
35.3/4 contributing trials had serious or very serious risk of bias issues according to QUADAS-2 checklist (see Table 79)
36. 3/4 contributing trials had serious applicability issues according to QUADAS-2 checklist (see Table 79)
37. I^2 value for sensitivity (64.0%) indicates substantial unexplained heterogeneity
38. Confidence intervals for sensitivity exceeds 20% range
39. Nagel 1999
40. Arnold 2010, Klein 2008, Klem 2006, Krittayaphong 2009, Stolzmann 2011
41. 5/5 contributing trials had serious applicability issues according to QUADAS-2 checklist (see Table 73)
42. Arnold 2010, Klem 2006, Kawase 2004
43. 3/3 contributing trials had serious applicability issues according to QUADAS-2 checklist (see Table 73)
44. I^2 value for specificity (82.9%) indicates very substantial unexplained heterogeneity
45. Confidence intervals for specificity exceeds 20% range
46. Budoff 1998, Cramer 1997, Di Bello 1996a, Di Bello 1996b, Fleming 1992, Kaminek 2015, Marwick 1993, San Roman 1998, Schepis 2007, Senior 2004, Yao 2004
47. 6/11 contributing trials had serious or very serious risk of bias issues according to QUADAS-2 checklist (see Table 73)
48. 9/11 contributing trials had serious applicability issues according to QUADAS-2 checklist (see Table 73)
49. I^2 value for sensisitivity (75.0%) indicates very substantial unexplained heterogeneity
50. Budoff 2007, Santoro 1998, Senior 2004
51. 2/3 contributing trials had serious risk of bias issues according to QUADAS-2 checklist (see Table 73)
52. 2/3 contributing trials had serious applicability issues according to QUADAS-2 checklist (see Table 73)
53. I^2 value for sensisitivity (88.4%) indicates very substantial unexplained heterogeneity
54. Confidence intervals for sensitivity exceeds 40% range. Confidence intervals for specificity exceeds 20% range
55. Thomassen 2013
56. Contributing trial had serious applicability issues according to QUADAS-2 checklist (see Table 73)
57. Confidence intervals for specificity exceeds 20% range
58. Bettencourt 2011
59. Contributing trial had serious applicability issues according to QUADAS-2 checklist (see Table 73)
60. Confidence intervals for sensitivity exceeds 20% range
61. Bettencourt 2011
62. Contributing trial had serious applicability issues according to QUADAS-2 checklist (see Table 73)
63. Confidence intervals for sensitivity exceeds 20% range

Modified GRADE profile – Combined analyses – CTCA + Myocardial Perfusion Scintigraphy (Index tests 2+7)

Study ID	N	Risk of bias	Indirectness	Imprecision	Inconsistency	TP	FP	FN	TN	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	GRADE quality
50% Stenosis												
C Chest pain, combination of types (typical, atypical or non-cardiac)												
Fujitaka et al 2009	125	NS	NS	S[3]	N/A	48	4	3	70	0.94 (0.84, 0.99)	0.95 (0.87, 0.99)	MODERATE
Thomassen et al 2013	44	NS	S[2]	S[3]	N/A	20	0	2	22	0.91 (0.71, 0.99)	1.00 (0.85, 1.00)	LOW

Quality ratings
(NS) No serious risk
(S) Serious
1. *Risk of bias: 2/4 QUADAS-2 domains rated as UNCLEAR or at least 1 rated as HIGH*
2. *Indirectness: 2/3 QUADAS-2 domains rated as UNCLEAR or 1 rated as HIGH with at least 1 UNCLEAR*
3. *Imprecision: 95% CIs for either Sensitivity or Specificity exceeds a range of 20%*

(VS) Very Serious
4. *Risk of bias: 3/4 or more QUADAS-2 domains rated as UNCLEAR or 1 rated as HIGH with 2 UNCLEAR, or 2 or more rated as HIGH*
5. *Indirectness: 2/3 QUADAS-2 domains rated as UNCLEAR or 1 rated as HIGH with 2 UNCLEAR, or 2 or more rated as HIGH*
6. *Imprecision: 95% CIs for either Sensitivity or Specificity exceeds a range of 40%*

Modified GRADE profile – Combined analyses – CTCA + CT Perfusion (Index tests 2+9)

Study ID	N	Risk of bias	Indirectness	Imprecision	Inconsistency	TP	FP	FN	TN	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	GRADE quality
50% Stenosis												
B Suspected CAD (with breakdown)												
Bettencourt et al 2011	90	NS	S[2]	S[3]	N/A	40	1	8	41	0.83 (0.70, 0.93)	0.98 (0.87, 1.00)	LOW

Study ID	N	Risk of bias	Indirectness	Imprecision	Inconsistency	TP	FP	FN	TN	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	GRADE quality
70% Stenosis												
B Suspected CAD (with breakdown)												
Bettencourt et al 2011	90	NS	S[2]	NS	N/A	36	3	2	49	0.95 (0.82, 0.99)	0.94 (0.84, 0.99)	MODERATE

Quality ratings
(NS) No serious risk
(S) Serious
1. *Risk of bias: 2/4 QUADAS-2 domains rated as UNCLEAR or at least 1 rated as HIGH*
2. *Indirectness: 2/3 QUADAS-2 domains rated as UNCLEAR or 1 rated as HIGH with at least 1 UNCLEAR*
3. *Imprecision: 95% CIs for either Sensitivity or Specificity exceeds a range of 20%*

(VS) Very Serious
4. *Risk of bias: 3/4 or more QUADAS-2 domains rated as UNCLEAR or 1 rated as HIGH with 2 UNCLEAR, or 2 or more rated as HIGH*
5. *Indirectness: 2/3 QUADAS-2 domains rated as UNCLEAR or 1 rated as HIGH with 2 UNCLEAR, or 2 or more rated as HIGH*
6. *Imprecision: 95% CIs for either Sensitivity or Specificity exceeds a range of 40%*

Modified GRADE profile – Combined analyses –Calcium Scoring and Stress CMR (Index tests 3+6)

Study ID	n	Risk of bias	Indirectness	Imprecision	Inconsistency	TP	FP	FN	TN	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	GRADE quality
50% Stenosis												
B Suspected CAD (with breakdown)												
Stolzmann et al 2011	60	NS	S[2]	S[3]	N/A	32	4	4	20	0.89 (0.74, 0.97)	0.83 (0.63, 0.95)	LOW

Quality ratings
(NS) No serious risk
(S) Serious
1. *Risk of bias: 2/4 QUADAS-2 domains rated as UNCLEAR or at least 1 rated as HIGH*
2. *Indirectness: 2/3 QUADAS-2 domains rated as UNCLEAR or 1 rated as HIGH with at least 1 UNCLEAR*

3. *Imprecision: 95% CIs for either Sensitivity or Specificity exceeds a range of 20%*

(VS) Very Serious

4. *Risk of bias: 3/4 or more QUADAS-2 domains rated as UNCLEAR or 1 rated as HIGH with 2 UNCLEAR, or 2 or more rated as HIGH*
5. *Indirectness: 2/3 QUADAS-2 domains rated as UNCLEAR or 1 rated as HIGH with 2 UNCLEAR, or 2 or more rated as HIGH*
6. *Imprecision: 95% CIs for either Sensitivity or Specificity exceeds a range of 40%*

Modified GRADE profile – Combined analyses –Calcium Scoring and Myocardial Perfusion Scintigraphy (SPECT) (Index tests 3+7)

Study ID	n	Risk of bias	Indirectness	Imprecision	Inconsistency	TP	FP	FN	TN	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	GRADE quality
50% Stenosis												
B Suspected CAD (with breakdown)												
Schepis et al 2007	77	NS	S[2]	S[3]	N/A	36	5	6	30	0.86 (0.71, 0.95)	0.86 (0.70, 0.95)	LOW

Quality ratings

(NS) No serious risk

(S) Serious

1. *Risk of bias: 2/4 QUADAS-2 domains rated as UNCLEAR or at least 1 rated as HIGH*
2. *Indirectness: 2/3 QUADAS-2 domains rated as UNCLEAR or 1 rated as HIGH with at least 1 UNCLEAR*
3. *Imprecision: 95% CIs for either Sensitivity or Specificity exceeds a range of 20%*

(VS) Very Serious

Modified GRADE profile – Combined analyses – Stress Echo Perfusion+Wall motion (Index tests 4a+4b)

Study ID	n	Risk of bias	Indirectness	Imprecision	Inconsistency	TP	FP	FN	TN	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	GRADE quality
50% Stenosis												
A Suspected CAD (No breakdown of numbers with chest pain)												
Arnold et al 2010	62	NS	S[2]	S[3]	N/A	35	5	6	16	0.85 (0.71, 0.94)	0.76 (0.53, 0.92)	LOW
70% Stenosis												

Study ID	n	Risk of bias	Indirectness	Imprecision	Inconsistency	TP	FP	FN	TN	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	GRADE quality
A Suspected CAD (No breakdown of numbers with chest pain)												
Arnold et al 2010	62	NS	S[2]	S[3]	N/A	28	12	1	21	0.97 (0.82, 1.00)	0.64 (0.45, 0.80)	LOW

Quality ratings
(NS) No serious risk
(S) Serious
4. *Risk of bias: 2/4 QUADAS-2 domains rated as UNCLEAR or at least 1 rated as HIGH*
5. *Indirectness: 2/3 QUADAS-2 domains rated as UNCLEAR or 1 rated as HIGH with at least 1 UNCLEAR*
6. *Imprecision: 95% CIs for either Sensitivity or Specificity exceeds a range of 20%*

(VS) Very Serious

I.2 Review question 2

I.2.1 Reference standard: coronary angiography (CA) – 50% stenosis

Number of studies	Number of participants	Risk of bias	Indirectness	Inconsistency	Imprecision	Area under the ROC curve Study c-statistic (95% CI)	Area under the ROC curve Median [range]	GRADE quality
Model: Diamond–Forrester								
5[1]	3473	No serious	Serious[2]	n/a	Very serious[3]	0.73 (not reported) 0.80 (0.74 to 0.85) 0.81 (0.79 to 0.83) 0.64 (not reported) 0.66 (0.61 to 0.71)	Median = 0.73 [range: 0.64 to 0.81]	VERY LOW

Number of studies	Number of participants	Risk of bias	Indirectness	Inconsistency	Imprecision	Area under the ROC curve Study c-statistic (95% CI)	Area under the ROC curve Median [range]	GRADE quality
Model: Framingham Risk Score								
3[4]	1334	No serious	Serious[5]	n/a	Serious[6]	0.67 (0.62 to 0.72) 0.74 (not reported) 0.76 (0.69 to 0.82)	Median = 0.74 [range: 0.67 to 0.76]	LOW
Model: Age-adjusted Framingham Risk Score								
1[7]	138	No serious	Serious[8]	n/a	No serious	0.86 (95% CI: 0.80 to 0.93)	n/a	MODERATE
Model: Modified Framingham Risk Score								
1[9]	350	No serious	Serious[8]	n/a	Serious[6]	0.73 (95% CI: 0.67 to 0.79)	n/a	LOW
Model: Duke Clinical Score								
4[10]	6242	Serious[11]	No serious	n/a	Very serious[3]	0.84 (0.79 to 0.89) 0.78 (0.76 to 0.81) 0.72 (not reported) 0.59 (not reported)	Median = 0.75, [range: 0.59 to 0.84]	VERY LOW
Model: Updated Diamond-Forrester (Genders)								
3[12]	5287	Serious[13]	No serious	n/a	No Serious	0.77 (not reported) 0.71 (not reported) 0.79 (0.72 to 0.86)	Median = 0.77, [range: 0.71 to 0.79]	MODERATE

Number of studies	Number of participants	Risk of bias	Indirectness	Inconsistency	Imprecision	Area under the ROC curve Study c-statistic (95% CI)	Area under the ROC curve Median [range]	GRADE quality
Model: Morise 1997								
2[14]	887	No serious	Serious[15]	n/a	Very serious[3]	0.84 (0.79 to 0.89) 0.68 (not reported)	Median = 0.76 [range: 0.68 to 0.84]	VERY LOW
Model: SCORE (– high risk regions)								
2[16]	889	No serious	Serious[15]	n/a	Serious[6]	0.75 (not reported) 0.65 (0.59 to 0.72)	Median = 0.70 [range: 0.65 to 0.75]	LOW
Model: Diagnostic Imaging for Coronary Artery Disease (DICAD)								
2[17]	4871	No serious	Very serious[18]	n/a	Very serious[3]	0.67 (0.62 to 0.73) 0.88 (not reported)	Median = 0.78 [range: 0.67 to 0.88]	VERY LOW
Model: PROCAM								
1[19]	350	No serious	Serious[20]	n/a	Serious[6]	0.69 (0.62 to 0.75)	n/a	LOW
Model: Morise 1994								
1[21]	254	No serious	Serious[20]	n/a	Serious[6]	0.83 (0.78 to 0.88)	n/a	LOW
Model: CORSCORE								
1[22]	633	Serious[23]	Serious[20]	n/a	Serious[24]	0.73 (not reported)	n/a	VERY LOW
Model: Severe Predicting Score (SPS)								
1[25]	204	No serious	Very serious[26]	n/a	Serious[24]	0.71 (not reported)	n/a	VERY LOW
Model: Combined Diamond-Forrester and Gene algorithm score								
1[27]	525	No serious	Very serious[26]	n/a	Serious[6]	0.72 (0.68 to 0.76)	n/a	VERY LOW
Model: Updated Diamond-Forrester (Genders) + risk factors [Clinical model]								
1[28]	4426	Serious[23]	No serious	n/a	Serious[24]	0.79 (not reported)	n/a	LOW

Number of studies	Number of participants	Risk of bias	Indirectness	Inconsistency	Imprecision	Area under the ROC curve Study c-statistic (95% CI)	Area under the ROC curve Median [range]	GRADE quality

1 Chen 2014, Genders 2010, Genders 2011, Jensen 2012, Rosenberg 2010
2 5/5 contributing studies had serious applicability issues according to QUADAS-2 checklist (See appendix H.2)
3 Evidence downgraded 2 levels as AUC range crosses two minimal important differences
4 Gaibazzi 2015, Kotecha 2010, Yalcin 2012
5 3/3 contributing studies had serious applicability issues according to QUADAS-2 checklist (See appendix H.2)
6 Evidence downgraded 1 level as AUC range crosses one minimal important difference
7 Park 2011
8 Evidence was downgraded by one due to serious applicability issues (See appendix H.2)
9 Yalcin 2012
10 Genders 2010, Genders 2012, Jensen 2012, Kumarmaru 2014
11 3/4 contributing studies had serious risk of bias issues according to QUADAS-2 checklist (See appendix H.2)
12 Genders 2012, Jensen 2012, Winther 2016
13 2/3 contributing studies had serious risk of bias issues according to QUADAS-2 checklist (See appendix H.2)

14 Genders 2010, Jensen 2012
15 2/2 contributing studies had serious applicability issues according to QUADAS-2 checklist (See appendix H.2)
16 Kotecha 2010, Yalcin 2012
17 Gaibazzi 2015, Genders 2012
18 2/2 contributing studies had very serious applicability issues according to QUADAS-2 checklist (See appendix H.2)
19 Yalcin 2012
20 Study had serious applicability issues according to QUADAS-2 checklist (See appendix H.2)
21 Genders 2010
22 Jensen 2012
23 Study had serious risk of bias issues according to QUADAS-2 checklist (See appendix H.2)
24 Evidence was downgraded by one as imprecision not calculable
25 Chen 2014
26 Study had very serious applicability issues according to QUADAS-2 checklist (See appendix H.2)
27 Rosenberg 2010
28 Genders 2012

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I.2.22 Reference standard: Computed tomography coronary angiography (CTCA) – 50% stenosis

Number of studies	Number of participants	Risk of bias	Indirectness	Inconsistency	Imprecision	Area under the ROC curve Study c-statistic (95% CI)	Area under the ROC curve Median [range]	GRADE quality
Model: Diamond–Forrester (original)								
5[1]	2800	No serious	No serious	n/a	Serious[2]	0.61 (not reported) 0.72 (0.66 to 0.78) 0.56 (0.49 to 0.64) 0.59 (not reported) 0.65 (0.61 to 0.68)	Median = 0.61 [range: 0.56 to 0.72]	MODERATE
Model: Framingham Risk Score								
2[3]	1548	No serious	No serious	n/a	Serious[2]	0.71 (not reported) 0.68 (0.64 to 0.72)	Median = 0.69 [range: 0.68 to 0.71]	MODERATE
Model: Duke Clinical Score								
2[4]	1385	Serious[5]	No serious	n/a	Serious[2]	0.71 (not reported) 0.59 (0.51 to 0.66)	Median = 0.65 [range: 0.59 to 0.71]	LOW
Model: Updated Diamond-Forrester (Genders)								
2[6]	632	Serious[7]	No serious	n/a	Serious[2]	0.76 (0.71 to 0.81) 0.61 (0.53 to 0.68)	Median = 0.69 [range: 0.61 to 0.76]	LOW
Model: Morise 1997								
3[8]	1345	No serious	Serious[9]	n/a	Serious[2]	0.77 (not reported) 0.68 (0.63 to 0.74) 0.67 (0.60 to 0.74)	Median = 0.68 [range: 0.67 to 0.77]	LOW

Number of studies	Number of participants	Risk of bias	Indirectness	Inconsistency	Imprecision	Area under the ROC curve Study c-statistic (95% CI)	Area under the ROC curve Median [range]	GRADE quality
Model: SCORE								
1[10]	1296	No serious	No serious	n/a	Serious[2]	0.69 (0.65 to 0.72)	n/a	MODERATE
Model: PROCAM								
1[10]		No serious	No serious	n/a	No serious	0.64 (0.61 to 0.68)	n/a	HIGH

1 *1 Hong 2012, Pickett 2013, Rademaker 2014, Shmilovich 2014, Versteylen 2011*
2 *2 Evidence downgraded 1 level as AUC range crosses one minimal important difference*
3 *3 Hwang 2010, Versteylen 2011*
4 *4 Kumarmaru 2014, Rademaker 2014*
5 *5 Largest study (Kumarmaru 2014) had serious risk of bias issues according to QUADAS-2 checklist (See appendix H.2)*
6 *6 Genders 2011, Rademaker 2014*
7 *7 Largest study (Genders 2011) had serious risk of bias issues according to QUADAS-2 checklist (See appendix H.2)*
8 *8 Hong 2012, Pickett 2013, Rademaker 2014*
9 *9 2/3 studies had serious risk of applicability issues according to QUADAS-2 checklist (See appendix H.2)*
10 *10 Versteylen 2011*

Appendix J: Evidence synthesis

J.1 Review question 1

Key

Forest plots:

Stenosis level: Indicates the stenosis level (50% or 70%) used to diagnose coronary artery disease using invasive coronary angiography (the reference standard).

Population Categories: A=Suspected CAD with no breakdown of numbers with chest pain, B=Suspected CAD with breakdown of numbers with chest pain, C=Chest pain (combination of types), D=Typical chest pain of suspected cardiac origin.

Meta-analysis plots:

Sensitivity and false positive rate (1-specificity) are plotted on the x and y axes, respectively.

Filled symbols indicate the overall summary estimate from either a meta-analysis, or single study. Open symbols indicate individual studies contributing to a meta-analysis.

Dashed lines indicate the 95% confidence region for sensitivity and specificity when meta-analysis was conducted (note that in cases where summary estimates correspond to a single study, this region is omitted).

J.1.11 Computer tomography cardiac angiography (CTCA)

Figure 1: Forest plot showing individual included studies comparing CTCA with the reference standard

Study	TP	FP	FN	TN	Stenosis level	Population	Sensitivity (95% CI)	Specificity (95% CI)
Herzog 2007	16	3	0	21	50%	A	1.00 [0.79, 1.00]	0.88 [0.68, 0.97]
Meng 2009	83	5	2	19	50%	A	0.98 [0.92, 1.00]	0.79 [0.58, 0.93]
Nazeri 2009	120	5	2	41	50%	A	0.98 [0.94, 1.00]	0.89 [0.76, 0.96]
Piers 2008	38	12	0	10	50%	A	1.00 [0.91, 1.00]	0.45 [0.24, 0.68]
Pontone 2014	78	8	0	5	50%	A	1.00 [0.95, 1.00]	0.38 [0.14, 0.68]
Pugliese 2008	38	0	0	13	50%	A	1.00 [0.91, 1.00]	1.00 [0.75, 1.00]
Raff 2005	38	3	2	27	50%	A	0.95 [0.83, 0.99]	0.90 [0.73, 0.98]
Rixe 2009	40	6	0	30	50%	A	1.00 [0.91, 1.00]	0.83 [0.67, 0.94]
Ropers 2006	25	5	1	50	50%	A	0.96 [0.80, 1.00]	0.91 [0.80, 0.97]
Swailam 2010	3	1	0	26	50%	A	1.00 [0.29, 1.00]	0.96 [0.81, 1.00]
Cademartiri 2008	82	21	2	29	50%	B	0.98 [0.92, 1.00]	0.58 [0.43, 0.72]
Carrascosa 2010	26	6	0	18	50%	B	1.00 [0.87, 1.00]	0.75 [0.53, 0.90]
Herzog 2008	18	2	0	10	50%	B	1.00 [0.81, 1.00]	0.83 [0.52, 0.98]
Herzog 2009	23	2	0	17	50%	B	1.00 [0.85, 1.00]	0.89 [0.67, 0.99]
Overhus 2010	28	14	1	57	50%	B	0.97 [0.82, 1.00]	0.80 [0.69, 0.89]
Bettencourt 2011a	47	12	1	30	50%	C	0.98 [0.89, 1.00]	0.71 [0.55, 0.84]
Budoff 2008 a	54	29	3	144	50%	C	0.95 [0.85, 0.99]	0.83 [0.77, 0.88]
Cademartiri 2007	20	1	0	21	50%	C	1.00 [0.83, 1.00]	0.95 [0.77, 1.00]
Chen et al 2011	76	7	4	26	50%	C	0.95 [0.88, 0.99]	0.79 [0.61, 0.91]
Donati 2007	32	2	0	18	50%	C	1.00 [0.89, 1.00]	0.90 [0.68, 0.99]
Fujitaka 2009	50	24	1	50	50%	C	0.98 [0.90, 1.00]	0.68 [0.56, 0.78]
Nieman 2009	53	26	2	15	50%	C	0.96 [0.87, 1.00]	0.37 [0.22, 0.53]
Sheikh 2009	48	1	3	21	50%	C	0.94 [0.84, 0.99]	0.95 [0.77, 1.00]
Thomassen 2013	20	8	2	14	50%	C	0.91 [0.71, 0.99]	0.64 [0.41, 0.83]
van Werkhoven 2010	16	5	0	40	50%	C	1.00 [0.79, 1.00]	0.89 [0.76, 0.96]
Muhlenbruch 2007	44	3	1	3	70%	A	0.98 [0.88, 1.00]	0.50 [0.12, 0.88]
Bettencourt 2011b	38	17	0	35	70%	C	1.00 [0.91, 1.00]	0.67 [0.53, 0.80]
Budoff 2008 b	30	34	2	164	70%	C	0.94 [0.79, 0.99]	0.83 [0.77, 0.88]

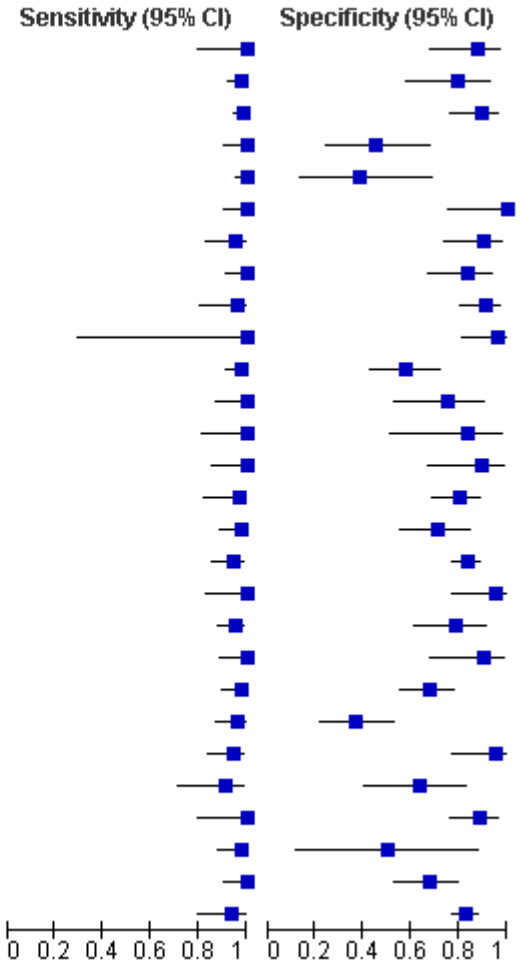
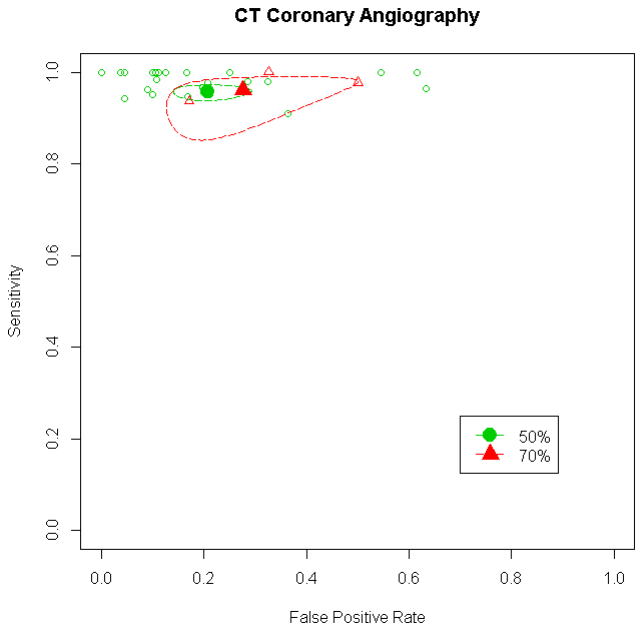


Figure 2: Meta-analysis results for computer tomography cardiac angiography (CTCA)



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J.1.21 Calcium scoring

Figure 3: Forest plot showing individual included studies comparing calcium scoring with the reference standard

Study	TP	FP	FN	TN	Population	Calcium Score category	Stenosis Level	Sensitivity (95% CI)	Specificity (95% CI)
von Zeigler 2014 a	2068	2747	21	3438	C	>0	50%	0.99 [0.98, 0.99]	0.56 [0.54, 0.57]
Budoff 2013 a	56	101	1	72	C	>0	50%	0.98 [0.91, 1.00]	0.42 [0.34, 0.49]
von Zeigler 2014 c	723	4357	9	3185	C	>0	70%	0.99 [0.98, 0.99]	0.42 [0.41, 0.43]
von Zeigler 2014 b	1134	768	955	5417	C	>400	50%	0.54 [0.52, 0.56]	0.88 [0.87, 0.88]
Budoff 2013 b	34	20	23	153	C	>400	50%	0.60 [0.46, 0.72]	0.88 [0.83, 0.93]
von Zeigler 2014 d	618	1226	114	6316	C	>400	70%	0.84 [0.82, 0.87]	0.84 [0.83, 0.85]

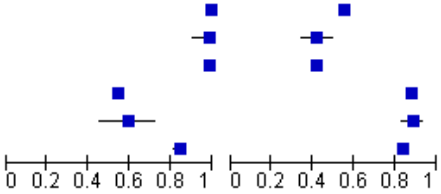

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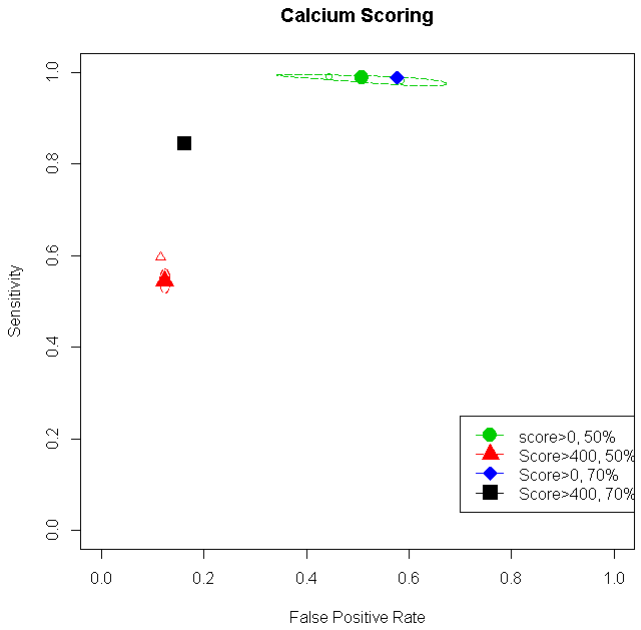
Figure 4: Meta-analysis results for calcium scoring



J.1.32 Stress echocardiography (perfusion)

Figure 5: Forest plot showing individual included studies comparing stress echocardiography (perfusion) with the reference standard

Study	TP	FP	FN	TN	Method of stress	Population	Stenosis level	Sensitivity (95% CI)	Specificity (95% CI)
Arnold 2010 a	31	4	10	17	Adenosine	A	50%	0.76 [0.60, 0.88]	0.81 [0.58, 0.95]
Onishi 2010	33	5	4	17	Dobutamine	A	50%	0.89 [0.75, 0.97]	0.77 [0.55, 0.92]
Miszalski-Jamka 2012	35	4	6	16	Exercise	B	50%	0.85 [0.71, 0.94]	0.80 [0.56, 0.94]
Arnold 2010 b	26	9	3	24	Adenosine	A	70%	0.90 [0.73, 0.98]	0.73 [0.54, 0.87]

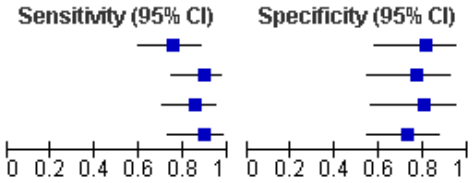
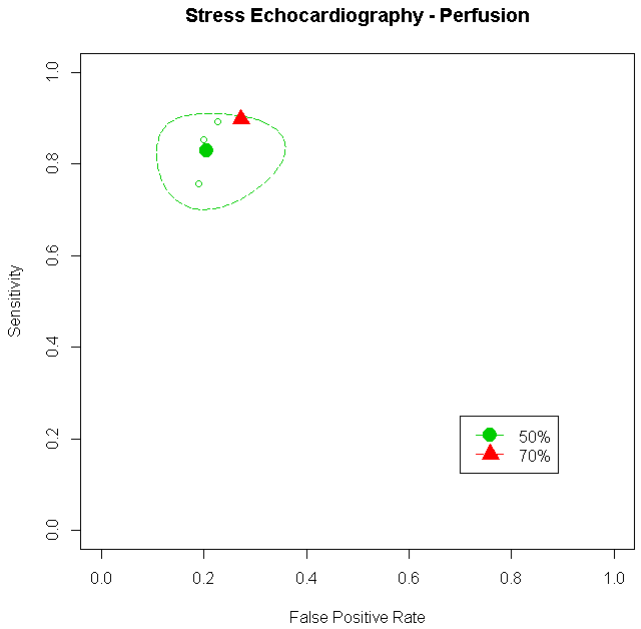


Figure 6: Meta-analysis results for stress echocardiography (perfusion)



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J.1.41 Stress echocardiography (wall motion)

Figure 7: Forest plot showing individual included studies comparing stress echocardiography (wall motion) with the reference standard

Study	TP	FP	FN	TN	Population	Stenosis level	Stress method	Sensitivity (95% CI)	Specificity (95% CI)
Arnold 2010 a	25	3	16	18	A	50%	Adenosine	0.61 [0.45, 0.76]	0.86 [0.64, 0.97]
Arnold 2010 b	22	6	7	27	A	70%	Adenosine	0.76 [0.56, 0.90]	0.82 [0.65, 0.93]
Senior 2004 a	36	5	7	7	C	50%	Dipyridamole	0.84 [0.69, 0.93]	0.58 [0.28, 0.85]
San Roman 1998 a	54	2	12	34	D	50%	Dipyridamole	0.82 [0.70, 0.90]	0.94 [0.81, 0.99]
San Roman 1996 a	49	1	14	38	D	50%	Dipyridamole	0.78 [0.66, 0.87]	0.97 [0.87, 1.00]
Parodi 1999	62	5	18	16	D	50%	Dipyridamole	0.78 [0.67, 0.86]	0.76 [0.53, 0.92]
Mazeika 1991	16	1	24	14	A	70%	Dipyridamole	0.40 [0.25, 0.57]	0.93 [0.68, 1.00]
Severi 1993	185	18	62	165	C	70%	Dipyridamole	0.75 [0.69, 0.80]	0.90 [0.85, 0.94]
Senior 2004 b	36	1	7	11	C	70%	Dipyridamole	0.84 [0.69, 0.93]	0.92 [0.62, 1.00]
Santoro 1998 a	18	1	15	26	C	70%	Dipyridamole	0.55 [0.36, 0.72]	0.96 [0.81, 1.00]
Marangelli 1994 a	15	2	20	23	C	70%	Dipyridamole	0.43 [0.26, 0.61]	0.92 [0.74, 0.99]
Onishi 2010	26	3	11	19	A	50%	Dobutamine	0.70 [0.53, 0.84]	0.86 [0.65, 0.97]
Nagel 1999	81	19	28	44	A	50%	Dobutamine	0.74 [0.65, 0.82]	0.70 [0.57, 0.81]
Marwick 1993	102	13	40	62	B	50%	Dobutamine	0.72 [0.64, 0.79]	0.83 [0.72, 0.90]
Di Bello 1996(i)	33	2	5	5	C	50%	Dobutamine	0.87 [0.72, 0.96]	0.71 [0.29, 0.96]
Di Bello 1996(ii)	29	1	9	6	C	50%	Dobutamine	0.76 [0.60, 0.89]	0.86 [0.42, 1.00]
Hennessy 1998	86	17	24	30	C	50%	Dobutamine	0.78 [0.69, 0.85]	0.64 [0.49, 0.77]
San Roman 1998 b	52	4	14	32	D	50%	Dobutamine	0.79 [0.67, 0.88]	0.89 [0.74, 0.97]
Nixdorff 2007	23	6	10	32	A	70%	Dobutamine	0.70 [0.51, 0.84]	0.84 [0.69, 0.94]
Santoro 1998 b	20	1	13	26	C	70%	Dobutamine	0.61 [0.42, 0.77]	0.96 [0.81, 1.00]
San Roman 1996 b	49	2	14	37	D	50%	Dobutmine-Adenosine	0.78 [0.66, 0.87]	0.95 [0.83, 0.99]
Hoffman 1993	40	2	10	14	A	70%	Exercise	0.80 [0.66, 0.90]	0.88 [0.62, 0.98]
Marangelli 1994 b	31	3	4	22	C	70%	Exercise	0.89 [0.73, 0.97]	0.88 [0.69, 0.97]
Shaikh 2013	14	3	9	19	A	70%	Regardenoson/atropine	0.61 [0.39, 0.80]	0.86 [0.65, 0.97]

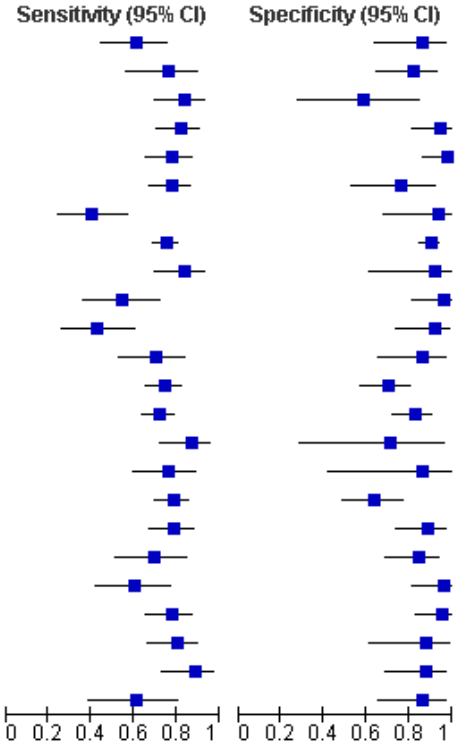

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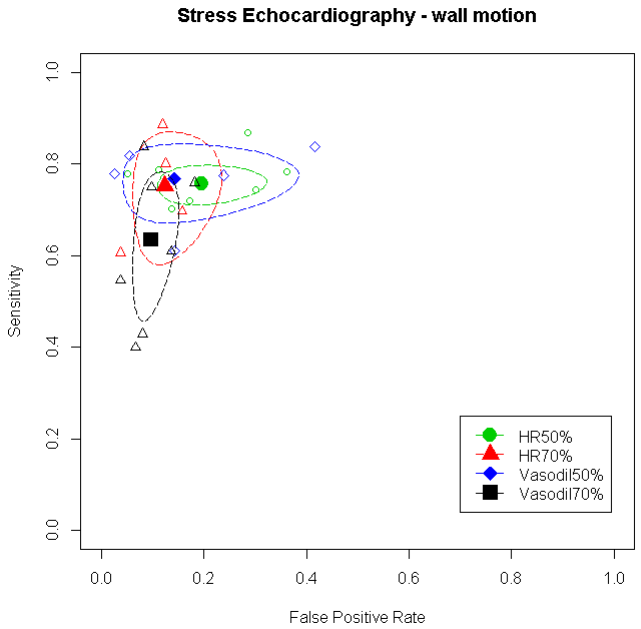
Figure 8: Meta-analysis results for stress echocardiography (wall motion)



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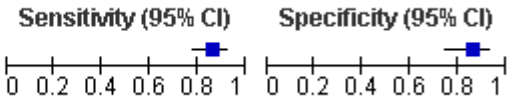
J.1.52 Cardiac magnetic resonance (CMR) (wall motion)

Figure 9: Forest plot showing individual included studies comparing cardiac magnetic resonance (wall motion) with the reference standard

Study	TP	FP	FN	TN	Population	Stenosis level	Sensitivity (95% CI)	Specificity (95% CI)
Nagel 1999	94	9	15	54	A	50%	0.86 [0.78, 0.92]	0.86 [0.75, 0.93]



J.1.62 Cardiac magnetic resonance (CMR) (perfusion)

Figure 10: Forest plot showing individual included studies comparing cardiac magnetic resonance (perfusion) with the reference standard

Study	TP	FP	FN	TN	Stenosis level	Population	Specific test	Sensitivity (95% CI)	Specificity (95% CI)
Klem 2006 e	36	18	8	30	50%	A	Perfusion	0.82 [0.67, 0.92]	0.63 [0.47, 0.76]
Arnold 2010 c	39	8	2	13	50%	A	Perfusion	0.95 [0.83, 0.99]	0.62 [0.38, 0.82]
Klein 2008 a	20	3	3	23	50%	B	Perfusion	0.87 [0.66, 0.97]	0.88 [0.70, 0.98]
Stolzmann 2011	28	3	8	21	50%	B	Perfusion	0.78 [0.61, 0.90]	0.88 [0.68, 0.97]
Krittayaphong 2009	34	6	4	22	50%	B	Perfusion	0.89 [0.75, 0.97]	0.79 [0.59, 0.92]
Kawase 2004	31	1	2	16	70%	A	Perfusion	0.94 [0.80, 0.99]	0.94 [0.71, 1.00]
Klem 2006 b	31	23	6	32	70%	A	Perfusion	0.84 [0.68, 0.94]	0.58 [0.44, 0.71]
Arnold 2010 d	29	18	0	15	70%	A	Perfusion	1.00 [0.88, 1.00]	0.45 [0.28, 0.64]
Klem 2006 d	34	6	10	42	50%	A	Perf+ DE	0.77 [0.62, 0.89]	0.88 [0.75, 0.95]
Arnold 2010 a	37	4	4	17	50%	A	Perf+ DE	0.90 [0.77, 0.97]	0.81 [0.58, 0.95]
Klein 2008 c	22	3	3	23	50%	B	Perf+ DE	0.88 [0.69, 0.97]	0.88 [0.70, 0.98]
Klem 2006 a	33	7	4	48	70%	A	Perf+ DE	0.89 [0.75, 0.97]	0.87 [0.76, 0.95]
Arnold 2010 b	28	13	1	20	70%	A	Perf+ DE	0.97 [0.82, 1.00]	0.61 [0.42, 0.77]
Klem 2006 f	18	1	26	47	50%	A	Delayed enhancement (DE)	0.41 [0.26, 0.57]	0.98 [0.89, 1.00]
Arnold 2010 e	18	1	23	20	50%	A	Delayed enhancement (DE)	0.44 [0.28, 0.60]	0.95 [0.76, 1.00]
Klein 2008 b	13	1	13	27	50%	B	Delayed enhancement (DE)	0.50 [0.30, 0.70]	0.96 [0.82, 1.00]
Klem 2006 c	18	1	19	54	70%	A	Delayed enhancement (DE)	0.49 [0.32, 0.66]	0.98 [0.90, 1.00]
Arnold 2010 f	14	5	15	28	70%	A	Delayed enhancement (DE)	0.48 [0.29, 0.67]	0.85 [0.68, 0.95]

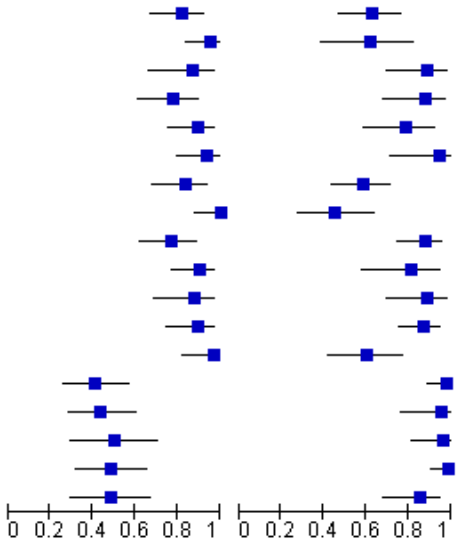
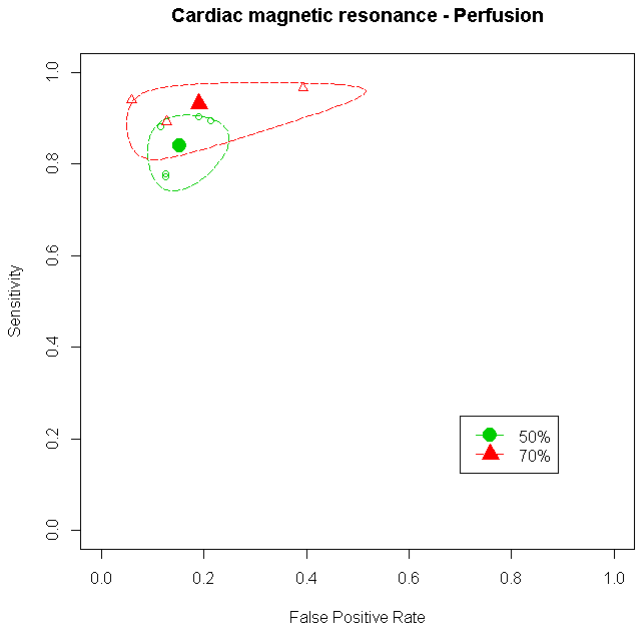


Figure 11: Meta-analysis results for cardiac magnetic resonance (perfusion)



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J.1.71 Myocardial perfusion scintigraphy (MPS) (SPECT)

Figure 12: Forest plot showing individual included studies comparing MPS (SPECT) with the reference standard

Study	TP	FP	FN	TN	Stenosis level	Population	Stress method	Sensitivity (95% CI)	Specificity (95% CI)
Schepis 2007	32	3	10	32	50%	B	Adenosine	0.76 [0.61, 0.88]	0.91 [0.77, 0.98]
Kaminek 2015	98	14	13	39	50%	A	DipryidORExercise	0.88 [0.81, 0.94]	0.74 [0.60, 0.85]
Cramer 1997	55	2	12	9	50%	D	Dipyrid+Exercise	0.82 [0.71, 0.90]	0.82 [0.48, 0.98]
Fleming 1992	29	4	3	8	50%	A	Dipyridamole	0.91 [0.75, 0.98]	0.67 [0.35, 0.90]
Senior 2004 a	21	1	22	11	50%	C	Dipyridamole	0.49 [0.33, 0.65]	0.92 [0.62, 1.00]
Santoro 1998 a	32	3	1	24	70%	C	Dipyridamole	0.97 [0.84, 1.00]	0.89 [0.71, 0.98]
Senior 2004 b	21	4	22	8	70%	C	Dipyridamole	0.49 [0.33, 0.65]	0.67 [0.35, 0.90]
Di Bello 1996i	33	1	5	6	50%	C	Dobutamine	0.87 [0.72, 0.96]	0.86 [0.42, 1.00]
Di Bello 1996ii	33	1	5	6	50%	C	Dobutamine	0.87 [0.72, 0.96]	0.86 [0.42, 1.00]
Marwick 1993	108	25	34	50	50%	B	Dobutamine	0.76 [0.68, 0.83]	0.67 [0.55, 0.77]
Santoro 1998 b	30	5	3	22	70%	C	Dobutamine	0.91 [0.76, 0.98]	0.81 [0.62, 0.94]
Budoff 1998	12	5	4	12	50%	C	Exercise (bicycle)	0.75 [0.48, 0.93]	0.71 [0.44, 0.90]
San Roman 1998	54	9	8	21	50%	D	Exercise (treadmill)	0.87 [0.76, 0.94]	0.70 [0.51, 0.85]
Yao 2004	28	3	7	35	50%	A	Exercise (treadmill)	0.80 [0.63, 0.92]	0.92 [0.79, 0.98]
Budoff 2007	17	2	4	7	70%	A	Exercise (treadmill)	0.81 [0.58, 0.95]	0.78 [0.40, 0.97]

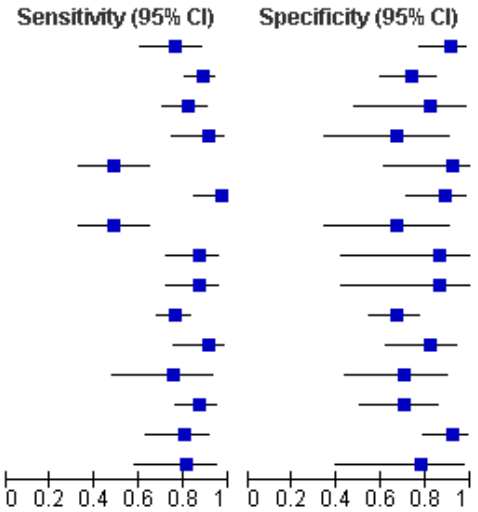

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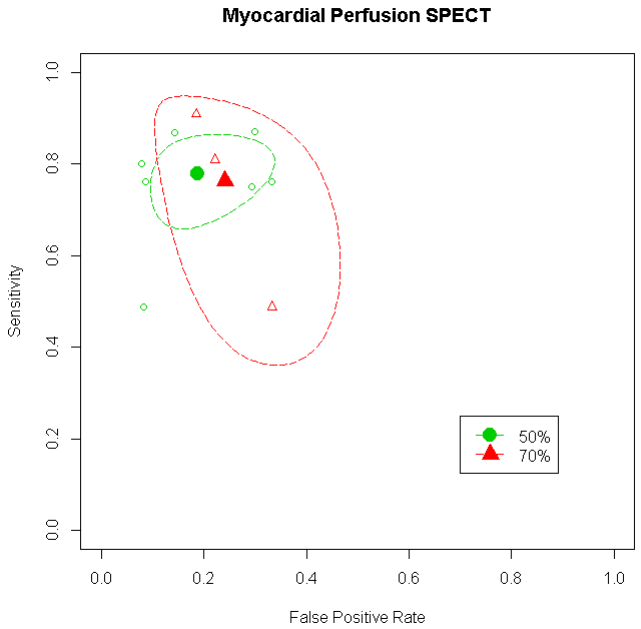
Figure 13: Meta-analysis results for MPS (SPECT)



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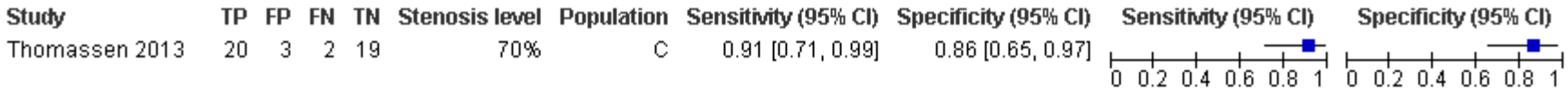
J.1.82 Myocardial perfusion scintigraphy (MPS) (PET)

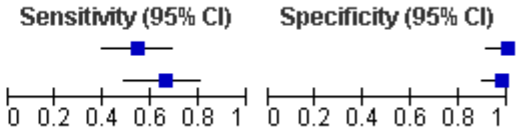
Figure 14: Forest plot showing individual included studies comparing MPS (PET) with the reference standard



J.1.9 Computer tomography (CT) perfusion

Figure 15: Forest plot showing individual included studies comparing CT perfusion with the reference standard

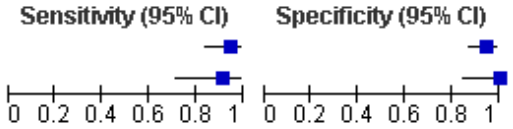
Study	TP	FP	FN	TN	Population	Stenosis level	Sensitivity (95% CI)	Specificity (95% CI)
Bettencourt 2011 b	26	0	22	42	B	50%	0.54 [0.39, 0.69]	1.00 [0.92, 1.00]
Bettencourt 2011a	25	1	13	51	B	70%	0.66 [0.49, 0.80]	0.98 [0.90, 1.00]



J.1.10 Combined analyses (CTCA and MPS SPECT)

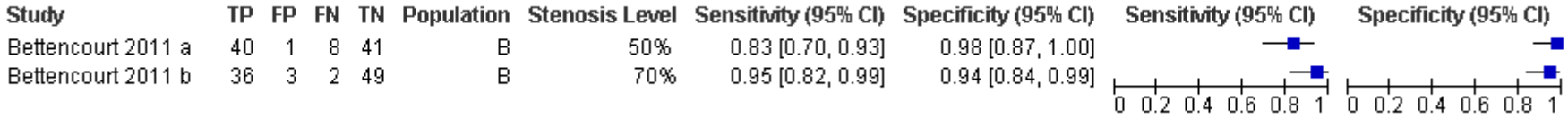
Figure 16: Forest plot showing individual included studies comparing a combined analysis of CTCA and MPS (SPECT) with the reference standard

Study	TP	FP	FN	TN	Population	Stenosis Level	MPS type	Sensitivity (95% CI)	Specificity (95% CI)
Fujitaka 2009	48	4	3	70	C	50%	SPECT	0.94 [0.84, 0.99]	0.95 [0.87, 0.99]
Thomassen 2013	20	0	2	22	C	50%	PET	0.91 [0.71, 0.99]	1.00 [0.85, 1.00]



J.1.111 Combined analyses (CTCA and CT perfusion)

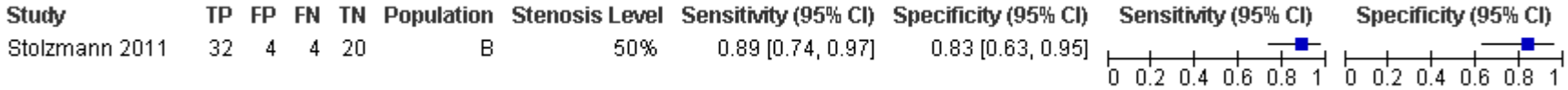
Figure 17: Forest plot showing individual included studies comparing a combined analysis of CTCA and CT perfusion with the reference standard



2

J.1.123 Combined analyses (Calcium scoring and CMR perfusion)

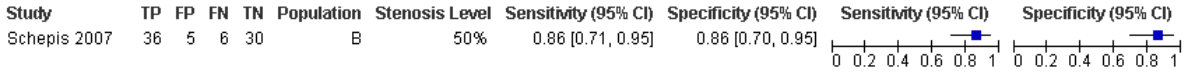
Figure 18: Forest plot showing individual included studies comparing a combined analysis of calcium scoring and CMR perfusion with the reference standard



4

J.1.135 Combined analyses (Calcium scoring and MPS SPECT)

Figure 19: Forest plot showing individual included studies comparing a combined analysis of calcium scoring and MPS (SPECT) with the reference standard

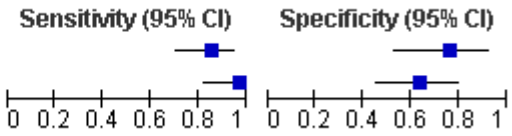


6

J.1.141 Combined analysis (Stress echocardiography - perfusion and wall motion)

Figure 20: Forest plot showing individual included studies comparing a combined analysis of stress echocardiography (wall motion and perfusion) with the reference standard

Study	TP	FP	FN	TN	Population	Stenosis Level	Sensitivity (95% CI)	Specificity (95% CI)
Arnold 2010 a	35	5	6	16	A	50%	0.85 [0.71, 0.94]	0.76 [0.53, 0.92]
Arnold 2010 b	28	12	1	21	A	70%	0.97 [0.82, 1.00]	0.64 [0.45, 0.80]



J.1.151 Summary meta-analyses comparing the four diagnostic testing strategies included in the economic model

Figure 21: Summary meta-analysis – 50% stenosis level (slide presented to committee)

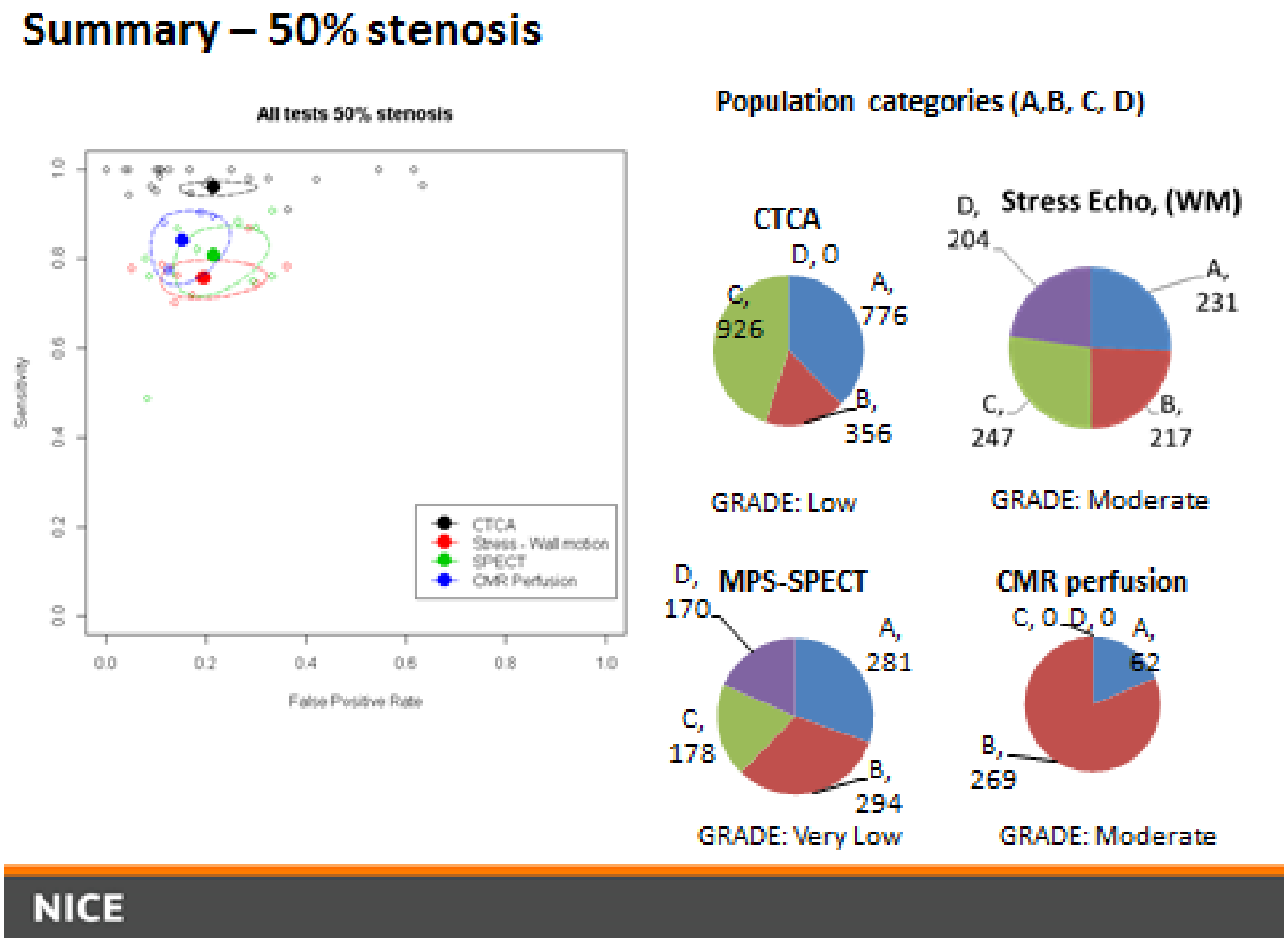
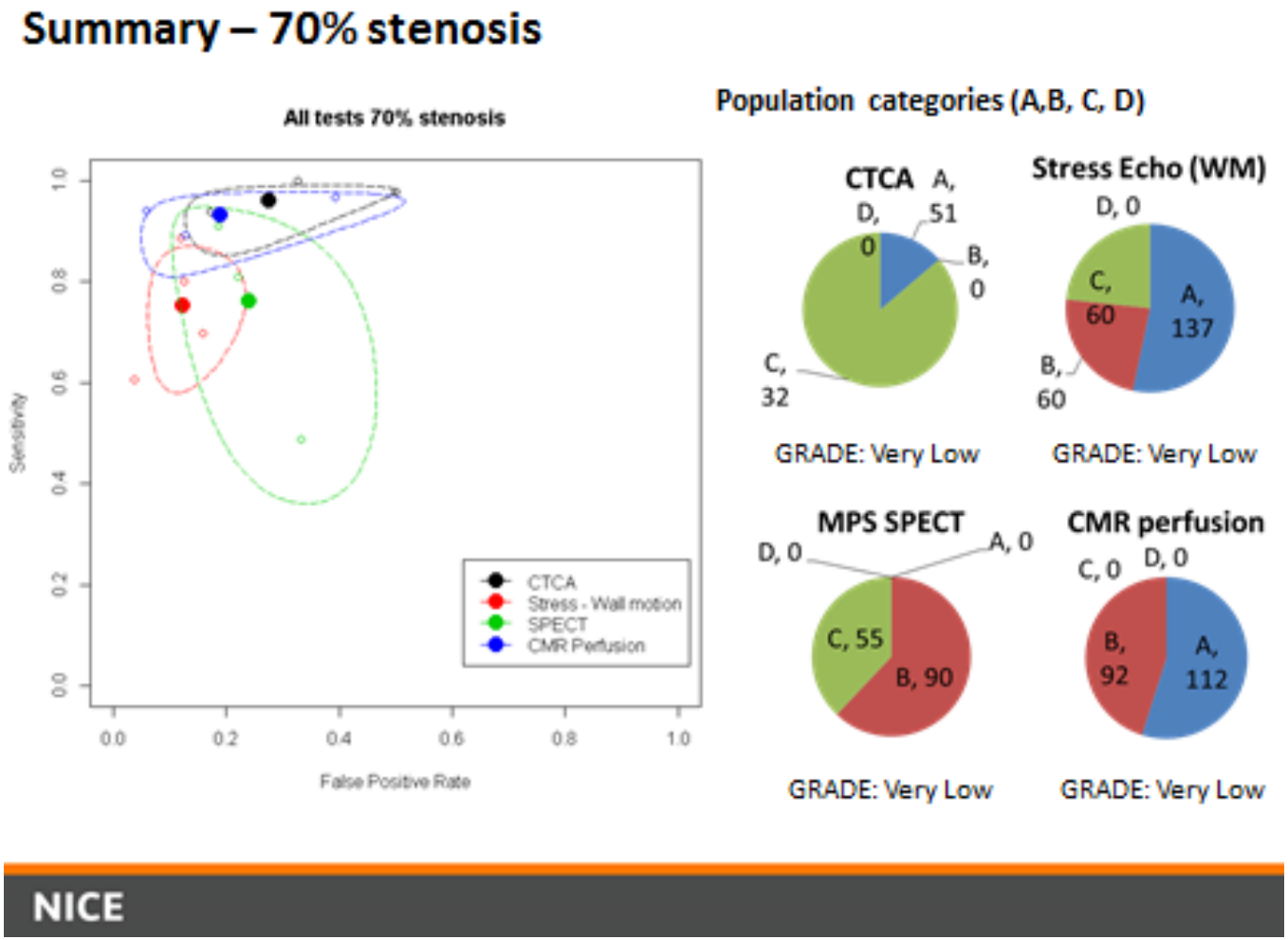


Figure 22: **Summary meta-analysis - 70% stenosis level (slide presented to committee)**



J.2 Review question 2

Table 80: Summary of evidence for the five most commonly evaluated probability models

Model	≥50% stenosis on CA				≥50% stenosis on CTCA			
	Lowest AUC	Median AUC	Highest AUC	GRADE (n studies, N patients)	Lowest AUC	Median AUC	Highest AUC	GRADE (n studies, N patients)
Diamond-Forrester (original)	0.64	0.73	0.81	**VERY LOW** (5, N=3473)	0.56	0.61	0.72	**MOD** (5, N=2800)
Framingham Risk Score	0.67	0.74	0.76	**LOW** (3, N=1334)	0.68	0.69	0.71	**MOD** (2, N=1548)
Duke Clinical Score	0.59	0.75	0.84	**VERY LOW** (4, N=6242)	0.59	0.65	0.71	**LOW** (2, N=1385)
Updated Diamond-Forrester (Genders)	0.71	0.77	0.79	**MOD** (3, N=5287)	0.61	0.69	0.76	**LOW** (2, N=632)
Morise 1997	0.68	0.76	0.84	**VERY LOW** (2, N=887)	0.67	0.68	0.77	**LOW** (3, N=1345)

Appendix K: Economic search strategies

K.1 Review question 1

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 81. The search strategy is shown in Table 82. The same strategy was translated for the other databases listed.

Table 81: Economic search summary, review question 1

Databases	Version/files	No. retrieved
NHS EED	Issue 2 of 4, April 2015	105
HTA database (CRD, Ovid, Wiley)*	Issue 2 of 4, April 2015	55
MEDLINE (Ovid)	1946 to May Week 4 2015	1573
MEDLINE In-Process (Ovid)	June 01, 2015	120
EMBASE (Ovid)	1980 to 2015 Week 22	1870

Table 82: Economic search strategy, review question 1

Database: Medline
Database: Ovid MEDLINE(R) <1946 to May Week 4 2015> Search Strategy: --- 1 Chest Pain/ (9730) 2 Angina Pectoris/ (30752) 3 Angina, Stable/ (516) 4 Microvascular Angina/ (895) 5 (angina* or stenocardia* or angor pectoris or cardiac syndrome x).tw. (45820) 6 ((chest* or thorax* or thorac*) adj4 (pain* or discomfort or distress or ache*)).tw. (27486) 7 *Coronary Artery Disease/ (33182) 8 (coronary adj (arterioscleros?s or atheroscleros?s or artery or arteries) adj disease*).tw. (59156) 9 or/1-8 (148375) 10 *Echocardiography, stress/ (1383) 11 (Echocardiograph* adj4 (stress* or dobutamine)).tw. (4257) 12 *Tomography, Emission-Computed, Single-Photon/ (13073) 13 *Tomography, Emission-Computed/ or *Tomography, X-Ray Computed/ (103628) 14 *Positron-Emission Tomography/ (18903) 15 ((single photon or single-photon) adj2 emission*).tw. (14556) 16 ((positron-emission or positron emission) adj tomography).tw. (34443) 17 (pet adj scan*).tw. (6678) 18 *Myocardial Perfusion Imaging/ (1834) 19 (Myocardial adj (scintigraph* or perfusion*)).tw. (12481) 20 ((thallium or sestamibi or tetrofosmin or technetium) adj2 SPECT).tw. (1402) 21 *Magnetic Resonance Imaging/ (111904) 22 ((cardiac or stress) adj2 magnetic adj2 resonance adj2 imag*).tw. (2956) 23 ("cardiac MR" or CMR).tw. (4276) 24 (stress adj3 perfusion*).tw. (1741) 25 ((Multi-slice or Multi slice) adj CT).tw. (374)

Database: Medline

26 ("new generation" adj4 tomograph*).tw. (36)
27 (fractional adj flow adj reserve).tw. (861)
28 (coronary adj2 computed adj2 tomographic adj2 angiograph*).tw. (475)
29 (MSCT or MRI or CCTA or CTCA or NGCCT or SPECT or PET or MPS or CTFFR).tw. (209179)
30 (stress adj2 (ECG or EKG or electrocardiogra* or electrokardiogra*)).tw. (959)
31 *Coronary Angiography/ (14675)
32 (coronary adj angiograph*).tw. (22911)
33 ((CAC or calcium) adj scor*).tw. (2114)
34 or/10-33 (399634)
35 9 and 34 (26412)
36 animals/ not humans/ (3949562)
37 35 not 36 (26206)
38 limit 37 to english language (22327)
39 "Sensitivity and Specificity"/ (288138)
40 (sensitivity or specificity or accuracy).tw. (867523)
41 "Predictive Value of Tests"/ (151548)
42 (predictive adj1 value*).tw. (68155)
43 (roc adj1 curve*).tw. (15220)
44 (false adj2 (positiv* or negativ*)).tw. (55656)
45 (observer adj variation*).tw. (938)
46 (likelihood adj1 ratio*).tw. (8877)
47 Diagnosis, Differential/ (389089)
48 Likelihood Functions/ (17932)
49 exp Diagnostic Errors/ (98004)
50 or/39-49 (1602513)
51 38 and 50 (8495)
52 Economics/ (26620)
53 exp "Costs and Cost Analysis"/ (187989)
54 Economics, Dental/ (1860)
55 exp Economics, Hospital/ (20278)
56 exp Economics, Medical/ (13556)
57 Economics, Nursing/ (3915)
58 Economics, Pharmaceutical/ (2572)
59 Budgets/ (9966)
60 exp Models, Economic/ (10775)
61 Markov Chains/ (10471)
62 Monte Carlo Method/ (21020)
63 Decision Trees/ (9104)
64 econom$.tw. (163059)
65 cba.tw. (8856)
66 cea.tw. (16732)
67 cua.tw. (809)
68 markov$.tw. (12267)
69 (monte adj carlo).tw. (21755)
70 (decision adj3 (tree$ or analys$)).tw. (8730)
71 (cost or costs or costing$ or costly or costed).tw. (319967)
72 (price$ or pricing$).tw. (23945)
73 budget$.tw. (17839)
74 expenditure$.tw. (36290)
75 (value adj3 (money or monetary)).tw. (1389)

Database: Medline

76 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2902)
77 or/52-76 (678225)
78 "Quality of Life"/ (126016)
79 quality of life.tw. (146144)
80 "Value of Life"/ (5442)
81 Quality-Adjusted Life Years/ (7565)
82 quality adjusted life.tw. (6378)
83 (qaly$ or qald$ or qale$ or qtime$).tw. (5249)
84 disability adjusted life.tw. (1279)
85 daly$.tw. (1250)
86 Health Status Indicators/ (20553)
87 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (16024)
88 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1023)
89 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2823)
90 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (21)
91 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (336)
92 (euroqol or euro qol or eq5d or eq 5d).tw. (4203)
93 (qol or hql or hqol or hrqol).tw. (26260)
94 (hye or hyes).tw. (54)
95 health$ year$ equivalent$.tw. (38)
96 utilit$.tw. (117236)
97 (hui or hui1 or hui2 or hui3).tw. (888)
98 disutili$.tw. (228)
99 rosser.tw. (71)
100 quality of wellbeing.tw. (5)
101 quality of well-being.tw. (337)
102 qwb.tw. (175)
103 willingness to pay.tw. (2376)
104 standard gamble$.tw. (665)
105 time trade off.tw. (768)
106 time tradeoff.tw. (208)
107 tto.tw. (615)
108 or/78-107 (334461)
109 77 or 108 (967208)
110 38 and 109 (1573)

1
2

K.2 Review question 2

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 83. The search strategy is shown in Table 84. The same strategy was translated for the other databases listed.

Table 83: Economic search summary, review question 2

Economics	Version/files	No. retrieved
MEDLINE (Ovid)	Ovid MEDLINE(R) 1946 to May Week 5 2015	876
MEDLINE in Process (Ovid)	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 05, 2015>	72
Embase (Ovid)	Embase 1974 to 2015 Week 23	1,098
NHS Economic Evaluation Database (NHS EED) (legacy database)	NHS Economic Evaluation Database : Issue 2 of 4, April 2015	71
Health Technology Assessment (HTA Database)	Health Technology Assessment Database : Issue 2 of 4, April 2015	10

Table 84: Economic search strategy, review question 2

Database: Ovid MEDLINE(R) 1946 to May Week 5 2015
Strategy used: 1 Chest Pain/ (9758) 2 Angina Pectoris/ (30764) 3 Angina, Stable/ (525) 4 Microvascular Angina/ (897) 5 (angina* or stenocardia* or angor pectoris or cardiac syndrome x).tw. (45873) 6 ((chest* or thorax* or thorac*) adj4 (pain* or discomfort or distress or ache*)).tw. (27541) 7 *Coronary Artery Disease/ (33356) 8 (coronary adj (arterioscleros?s or atheroscleros?s or artery or arteries) adj disease*).tw. (59315) 9 or/1-8 (148735) 10 *Risk Assessment/ (19703) 11 *Risk Factors/ (933) 12 *Medical-History Taking/ (4496) 13 *Physical Examination/ (9804) 14 *Risk/ (2863) 15 (history adj tak*).tw. (3766) 16 (pretest* adj (probab* or likel*)).tw. (1124) 17 (risk* adj4 assess*).tw. (71618) 18 cardiovascular risk factor*.tw. (22412) 19 ((physic* or clinic*) adj4 exam*).tw. (131375) 20 ((medic* or famil* or patient* or clinic*) adj histor*).tw. (81863) 21 (probab* adj4 disease*).tw. (8806) 22 Framingham*.tw. (6233) 23 clinic* predict*.tw. (4973) 24 or/10-23 (339545) 25 9 and 24 (10899) 26 Economics/ (26627)

Database: Ovid MEDLINE(R) 1946 to May Week 5 2015

27 exp "Costs and Cost Analysis"/ (188408)
28 Economics, Dental/ (1861)
29 exp Economics, Hospital/ (20315)
30 exp Economics, Medical/ (13560)
31 Economics, Nursing/ (3916)
32 Economics, Pharmaceutical/ (2575)
33 Budgets/ (9975)
34 exp Models, Economic/ (10822)
35 Markov Chains/ (10515)
36 Monte Carlo Method/ (21209)
37 Decision Trees/ (9121)
38 econom$.tw. (163542)
39 cba.tw. (8880)
40 cea.tw. (16777)
41 cua.tw. (810)
42 markov$.tw. (12338)
43 (monte adj carlo).tw. (21954)
44 (decision adj3 (tree$ or analys$)).tw. (8769)
45 (cost or costs or costing$ or costly or costed).tw. (321094)
46 (price$ or pricing$).tw. (24015)
47 budget$.tw. (17871)
48 expenditure$.tw. (36429)
49 (value adj3 (money or monetary)).tw. (1399)
50 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2909)
51 or/26-50 (680372)
52 "Quality of Life"/ (126536)
53 quality of life.tw. (146811)
54 "Value of Life"/ (5449)
55 Quality-Adjusted Life Years/ (7615)
56 quality adjusted life.tw. (6427)
57 (qaly$ or qald$ or qale$ or qtime$).tw. (5284)
58 disability adjusted life.tw. (1288)
59 daly$.tw. (1259)
60 Health Status Indicators/ (20598)
61 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (16076)
62 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1033)
63 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2845)
64 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (21)
65 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (336)
66 (euroqol or euro qol or eq5d or eq 5d).tw. (4232)
67 (qol or hql or hqol or hrqol).tw. (26394)
68 (hye or hyes).tw. (54)
69 health$ year$ equivalent$.tw. (38)
70 utilit$.tw. (117996)
71 (hui or hui1 or hui2 or hui3).tw. (889)
72 disutili$.tw. (230)
73 rosser.tw. (71)

Database: Ovid MEDLINE(R) 1946 to May Week 5 2015	
74	quality of wellbeing.tw. (5)
75	quality of well-being.tw. (339)
76	qwb.tw. (175)
77	willingness to pay.tw. (2388)
78	standard gamble$.tw. (667)
79	time trade off.tw. (771)
80	time tradeoff.tw. (208)
81	tto.tw. (616)
82	or/52-81 (336071)
83	51 or 82 (970758)
84	25 and 83 (985)
85	Animals/ not Humans/ (3961836)
86	84 not 85 (984)
87	limit 86 to english language (876)

1

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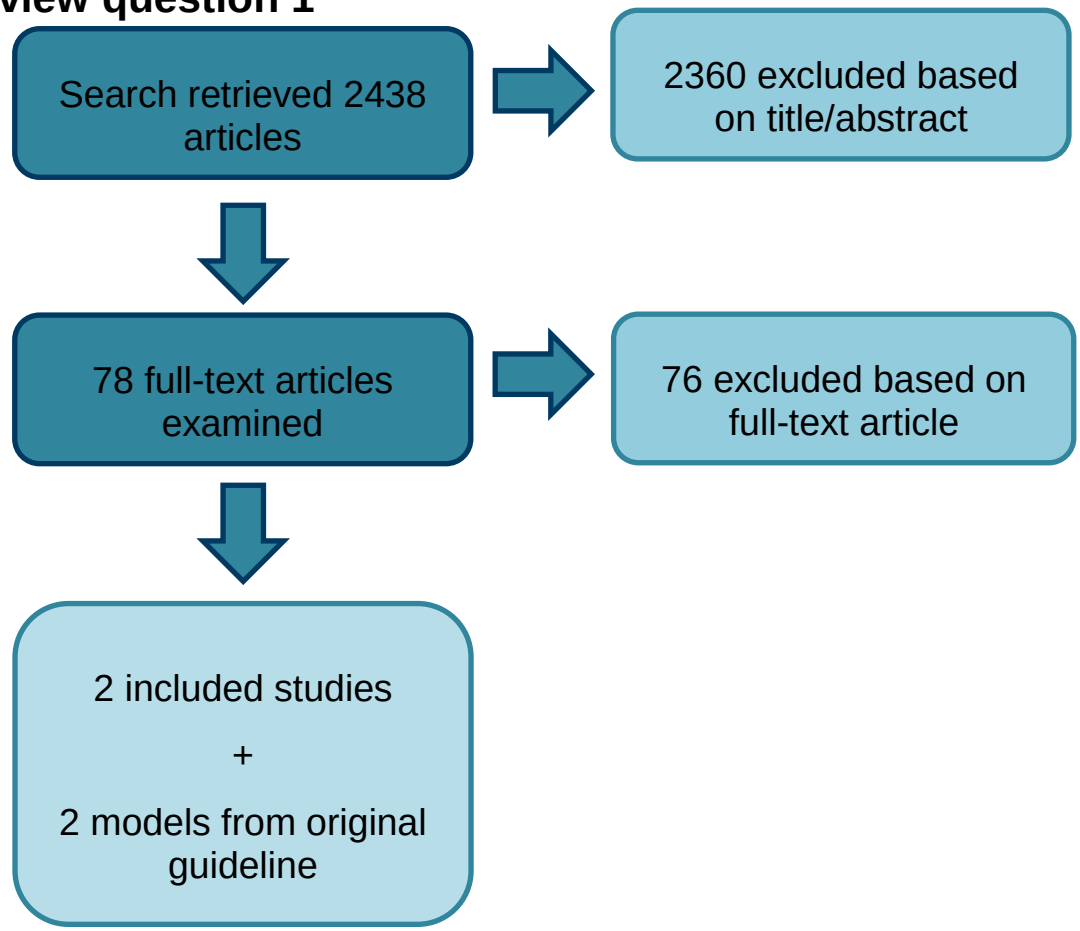
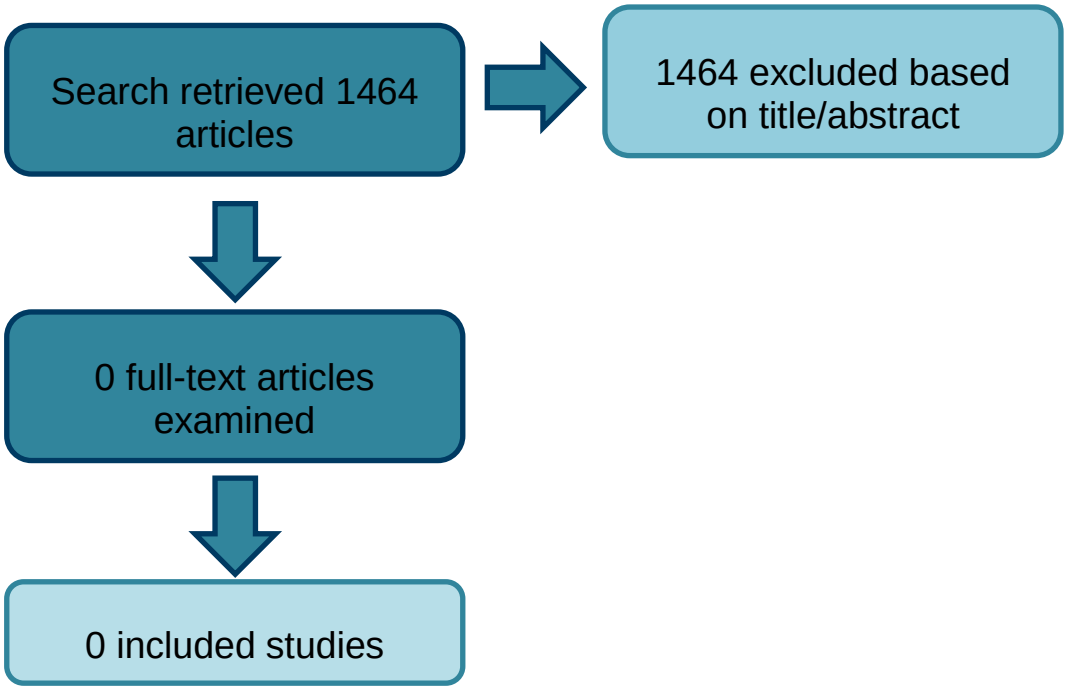
Appendix L:Economic review flowchart

L.1 Review question 1



L.2 Review question 2



1 Appendix M: Excluded economic studies

M.1 2 Review Question 1

Study	Reason for Exclusion
Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction (Structured abstract), Health Technology Assessment Database, 25-, 2003	Refers to NICE TA73 which was superseded by NICE CG95
The use of multislice computed tomography angiography (CTA) for the diagnosis of coronary artery disease (Structured abstract), Health Technology Assessment Database, 2-, 2005	Narrative review only
Amemiya,Shiori, Takao,Hidemasa, Computed tomographic coronary angiography for diagnosing stable coronary artery disease: a cost-utility and cost-effectiveness analysis, Circulation journal : official journal of the Japanese Circulation SocietyCirc J, 73, 1263-1270, 2009	Selectively excluded - more applicable studies with UK costs have been included
Bedetti,Gigliola, Pasanisi,Emilio Maria, Pizzi,Carmine, Turchetti,Giuseppe, Lore,Cosimo, Economic analysis including long-term risks and costs of alternative diagnostic strategies to evaluate patients with chest pain, Cardiovascular ultrasoundCardiovasc Ultrasound, 6, 21-, 2008	Selectively excluded - more appropriate studies with UK costs and health benefits represented by QALYs have been included
Boldt,Julia, Leber,Alexander W., Bonaventura,Klaus, Sohns,Christian, Stula,Martin, Huppertz,Alexander, Haverkamp,Wilhelm, Dorenkamp,Marc, Cost-effectiveness of cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary artery disease in Germany, Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic ResonanceJ Cardiovasc Magn Reson, 15, 30-, 2013	Selectively excluded - more applicable studies with UK costs have been included
Brabandt,H., Camberlin,C., Cleemput,I., 64-slice computed tomography imaging of coronary arteries in patients suspected for coronary artery disease (Structured abstract), Health Technology Assessment Database, -, 2008	Systematic review only
Cheezum,Michael K., Hulten,Edward A., Taylor,Allen J., Gibbs,Barnett T., Hinds,Sidney R., Feuerstein,Irwin M., Stack,Aaron L., Villines,Todd C., Cardiac CT angiography compared with myocardial perfusion stress testing on downstream resource utilization, Journal of cardiovascular computed tomographyJ Cardiovasc Comput Tomogr, 5, 101-109, 2011	US Cost analysis only
Chinnaiyan,Kavitha M., Raff,Gilbert L., Ananthasubramaniam,Karthik, Coronary CT angiography after stress testing: an efficient use of resources? Implications of the Advanced Cardiovascular Imaging Consortium (ACIC) results, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 19, 649-657, 2012	Editorial
Darlington,M., Gueret,P., Laissy,J.P., Pierucci,A.F., Maoulida,H., Quelen,C., Niarra,R., Chatellier,G., Durand-Zaleski,I., Cost-effectiveness of computed tomography coronary angiography versus conventional invasive coronary angiography (Provisional abstract), European Journal of Health EconomicsEur.J.Health Econ., -, 2014	Selectively excluded - more applicable studies with UK costs and health benefits represented by QALYs have been included
Demir,Ozan M., Bashir,Abdullah, Marshall,Kathy, Douglas,Martina, Wasan,Balvinder, Plein,Sven, Alfakih,Khaled, Comparison of clinical efficacy and cost of a cardiac imaging strategy versus a traditional exercise test strategy for the investigation of patients with suspected stable coronary artery disease, The American journal of	Excluded diagnostic strategy - exercise tolerance test as comparator

Study	Reason for Exclusion
cardiologyAm J Cardiol, 115, 1631-1635, 2015	
Dewey,Marc, Hamm,Bernd, Cost effectiveness of coronary angiography and calcium scoring using CT and stress MRI for diagnosis of coronary artery disease, European RadiologyEur.Radiol., 17, 1301-1309, 2007	Selectively excluded - more applicable studies with UK costs and health effects represented by QALYs have been included
Dorenkamp,Marc, Bonaventura,Klaus, Sohns,Christian, Becker,Christoph R., Leber,Alexander W., Direct costs and cost-effectiveness of dual-source computed tomography and invasive coronary angiography in patients with an intermediate pretest likelihood for coronary artery disease, Heart (British Cardiac Society), 98, 460-467, 2012	Selectively excluded - more appropriate studies with UK costs and health benefits represented by QALYs have been included
Fearon,William F., Bornschein,Bernhard, Tonino,Pim A.L., Gothe,Raffaella M., Bruyne,Bernard De, Pijls,Nico H.J., Siebert,Uwe, Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) Study Investigators, Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease, Circulation, 122, 2545-2550, 2010	Excluded population - known CAD
Fearon,William F., Shilane,David, Pijls,Nico H.J., Boothroyd,Derek B., Tonino,Pim A.L., Barbato,Emanuele, Juni,Peter, De Bruyne,Bernard, Hlatky,Mark A., Fractional Flow Reserve Versus Angiography for Multivessel Evaluation, Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve, Circulation, 128, 1335-1340, 2013	Excluded population with known CAD
Fearon,William F., Yeung,Alan C., Lee,David P., Yock,Paul G., Heidenreich,Paul A., Cost-effectiveness of measuring fractional flow reserve to guide coronary interventions, American Heart JournalAm.Heart J., 145, 882-887, 2003	Excluded population with known CAD
Ferreira,Antonio Miguel, Marques,Hugo, Goncalves,Pedro Araujo, Cardim,Nuno, Cost-effectiveness of different diagnostic strategies in suspected stable coronary artery disease in Portugal, Arquivos Brasileiros de CardiologiaArq.Bras.Cardiol., 102, 391-402, 2014	Selectively excluded - more appropriate studies with UK costs and health benefits represented by QALYs have been included
Genders,Tessa S.S., Ferket,Bart S., Dedic,Admir, Galema,Tjebbe W., Mollet,Nico R.A., de Feyter,Pim J., Fleischmann,Kirsten E., Nieman,Koen, Hunink,M.G.M., Coronary computed tomography versus exercise testing in patients with stable chest pain: comparative effectiveness and costs, International journal of cardiologyInt.J.Cardiol., 167, 1268-1275, 2013	Excluded diagnostic strategy
Genders,Tessa S.S., Meijboom,W.Bob, Meijs,Matthijs F.L., Schuijf,Joanne D., Mollet,Nico R., Weustink,Annick C., Pugliese,Francesca, Bax,Jeroen J., Cramer,Maarten J., Krestin,Gabriel P., de Feyter,Pim J., Hunink,M.G.M., CT coronary angiography in patients suspected of having coronary artery disease: decision making from various perspectives in the face of uncertainty, Radiology, 253, 734-744, 2009	Superseded by Genders et al. 2015 (included)
Ghosh,Anjan, Qasim,Asif, Woollcombe,Kate, Mechery,Anthony, Cost implications of implementing NICE guideline on chest pain in rapid access chest pain clinics: an audit and cost analysis, Journal of public health (Oxford, England)J Public Health (Oxf), 34, 397-402, 2012	Cost analysis only
Goeree,Ron, Blackhouse,Gord, Bowen,James M., O'Reilly,Daria, Sutherland,Simone, Hopkins,Robert, Chow,Benjamin, Freeman,Michael, Provost,Yves, Dennie,Carole, Cohen,Eric, Marcuzzi,Dan, Iwanochko,Robert, Moody,Alan, Paul,Narinder,	Selectively excluded - a more applicable study with UK costs has been included

Study	Reason for Exclusion
Parker,John D., Cost-effectiveness of 64-slice CT angiography compared to conventional coronary angiography based on a coverage with evidence development study in Ontario, Expert review of pharmacoeconomics & outcomes researchExpert rev.pharmacoecon.outcomes res., 13, 675-690, 2013	
Hachamovitch,Rory, Johnson,James R., Hlatky,Mark A., Cantagallo,Lisa, Johnson,Barbara H., Coughlan,Martha, Hainer,Jon, Gierbolini,Jeselle, Di Carli,Marcelo F., SPARC,Investigators, The study of myocardial perfusion and coronary anatomy imaging roles in CAD (SPARC): design, rationale, and baseline patient characteristics of a prospective, multicenter observational registry comparing PET, SPECT, and CTA for resource utilization and clinical outcomes, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 16, 935-948, 2009	Study protocol only
Halpern,Ethan J., Fischman,David, Savage,Michael P., Koka,Anish R., DeCaro,Matthew, Levin,David C., Decision analytic model for evaluation of suspected coronary disease with stress testing and coronary CT angiography, Academic RadiologyAcad.Radiol., 17, 577-586, 2010	Selectively excluded - more appropriate studies with UK costs and health benefits represented by QALYs have been included
Health,Quality Ontario, Functional cardiac magnetic resonance imaging (MRI) in the assessment of myocardial viability and perfusion: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 3, 1-82, 2003	Systematic review only
Health,Quality Ontario, Multi-detector computed tomography angiography for coronary artery disease: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 5, 1-57, 2005	Systematic review only
Health,Quality Ontario, Stress echocardiography for the diagnosis of coronary artery disease: an evidence-based analysis, Ontario health technology assessment seriesOnt Health Technol Assess Ser, 10, 1-61, 2010	Systematic review only
Health,Quality Ontario, Single photon emission computed tomography for the diagnosis of coronary artery disease: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 10, 1-64, 2010	Systematic review only
Health,Quality Ontario, Positron emission tomography for the assessment of myocardial viability: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 10, 1-80, 2010	Systematic review only
Health,Quality Ontario, Magnetic resonance imaging (MRI) for the assessment of myocardial viability: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 10, 1-45, 2010	Systematic review only
Health,Quality Ontario, Cardiac magnetic resonance imaging for the diagnosis of coronary artery disease: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 10, 1-38, 2010	Systematic review only
Health,Quality Ontario, 64-slice computed tomographic angiography for the diagnosis of intermediate risk coronary artery disease: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 10, 1-44, 2010	Systematic review only
Health,Quality Ontario, Stress echocardiography with contrast for the diagnosis of coronary artery disease: an evidence-based analysis, Ontario Health Technology Assessment SeriesOnt.Health Technol.Assess.Ser., 10, 1-59, 2010	Systematic review only

Study	Reason for Exclusion
Hlatky,Mark A., Saxena,Akshay, Koo,Bon Kwon, Erglis,Andrejs, Zarins,Christopher K., Min,James K., Projected costs and consequences of computed tomography-determined fractional flow reserve, Clinical CardiologyClin.Cardiol., 36, 743-748, 2013	US based cost analysis only
Hlatky,Mark A., Shilane,David, Hachamovitch,Rory, Dicarli,Marcelo F., SPARC,Investigators, Economic outcomes in the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease registry: the SPARC Study, Journal of the American College of CardiologyJ.Am.Coll.Cardiol., 63, 1002-1008, 2014	Selectively excluded - more appropriate studies with UK costs and health benefits represented by QALYs have been included
Iwata,Kunihiro, Ogasawara,Katsuhiko, Comparison of the cost-effectiveness of stress myocardial perfusion MRI and SPECT in patients with suspected coronary artery disease, Radiological Physics and TechnologyRadiol.Phys.Technol., 6, 28-34, 2013	Selectively excluded - more appropriate studies with UK costs and health benefits represented by QALYs have been included
Kelly,D., Cole,S., Rossiter,F., Mallinson,K., Smith,A., Simpson,I., Implementation of the new NICE guidelines for stable chest pain: Likely impact on chest pain services in the UK, British Journal of CardiologyBr.J.Cardiol., 18, 185-188, 2011	No health outcomes
Khare,Rahul K., Courtney,D.Mark, Powell,Emilie S., Venkatesh,Arjun K., Lee,Todd A., Sixty-four-slice computed tomography of the coronary arteries: cost-effectiveness analysis of patients presenting to the emergency department with low-risk chest pain, Academic emergency medicine : official journal of the Society for Academic Emergency MedicineAcad Emerg Med, 15, 623-632, 2008	Selectively excluded - more applicable studies with UK costs have been included
Kreisz,Florian P., Merlin,Tracy, Moss,John, Atherton,John, Hiller,Janet E., Gericke,Christian A., The pre-test risk stratified cost-effectiveness of 64-slice computed tomography coronary angiography in the detection of significant obstructive coronary artery disease in patients otherwise referred to invasive coronary angiography, Heart, lung & circulation, 18, 200-207, 2009	Selectively excluded - more applicable studies with UK costs have been included
Ladapo,Joseph A., Jaffer,Farouc A., Hoffmann,Udo, Thomson,Carey C., Bamberg,Fabian, Dec,William, Cutler,David M., Weinstein,Milton C., Gazelle,G.Scott, Clinical outcomes and cost-effectiveness of coronary computed tomography angiography in the evaluation of patients with chest pain, Journal of the American College of CardiologyJ Am Coll Cardiol, 54, 2409-2422, 2009	Selectively excluded - more applicable studies with UK costs have been included
Lakic,Dragana, Bogavac-Stanojevic,Natasa, Jelic-Ivanovic,Zorana, Kotur-Stevuljevic,Jelena, Spasic,Slavica, Kos,Mitja, A multimarker approach for the prediction of coronary artery disease: cost-effectiveness analysis, Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research, 13, 770-777, 2010	Excluded diagnostic strategies
Lee,Dong Soo, Jang,Myoung Jin, Cheon,Gi Jeong, Chung,June Key, Lee,Myung Chul, Comparison of the cost-effectiveness of stress myocardial SPECT and stress echocardiography in suspected coronary artery disease considering the prognostic value of false-negative results, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 9, 515-522, 2002	Selectively excluded - more appropriate studies with UK costs have been included
Lee,H.J., Kim,Y.J., Ahn,J., Jang,E.J., Choi,J.E., Park,S., Song,H., Shim,J., Cha,M.J., Shon,D.W., Kim,H.K., Jang,H.J., Jung,H.W., Yoon,C.H., Kim,D.H., Lee,S.P., Lee,H., Pang,J.C., The clinical usefulness and cost-effectiveness of CT coronary angiography for the diagnosis of ischemic heart disease in patients with chest pain (Structured abstract), Health Technology Assessment Database, -,	Chinese

Study	Reason for Exclusion
2012	
Malago,Roberto, Pezzato,Andrea, Barbiani,Camilla, Tavella,Domenico, Vallerio,Paola, Pasini,Anna Fratta, Cominacini,Luciano, Mucelli,Roberto Pozzi, Role of MDCT coronary angiography in the clinical setting: economic implications, La Radiologia medicaRadiol Med, 118, 1294-1308, 2013	Selectively excluded - more appropriate studies with UK costs and health benefits represented by QALYs have been included
McKavanagh,Peter, Lusk,Lisa, Ball,Peter A., Trinick,Tom R., Duly,Ellie, Walls,Gerard M., Orr,Clare, Harbinson,Mark T., Donnelly,Patrick M., A comparison of Diamond Forrester and coronary calcium scores as gatekeepers for investigations of stable chest pain, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 29, 1547-1555, 2013	Comparison of clinical prediction tools rather than diagnostic strategies
Menon,Madhav, Lesser,John R., Hara,Hidehiko, Birkett,Richard, Knickelbine,Thomas, Longe,Terry, Flygenring,Bjorn, Henry,Jason, Schwartz,Robert, Multidetector CT coronary angiography for patient triage to invasive coronary angiography: Performance and cost in ambulatory patients with equivocal or suspected inaccurate noninvasive stress tests, Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions, 73, 497-502, 2009	Selectively excluded - more appropriate studies with UK costs and health benefits represented by QALYs have been included
Merhige,M.E., Breen,W.J., Shelton,V., Houston,T., D'Arcy,B.J., Perna,A.F., Impact of myocardial perfusion imaging with PET and 82Rb on downstream invasive procedure utilization, costs, and outcomes in coronary disease management, Journal of Nuclear MedicineJ.NUCL.MED., 48, 1069-1076, 2007	Selectively excluded - more appropriate studies with UK costs and health benefits represented by QALYs have been included
Meyer,Mathias, Nance,John W.J., Schoepf,U.Joseph, Moscariello,Antonio, Weininger,Markus, Rowe,Garrett W., Ruzsics,Balazs, Kang,Doo Kyoung, Chiaramida,Salvatore A., Schoenberg,Stefan O., Fink,Christian, Henzler,Thomas, Cost-effectiveness of substituting dual-energy CT for SPECT in the assessment of myocardial perfusion for the workup of coronary artery disease, European Journal of RadiologyEur.J.Radiol., 81, 3719-3725, 2012	Excluded population with known CAD
Min,James K., Gilmore,Amanda, Budoff,Matthew J., Berman,Daniel S., O'Day,Ken, Cost-effectiveness of coronary CT angiography versus myocardial perfusion SPECT for evaluation of patients with chest pain and no known coronary artery disease, Radiology, 254, 801-808, 2010	Selectively excluded - more applicable studies with UK costs have been included
Min,James K., Kang,Ning, Shaw,Leslee J., Devereux,Richard B., Robinson,Matthew, Lin,Fay, Legorreta,Antonio P., Gilmore,Amanda, Costs and clinical outcomes after coronary multidetector CT angiography in patients without known coronary artery disease: comparison to myocardial perfusion SPECT, Radiology, 249, 62-70, 2008	US cost analysis only
Min,James K., Shaw,Leslee J., Berman,Daniel S., Gilmore,Amanda, Kang,Ning, 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, The American journal of cardiologyAm J Cardiol, 102, 672-678, 2008	US cost analysis only
Moschetti,Karine, Favre,David, Pinget,Christophe, Pilz,Guenter, Petersen,Steffen E., Wagner,Anja, Wasserfallen,Jean Blaise, Schwitter,Juerg J., Comparative cost-effectiveness analyses of cardiovascular magnetic resonance and coronary angiography combined with fractional flow reserve for the diagnosis of coronary artery disease, Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic	Excluded diagnostic test - invasive angiography with fractional flow reserve is the comparator

Study	Reason for Exclusion
ResonanceJ Cardiovasc Magn Reson, 16, 13-, 2014	
Moschetti,Karine, Muzzarelli,Stefano, Pinget,Christophe, Wagner,Anja, Pilz,Gunther, Wasserfallen,Jean Blaise, Schulz-Menger,Jeanette, Nothnagel,Detle, Dill,Torsten, Frank,Herbert, Lombardi,Massimo, Bruder,Oliver, Mahrholdt,Heiko, Schwitter,Jurg, Cost evaluation of cardiovascular magnetic resonance versus coronary angiography for the diagnostic work-up of coronary artery disease: application of the European Cardiovascular Magnetic Resonance registry data to the German, United Kingdom, Swiss, and United States health care systems, Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic ResonanceJ Cardiovasc Magn Reson, 14, 35-, 2012	Cost analysis only
Mowatt,G., Cummins,E., Waugh,N., Walker,S., Cook,J., Jia,X., Hillis,G.S., Fraser,C., Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease, Health technology assessment (Winchester, England)Health Technol Assess, 12, iii-143, 2008	Superseded by CG95
Mowatt,G., Vale,L., Brazzelli,M., Hernandez,R., Murray,A., Scott,N., Fraser,C., McKenzie,L., Gemmell,H., Hillis,G., Metcalfe,M., Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction, Health technology assessment (Winchester, England)Health Technol Assess, 8, iii-207, 2004	Superseded by Hernandez and Vale 2007
Mundy,L., Hiller,J.E., Merlin,T., Computed tomography coronary angiography for the detection of coronary artery disease (Structured abstract), Health Technology Assessment Database, -, 2006	Narrative review only
Nance,John William Jr, Bamberg,Fabian, Schoepf,U.Joseph, Coronary computed tomography angiography in patients with chronic chest pain: systematic review of evidence base and cost-effectiveness, Journal of Thoracic ImagingJ.Thorac.Imaging, 27, 277-288, 2012	Systematic review only
Nielsen,Lene H., Olsen,Jens, Markenvard,John, Jensen,Jesper M., Norgaard,Bjarne L., Effects on costs of frontline diagnostic evaluation in patients suspected of angina: coronary computed tomography angiography vs. conventional ischaemia testing, European heart journal cardiovascular ImagingEur Heart J Cardiovasc Imaging, 14, 449-455, 2013	Selectively excluded - more appropriate studies with UK costs and health benefits represented by QALYs have been included
O'Malley,Patrick G., Greenberg,Bruce A., Taylor,Allen J., Cost-effectiveness of using electron beam computed tomography to identify patients at risk for clinical coronary artery disease, American heart journalAm Heart J, 148, 106-113, 2004	Excluded diagnostic strategy
Park,Gyung Min, Kim,Seon Ha, Jo,Min Woo, Her,Sung Ho, Han,Seungbong, Ahn,Jung Min, Park,Duk Woo, Kang,Soo Jin, Lee,Seung Whan, Kim,Young Hak, Lee,Cheol Whan, Kim,Beom Jun, Koh,Jung Min, Kim,Hong Kyu, Choe,Jaewon, Park,Seong Wook, Park,Seung Jung, Clinical impact and cost-effectiveness of coronary computed tomography angiography or exercise electrocardiogram in individuals without known cardiovascular disease, MedicineMedicine (Baltimore), 94, e917-, 2015	Excluded population - asymptomatic individuals presenting for general health checkups
Petrov,George, Kelle,Sebastian, Fleck,Eckart, Wellnhofer,Ernst, Incremental cost-effectiveness of dobutamine stress cardiac magnetic resonance imaging in patients at intermediate risk for coronary artery disease, Clinical research in cardiology : official	Selectively excluded - more applicable studies with UK costs and health benefits represented by QALYs have

Study	Reason for Exclusion
journal of the German Cardiac SocietyClin.res.cardiol., 104, 401-409, 2015	been included
Phelps,Charles E., O'Sullivan,Amy K., Ladapo,Joseph A., Weinstein,Milton C., Leahy,Kevin, Douglas,Pamela S., Cost effectiveness of a gene expression score and myocardial perfusion imaging for diagnosis of coronary artery disease, American Heart JournalAm.Heart J., 167, 697-706, 2014	Excluded diagnostic strategy
Pilz,Guenter, Patel,Pankaj A., Fell,Ulrich, Ladapo,Joseph A., Rizzo,John A., Fang,Hai, Gunnarsson,Candace, Heer,Tobias, Hoefling,Berthold, Adenosine-stress cardiac magnetic resonance imaging in suspected coronary artery disease: a net cost analysis and reimbursement implications, The international journal of cardiovascular imagingInt J Cardiovasc Imaging, 27, 113-121, 2011	German cost analysis only
Powell,Emilie S., Patterson,Brian W., Venkatesh,Arjun K., Khare,Rahul K., Cost-effectiveness of a novel indication of computed tomography of the coronary arteries, Critical Pathways in CardiologyCrit.Pathways Cardiol., 11, 20-25, 2012	Excluded population - chest pain patients with indeterminate or positive stress test results
Priest,Virginia L., Scuffham,Paul A., Hachamovitch,Rory, Marwick,Thomas H., Cost-effectiveness of coronary computed tomography and cardiac stress imaging in the emergency department: a decision analytic model comparing diagnostic strategies for chest pain in patients at low risk of acute coronary syndromes, JACC.Cardiovascular imagingJACC Cardiovasc Imaging, 4, 549-556, 2011	Selectively excluded - more applicable studies with UK costs have been included
Raman,Vivek, McWilliams,Eric T.M., Holmberg,Stephen R.M., Miles,Ken, Economic analysis of the use of coronary calcium scoring as an alternative to stress ECG in the non-invasive diagnosis of coronary artery disease, European RadiologyEur.Radiol., 22, 579-587, 2012	Excluded diagnostic strategies - ECG; calcium scoring evidence based on studies using EBCT
Sabharwal,Nikant K., Stoykova,Boyka, Taneja,Anil K., Lahiri,Avijit, 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, Journal of nuclear cardiology : official publication of the American Society of Nuclear CardiologyJ Nucl Cardiol, 14, 174-186, 2007	Cost analysis only
Sharples,L., Hughes,V., Crean,A., Dyer,M., Buxton,M., Goldsmith,K., Stone,D., Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial, Health technology assessment (Winchester, England)Health Technol Assess, 11, iii-115, 2007	Excluded population with known CAD
Shaw,L., Cost-effectiveness of myocardial perfusion scintigraphy SPECT versus other modalities, British Journal of CardiologyBr.J.Cardiol., 12, S8-S10, 2005	Narrative review only
Stacul,F., Sironi,D., Grisi,G., Belgrano,M., Salvi,A., Cova,M., 64-Slice CT coronary angiography versus conventional coronary angiography: activity-based cost analysis, La Radiologia medicaRadiol Med (Torino), 114, 239-252, 2009	Selectively excluded - more appropriate studies with UK costs and health benefits represented by QALYs have been included
Thom,Howard, West,Nicholas E.J., Hughes,Vikki, Dyer,Matthew, Buxton,Martin, Sharples,Linda D., Jackson,Christopher H., Crean,Andrew M., CECaT study group, Cost-effectiveness of initial stress cardiovascular MR, stress SPECT or stress echocardiography as a gate-keeper test, compared with upfront invasive coronary angiography in the investigation and management of patients with stable chest pain: mid-term outcomes from the CECaT randomised controlled trial, BMJ open, 4,	Excluded population - includes known CAD

Study	Reason for Exclusion
e003419-, 2014	
van der Wall,E.E., Cost analysis favours SPECT over PET and CTA for evaluation of coronary artery disease: the SPARC study, Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart FoundationNeth Heart J, 22, 257-258, 2014	Editorial
van Waardhuizen,C.N., Langhout,M., Ly,F., Braun,L., Genders,T.S.S., Petersen,S.E., Fleischmann,K.E., Nieman,K., Hunink,M.G.M., Diagnostic Performance and Comparative Cost-Effectiveness of Non-invasive Imaging Tests in Patients Presenting with Chronic Stable Chest Pain with Suspected Coronary Artery Disease: A Systematic Overview, Current Cardiology ReportsCurr.Cardiol.Rep., 16, 1-14, 2014	German
van Waardhuizen,Claudia N., Langhout,Marieke, Ly,Felisia, Braun,Loes, Genders,Tessa S.S., Petersen,Steffen E., Fleischmann,Kirsten E., Nieman,Koen, Hunink,M.G.M., Diagnostic performance and comparative cost-effectiveness of non-invasive imaging tests in patients presenting with chronic stable chest pain with suspected coronary artery disease: a systematic overview, Current cardiology reportsCurr Cardiol Rep, 16, 537-, 2014	Systematic review only
Villines,Todd C., Min,James K., Comparing outcomes and costs following cardiovascular imaging: a SPARC...but further illumination is needed, Journal of the American College of CardiologyJ Am Coll Cardiol, 63, 1009-1010, 2014	Editorial
Walker,Simon, Girardin,Francois, McKenna,Claire, Ball,Stephen G., Nixon,Jane, Plein,Sven, Greenwood,John P., Sculpher,Mark, Cost-effectiveness of cardiovascular magnetic resonance in the diagnosis of coronary heart disease: an economic evaluation using data from the CE-MARC study, Heart (British Cardiac Society), 99, 873-881, 2013	Excluded population - CE-MARC study excluded from the clinical review due to included population with known CAD
Westwood,M., Al,M., Burgers,L., Redekop,K., Lhachimi,S., Armstrong,N., Raatz,H., Misso,K., Severens,J., Kleijnen,J., A systematic review and economic evaluation of new-generation computed tomography scanners for imaging in coronary artery disease and congenital heart disease: Somatom Definition Flash, Aquilion ONE, Brilliance iCT and Discovery CT750 HD, Health technology assessment (Winchester, England)Health Technol Assess, 17, 1-243, 2013	Excluded population (this is the HTA for NICE DG3)
Zeb,Irfan, Abbas,Naeem, Nasir,Khurram, Budoff,Matthew J., Coronary computed tomography as a cost-effective test strategy for coronary artery disease assessment - a systematic review, Atherosclerosis, 234, 426-435, 2014	Systematic review only

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Appendix N: Full economic evidence tables

N.1 Review question 1

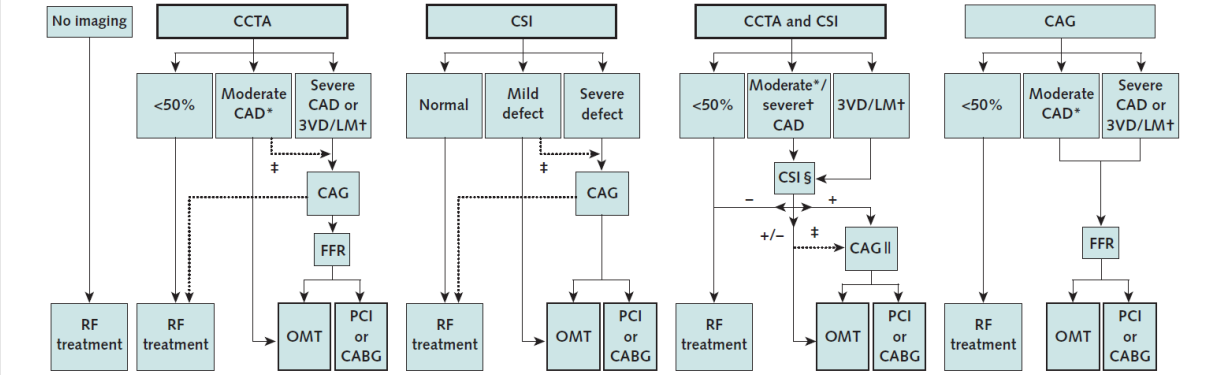
These are the full evidence tables for included economic studies. The studies are presented in reverse chronological order (latest to oldest).

Table 85:

Bibliographic reference	**Genders,Tessa S.S., Petersen,Steffen E., Pugliese,Francesca, Dastidar,Amardeep G., Fleischmann,Kirsten E., Nieman,Koen, Hunink,M.G.M., The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis, Annals of Internal Medicine. 162, 474-484, 2015**
Evaluation design	

Interventions	4 main diagnostic pathways were analysed in this study: • Coronary CT angiography (CCTA) • Cardiac stress imaging (CSI) • Coronary CT angiography with positive results followed by cardiac stress imaging • Direct catheter-based coronary angiography (CAG) The CCTA, CSI and CCTA with positive results followed by CSI pathways were analysed as both conservative and invasive diagnostic work-ups (see Other Comments field below). There are 3 alternatives for CSI: cardiac stress MRI, stress single-photon emission CT, and stress echocardiography. Therefore, there were 16 individual diagnostic strategies compared in this analysis, including no imaging. 1. No imaging **Conservative** diagnostic work-ups: 2. Stress echocardiography (ECHO) 3. Coronary computed tomography angiograph (CCTA) 4. Coronary computed tomography angiography and stress echocardiography if CCTA positive (CCTA+ECHO) 5. Coronary computed tomography angiography and single-photon emission computed tomography if CCTA positive (CCTA+SPECT) 6. Coronary computed tomography angiography and cardiac magnetic resonance imaging if CCTA positive (CCTA+CMR)

Bibliographic reference	Genders,Tessa S.S., Petersen,Steffen E., Pugliese,Francesca, Dastidar,Amardeep G., Fleischmann,Kirsten E., Nieman,Koen, Hunink,M.G.M., The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis, Annals of Internal Medicine. 162, 474-484, 2015	
		7. Single-photon emission computed tomography (SPECT) 8. Cardiac magnetic resonance imaging (CMR) **Invasive** diagnostic work-ups: 9. Stress echocardiography (ECHO-i) 10. Coronary computed tomography angiography (CCTA-i) 11. Coronary computed tomography angiography and stress echocardiography if CCTA positive (CCTA+ECHO-i) 12. Coronary computed tomography angiography and single-photon emission computed tomography if CCTA positive (CCTA+SPECT-i) 13. Coronary computed tomography angiography + cardiac magnetic resonance imaging if CCTA positive (CCTA+CMR-i) 14. Single-photon emission computed tomography (SPECT-i) 15. Cardiac magnetic resonance imaging (CMR-i) And: 16. Direct catheter-based coronary angiography (CAG) The following figure shows the range of possible diagnostic pathways. It has been sourced from the original article.

Bibliographic reference	**Genders,Tessa S.S., Petersen,Steffen E., Pugliese,Francesca, Dastidar,Amardeep G., Fleischmann,Kirsten E., Nieman,Koen, Hunink,M.G.M., The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis, Annals of Internal Medicine. 162, 474-484, 2015**
	 Diagnostic test results and treatment decisions based on them are shown. For simplicity, true disease severity (unknown to the physician) is not shown. 3VD = 3-vessel disease; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CSI = cardiac stress imaging; FFR = fractional flow reserve; LM = left main coronary stenosis; OMT = optimal medical treatment; PCI = percutaneous coronary intervention; RF = risk factor. * Defined as 1- or 2-vessel disease (50% to 70%) or ≥70% stenosis in small vessels (no or mild inducible ischemia). † Severe CAD was defined as 1- or 2-vessel disease with ≥70% stenosis (mild or severe inducible ischemia). 3VD/LM was defined as 3-vessel disease (≥50%) or left main coronary stenosis (≥50%) (severe inducible ischemia). ‡ The CCTA, CSI, and CCTA plus CSI strategies were analyzed according to conservative and invasive diagnostic work-ups. In the conservative strategy, patients with moderate CAD on CCTA or mild inducible ischemia on CSI (including those with false-positive results) were treated medically, without CAG. In the invasive strategy (*dashed lines*), patients with moderate CAD on CCTA or mild inducible ischemia were referred for CAG. Those with false-positive results on CCTA and CSI were thus identified as free of obstructive CAD or inducible ischemia, respectively. § Can show no inducible ischemia (−), suspected/mild inducible ischemia (+/−), or severe inducible ischemia (+). For patients with severe CAD and those with 3VD/LM, we assumed that 33% had mild ischemia and 67% had severe ischemia. ‖ FFR only if CSI was not done before CAG.
Base-line cohort characteristics	• 60-year-old people with stable chest pain and a low to intermediate “preimaging” probability of CAD (defined as ≥50% stenosis) based on clinical characteristics and laboratory testing, regardless of whether they had undergone previous exercise electrocardiogram • 30% probability of CAD • Without history of CAD, percutaneous coronary intervention, or coronary artery bypass graft surgery • Eligible for cardiac imaging
Type of Analysis	Cost-utility analysis
Structure	Microsimulation, decision tree for diagnostic outcomes, state-transition model for lifetime prognosis
Cycle length	1 year
Time horizon	Lifetime
Perspective	Health care

Bibliographic reference	Genders,Tessa S.S., Petersen,Steffen E., Pugliese,Francesca, Dastidar,Amardeep G., Fleischmann,Kirsten E., Nieman,Koen, Hunink,M.G.M., The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis, Annals of Internal Medicine. 162, 474-484, 2015

Country	United Kingdom, United States and the Netherlands (only UK reported here)
Currency unit	£
Cost year	2011
Discounting	3.5%
Other comments	All strategies were analysed as both conservative and invasive diagnostic work-ups. • In the invasive diagnostic work-up, people with moderate CAD on coronary CT angiography (≥50% stenosis in ≥1 vessel, regardless of severity) and patients with inducible ischaemia on cardiac stress imaging (regardless of severity) were referred for catheter-based coronary angiography. • In the conservative diagnostic work-up, patients with moderate CAD on coronary CT angiography or mild inducible ischaemia on cardiac stress imaging received optimal medical treatment without referral to catheter-based coronary angiography. Treatment and prognosis: • Normal coronary arteries, mild CAD, moderate CAD without ischaemia: risk factor management • Mild ischaemia and moderate to severe CAD: optimal medical treatment • Severe CAD and severe ischaemia: percutaneous coronary intervention • 3-vessel or left main coronary stenosis: Coronary artery bypass graft surgery Key assumptions: • Sensitivity applied equally to moderate CAD, severe CAD and 3-vessel disease or left main coronary disease • Conditional independence with regard to the sensitivity and specificity for CCTA and CSI • For CTCA and CSI, it was assumed that false positive results only showed mild CAD and mild inducible ischaemia respectively • Did not differentiate between the presence of perfusion defects and wall-motion abnormalities (both manifestations of inducible ischaemia) • Harmful effects of radiation exposure were not modelled but cumulative lifetime radiation exposure was reported • Rates of major adverse cardiac events were calculated separately for first year and all subsequent years

Bibliographic reference	**Genders,Tessa S.S., Petersen,Steffen E., Pugliese,Francesca, Dastidar,Amardeep G., Fleischmann,Kirsten E., Nieman,Koen, Hunink,M.G.M., The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis, Annals of Internal Medicine. 162, 474-484, 2015**
	Software used: DATA Pro 2009 Suite (TreeAge Pro)

Results (base case)

60 year old **men** with a pre-test probability of 30%

Test	Cost (£)	QALYs	ICER (£/QALY)
No imaging	1577	11.55	-
ECHO	2717	11.77	5000
CCTA+ECHO	2763	11.78	7000
ECHO-i	2789	11.78	Extended dominance
CCTA+SPECT	2832	11.78	Dominated
CCTA+ECHO-i	2853	11.78	32,000
CCTA	2859	11.77	Dominated
CCTA+CMR	2893	11.78	Dominated
CCTA+SPECT-i	2920	11.78	Dominated
CCTA+CMR-i	2986	11.78	Dominated
CCTA-i	2988	11.78	Dominated
SPECT	3085	11.76	Dominated
SPECT-i	3091	11.78	Dominated
CMR	3143	11.76	Dominated
CMR-i	3186	11.78	Dominated
CAG	3341	11.77	Dominated

Study author's conclusion: For UK men, the preferred strategy was optimal medical therapy without catheter-based coronary angiography if coronary CT angiography found only moderate CAD or stress imaging induced only mild ischaemia. In these strategies, stress echocardiography was consistently more effective and less expensive than other stress imaging tests.

60 year old **women** with a pre-test probability of 30%

Test	Cost (£)	QALYs	ICER (£/QALY)
No imaging	1687	11.85	-
ECHO	2844	12.08	5000

Bibliographic reference	**Genders,Tessa S.S., Petersen,Steffen E., Pugliese,Francesca, Dastidar,Amardeep G., Fleischmann,Kirsten E., Nieman,Koen, Hunink,M.G.M., The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis, Annals of Internal Medicine. 162, 474-484, 2015**

CCTA+ECHO	2881	12.08	7000
ECHO-i	2900	12.06	8000
CCTA+SPECT	2952	12.08	Dominated
CCTA+ECHO-i	2964	12.09	53,000
CCTA	2984	12.07	Dominated
CCTA+CMR	3012	12.08	Dominated
CCTA+SPECT-i	3031	12.09	Dominated
CCTA+CMR-i	3096	12.09	Dominated
CCTA-i	3098	12.08	Dominated
SPECT-i	3200	12.08	Dominated
SPECT	3231	12.06	Dominated
CMR	3277	12.07	Dominated
CMR-i	3295	12.08	Dominated
CAG	3450	12.08	Dominated

Study author's conclusion: For UK women, the optimal strategy was stress echocardiography followed by catheter-based coronary angiography if echocardiography induced mild or moderate ischaemia.

Data sources

Base-line data	Severity of disease based on CTCA and CAG data from the authors' hospital:
	• Normal coronary arteries: 40%
	• Mild CAD: 30%
	• Moderate CAD (assumed)
	  ○ No inducible ischaemia: 12%
	  ○ Mild inducible ischaemia: 6%
	• Severe CAD (assumed)
	  ○ Mild inducible ischaemia: 2%
	  ○ Severe inducible ischaemia: 4%
	• 3-vessel disease or left main coronary stenosis (assumed)
	  ○ Mild inducible ischaemia: 2%
	  ○ Severe inducible ischaemia: 4%
	Rates of major adverse cardiac events:
	• 3-vessel disease or left main coronary stenosis: CABG group from one RCT (SYNTAX trial)

Bibliographic reference	Genders,Tessa S.S., Petersen,Steffen E., Pugliese,Francesca, Dastidar,Amardeep G., Fleischmann,Kirsten E., Nieman,Koen, Hunink,M.G.M., The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis, Annals of Internal Medicine. 162, 474-484, 2015	
		• Suspected or mild inducible ischaemia and moderate to severe CAD (treated with optimal medical treatment) and patients with severe CAD and severe inducible ischaemia (treated with PCI): optimal medical treatment and PCI groups of one RCT (COURAGE trial) Risk of death from non-cardiac causes based on UK mortality rates, Office for National Statistics
	Effectiveness data	Mean diagnostic accuracy, all from meta-analyses in published literature: • CCTA sensitivity: 0.98 • CCTA specificity: 0.89 • CMR sensitivity: 0.89 • CMR specificity: 0.76 • SPECT sensitivity: 0.88 • SPECT specificity: 0.61 • ECHO sensitivity: 0.79 • ECHO specificity: 0.87 • CAG sensitivity: 1 • CAG specificity: 1 Mortality: • CCTA: 0.0006 (literature) • CMR: 0.01 (assumed) • SPECT: 0.01 (assumed) • ECHO: 0.01 (assumed) • CAG: 0.11 (literature) Periprocedural myocardial infarction (%): • CCTA: nil • CMR: nil • SPECT: nil • ECHO: nil • CAG: 0.05
	Cost data	Mean cost of diagnostic tests from NHS National Reference Costs: • CCTA: £286 • CMR: £548

<table>
<tr><td>Bibliographic reference</td><td colspan="2">Genders,Tessa S.S., Petersen,Steffen E., Pugliese,Francesca, Dastidar,Amardeep G., Fleischmann,Kirsten E., Nieman,Koen, Hunink,M.G.M., The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis, Annals of Internal Medicine. 162, 474-484, 2015</td></tr>
<tr><td rowspan="2"></td><td></td><td>• SPECT: £343
• ECHO: £236
• CAG: £1,052
Mean cost of other interventions:
• CABG: £7,318
• Myocardial infarction: £5,195
• Percutaneous coronary intervention: £3,676
• Fractional flow reserve: £460
Drug costs from Drug Tariff November 2011
Annual medication use from the literature</td></tr>
<tr><td>Utility data</td><td>EQ-5D reference values based on US general population preferences from the literature
Disutility due to tests (all assumed):
• CCTA: 0.0005
• CMR: 0.00075
• SPECT: 0.00075
• ECHO: 0.00075
• CAG: 0.005</td></tr>
<tr><td>Uncertainty</td><td colspan="2"></td></tr>
<tr><td></td><td>One-way sensitivity analysis</td><td>• The model was reanalysed at pre-test probabilities of 10%, 30%, 50%, 70% and 90%.
○ Coronary CT angiography was cost effective as a triage test before stress echocardiography when the probability was 30% or less for men and 10% for women.
○ Above this threshold, stress echocardiography alone (invasive or conservative diagnostic work-up) was cost-effective.
Men (bold text indicates optimal strategy):
<table>
<tr><th colspan="2">10%</th><th colspan="2">30%</th><th colspan="2">50%</th><th colspan="2">70%</th><th colspan="2">90%</th></tr>
<tr><td>Strategy</td><td>ICER</td><td>Strategy</td><td>ICER</td><td>Strategy</td><td>ICER</td><td>Strategy</td><td>ICER</td><td>Strategy</td><td>ICER</td></tr>
<tr><td>CCTA+ ECHO</td><td>£9000</td><td>ECHO</td><td>£5000</td><td>ECHO</td><td>£4000</td><td>ECHO</td><td>£4000</td><td>ECHO</td><td>£4000</td></tr>
<tr><td>CCTA+ ECHO-i</td><td>£20,000</td><td>CCTA+ ECHO</td><td>£7000</td><td>ECHO-i</td><td>£19,000</td><td>ECHO-i</td><td>£30,000</td><td>ECHO-i</td><td>£47,000</td></tr>
<tr><td>-</td><td></td><td>CCTA+</td><td>£32,000</td><td>CCTA+</td><td>£51,000</td><td>CCTA+</td><td>£300,00</td><td>-</td><td>-</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="2">Genders,Tessa S.S., Petersen,Steffen E., Pugliese,Francesca, Dastidar,Amardeep G., Fleischmann,Kirsten E., Nieman,Koen, Hunink,M.G.M., The optimal imaging strategy for patients with stable chest pain: a cost-effectiveness analysis, Annals of Internal Medicine. 162, 474-484, 2015</td></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td></td><td>ECHO-i</td><td></td><td>ECHO-i</td><td></td><td>ECHO-i</td><td>0</td><td></td><td></td></tr>
</table>
Women (bold text indicates optimal strategy):
<table>
<tr><th colspan="2">10%</th><th colspan="2">30%</th><th colspan="2">50%</th><th colspan="2">70%</th><th colspan="2">90%</th></tr>
<tr><td>Strategy</td><td>ICER</td><td>Strategy</td><td>ICER</td><td>Strategy</td><td>ICER</td><td>Strategy</td><td>ICER</td><td>Strategy</td><td>ICER</td></tr>
<tr><td>CCTA+ ECHO</td><td>£8000</td><td>ECHO</td><td>£5000</td><td>ECHO</td><td>£4000</td><td>ECHO</td><td>£4000</td><td>ECHO</td><td>£4000</td></tr>
<tr><td>CCTA+ ECHO-i</td><td>£12,000</td><td>CCTA+ECHO</td><td>£7000</td><td>ECHO-i</td><td>£15,000</td><td>ECHO-i</td><td>£23,000</td><td>ECHO-i</td><td>£30,000</td></tr>
<tr><td>-</td><td>-</td><td>ECHO-i</td><td>£8000</td><td>CCTA+ECHO-i</td><td>£462,000</td><td>CCTA+ECHO-i</td><td>£394,000</td><td>CCTA+ECHO-i</td><td>£181,000</td></tr>
<tr><td>-</td><td>-</td><td>CCTA+ECHO-i</td><td>£53,000</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
• Changing the sensitivity to 0.70 (from 0.79) and specificity to 0.80 (from 0.87) of stress echocardiography resulted in CCTA+ECHO-i as the optimal strategy.

• Decreasing the cost of cardiac stress MRI from £548 to £200 does not change the conclusion.</td></tr>
<tr><td>Probabilistic sensitivity analysis</td><td>Conducted but only credible intervals for mean cost and QALYs provided</td></tr>
<tr><td>Applicability</td><td colspan="2">Directly Applicable

• EQ-5D reference values based on US general population preferences, rather than UK general population preferences</td></tr>
<tr><td>Limitations</td><td colspan="2">Minor Limitations</td></tr>
<tr><td>Conflicts</td><td colspan="2">Nil. Funding provided by national health care organisations and charities.</td></tr>
</table>

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Bibliographic reference	***CG95 Model 1*** **National Clinical Guideline Centre for Acute and Chronic Conditions. 2010. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE Clinical Guideline 95**
Evaluation design	

Interventions	People only move on to subsequent tests if they test positive or indeterminate. Calcium scoring is obtained using a 64-slice CT scanner. [1] 1. Exercise electrocardiogram, then MPS with SPECT, then coronary angiography (ECG+MPS+CA) 2. Exercise electrocardiogram, then CT coronary angiography, then coronary angiography (ECG+CT+CA) 3. Exercise electrocardiogram, then coronary angiography (ECG+CA) 4. MPS with SPECT, then coronary angiography (MPS+CA) 5. CT coronary angiography, then coronary angiography (CT+CA) 6. Coronary angiography (CA) 7. Exercise electrocardiogram, then CT coronary angiography (ECG+CT) 8. CT coronary angiography (CT) 9. Calcium scoring, then CT coronary angiography (CaScore+CT) 10. Calcium scoring, then CT coronary angiography, then coronary angiography (CaScore+CT+CA) Only the results for diagnostic strategies that do not involve an exercise electrocardiogram are reported here. Exercise electrocardiogram was an excluded test in the review protocol.
Base-line cohort characteristics	Not applicable
Type of Analysis	Cost-effectiveness analysis
Structure	Decision tree
Cycle length	Not applicable
Time horizon	Not applicable – short term diagnostic model
Perspective	NHS and Personal Social Services
Country	UK
Currency unit	£
Cost year	Not specified
Discounting	Not applicable
Other comments	Key assumptions: Invasive coronary angiography is the gold standard with 100% diagnostic sensitivity and specificity

Bibliographic reference	***CG95 Model 1*** **National Clinical Guideline Centre for Acute and Chronic Conditions. 2010. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE Clinical Guideline 95**
	Software: Microsoft Excel
Results	From the study authors: • Results indicate that Ca-CT, calcium scoring followed by CT coronary angiography, is the least cost option at all levels of CAD prevalence but gives a non-negligible number of false positives and false negatives. • At 5% CAD prevalence, Ca-CT-CA has a favourable incremental cost effectiveness. CT-CA and CA only, though more effective, are considerably more expensive. • At 20% CAD prevalence, the move to Ca-CT-CA is likely to be considered cost-effective as is the further move to CT-CA. CA is the most effective and most costly. • At higher levels of prevalence (40%, 60%, 80%) the ICER for Ca-CT compared with CA only is likely to be cost effective. At 60% and 80%, CT only appears to have a favourable ICER compared to Ca-CT but there are an increased number of false positives. These false positives are more than offset by a substantial decrease in the number of false negatives identified but the most clinically and cost-effective option in this high prevalence population is likely to be CA only.

5%							
Strategy	**Total cost**	**% accurately diagnosed**	**False positives**	**False negatives**	**Total deaths**	**CAD negative deaths**	**Incremental cost per correct diagnosis**
Ca-CT	£164,211	92.66%	59.3	14.1	0.01	0.01	-
CT	£223,000	88.78%	102.4	9.8	0.02	0.02	Dominated
Ca-CT-CA	£254,407	98.58%	0	14.1	0.03	0.02	£1,524
CT-CA	£343,367	99.02%	0	9.8	0.04	0.04	£2,817
MPS-CA	£651,597	99.33%	0	6.6	0.13	0.12	Extended-dominated
CA	£850,000	99.98%	0	0	0.2	0.19	£52,774

20%							
Strategy	**Total cost**	**% accurately diagnosed**	**False positives**	**False negatives**	**Total deaths**	**CAD negative deaths**	**Incremental cost per correct diagnosis**

Bibliographic reference	***CG95 Model 1*** **National Clinical Guideline Centre for Acute and Chronic Conditions. 2010. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE Clinical Guideline 95**

Ca-CT	£169,056	89.36%	49.9	56.5	0.01	0.01	-
CT	£223,000	87.45%	86.2	39.2	0.02	0.01	Dominated
Ca-CT-CA	£341,282	94.34%	0	56.5	0.05	0.02	£3,458
CT-CA	£429,581	96.07%	0	39.2	0.07	0.03	£5,104
MPS-CA	£711,519	97.35%	0	26.3	0.15	0.1	Extended-dominated
CA	£850,000	99.98%	0	0	0.2	0.16	£10,752

40%

Strategy	Total cost	% accurately diagnosed	False positives	False negatives	Total deaths	CAD negative deaths	Incremental cost per correct diagnosis
Ca-CT	£175,516	84.95%	37.4	113.1	0.01	0	-
CT	£223,000	85.69%	64.7	78.4	0.02	0.01	Extended-dominated
Ca-CT-CA	£457,116	88.69%	0	113.1	0.08	0.01	Extended-dominated
CT-CA	£544,534	92.15%	0	78.4	0.09	0.02	Extended-dominated
MPS-CA	£791,415	94.72%	0	52.6	0.17	0.08	Extended-dominated
CA	£850,000	99.98%	0	0	0.2	0.12	£4,488

60%

Strategy	Total cost	% accurately diagnosed	False positives	False negatives	Total deaths	CAD negative deaths	Incremental cost per correct diagnosis
Ca-CT	£181,976	80.54%	24.9	169.6	0.01	0	-
CT	£223,000	83.93%	43.1	117.6	0.02	0.01	£1,210
Ca-CT-CA	£572,950	83.03%	0	169.6	0.1	0.01	Dominated
CT-CA	£659,486	88.23%	0	117.6	0.12	0.02	Extended-dominated
CA	£850,000	99.98%	0	0	0.2	0.08	£3,907
MPS-CA	£871,311	92.09%	0	79	0.19	0.05	Dominated

Bibliographic reference	***CG95 Model 1*** **National Clinical Guideline Centre for Acute and Chronic Conditions. 2010. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE Clinical Guideline 95**

80%							
Strategy	**Total cost**	**% accurately diagnosed**	**False positives**	**False negatives**	**Total deaths**	**CAD negative deaths**	**Incremental cost per correct diagnosis**
Ca-CT	£188,436	76.14%	12.5	226.1	0.01	0	-
CT	£223,000	82.16%	21.6	156.8	0.02	0	£574
Ca-CT-CA	£688,784	77.37%	0	226.1	0.13	0	Dominated
CT-CA	£774,439	84.31%	0	156.8	0.15	0.01	Extended-dominated
CA	£850,000	99.98%	0	0	0.2	0.04	£3,519
MPS-CA	£951,207	89.45%	0	105.3	0.2	0.03	Dominated

Data sources

Base-line data	
Effectiveness data	MPS with SPECT • Sensitivity: 86% (2008 HTA) • Specificity: 64% (2008 HTA) • Indeterminacy: 6% (2008 HTA) • Mortality risk: 0.005% (2008 HTA) Calcium scoring (>0) with MSCT • Sensitivity: 89% (one clinical trial using 4-slice CT) • Specificity: 43% (one clinical trial using 4-slice CT) • Indeterminacy: 2% (literature) • Mortality risk: 0% (literature) 64-slice CT coronary angiography • Sensitivity: 80% (expert opinion based on CAD threshold of 70% stenosis) • Specificity: 89% (2008 HTA) • Indeterminacy: 2% (2008 HTA)

Bibliographic reference	***CG95 Model 1*** **National Clinical Guideline Centre for Acute and Chronic Conditions. 2010. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE Clinical Guideline 95**	
		• Mortality risk: 0.001% (expert opinion, due to contrast) Invasive coronary angiography • Sensitivity: 100% (assumed) • Specificity: 100% (assumed) • Indeterminacy: 0% (assumed) • Mortality risk: 0.020% (expert opinion)
	Cost data	• MPS with SPECT: £293 (2008 HTA) • Calcium scoring: £103 (expert opinion based on half the cost of CTCA) • 64-slice CT coronary angiography: £206 (2008 HTA) • 64-slice CT coronary angiography after calcium scoring: £103 (expert opinion) • Invasive coronary angiography: £850 (assumed; average of various sources)
	Utility data	Not applicable
Uncertainty		
	One-way sensitivity analysis	• Reducing the specificity of 64-slice CT coronary angiography to 67% from 89%: ○ At 5% CAD prevalence, Ca-CT-CA is still likely to be cost-effective although with a higher ICER than base case ○ At 20% CAD prevalence, the ICER for Ca-CT-CA compared with Ca-CT is lower than the base case because the number of correct diagnoses is higher ○ At 40% CAD prevalence and above, the most cost-effective strategy is still sending all patients directly for invasive coronary angiography • Increasing the calcium score threshold from >0 to >100, the sensitivity of calcium scoring decreases to 72% but the specificity increases to 81% • Ca-CT remains the least cost option at all levels of CAD prevalence but Ca-CT-CA is less cost effective compared to the base case. • At 5% CAD prevalence, Ca-CT-CA is still likely to be cost effective with an increased ICER of £2183 • At 20% CAD prevalence, Ca-CT-CA is ruled out due to extended dominance so CT-CA is likely to be the cost effective option with an ICER of $4764 compared with Ca-CT. • At 40% CAD prevalence and greater, the strategy of sending all patients directly to invasive CA is still likely to be cost effective.

Bibliographic reference	***CG95 Model 1*** **National Clinical Guideline Centre for Acute and Chronic Conditions. 2010. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE Clinical Guideline 95**
	Probabilistic sensitivity analysis: Not done
Applicability	**Partially Applicable** • Health benefits are represented by the number of correctly diagnosed patients. There is no known threshold for cost effectiveness in terms of cost per correct diagnosis. This makes decision-making difficult compared to NICE's reference case of cost per QALY.
Limitations	**Very Serious Limitations** • Some important parameters were based on GDG expert opinion. This includes the sensitivity of CTCA, the cost of calcium scoring and the mortality risk of invasive coronary angiography. • Only the diagnostic timeframe has been modelled. No attempt has been made to extend the model to account for resource and health implications beyond this.
Conflicts	Please refer to the conflict of interest declarations for CG95

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year
[1] Acronyms reported here reflect those used in the study.

Bibliographic reference	***CG95 Model 2*** **National Clinical Guideline Centre for Acute and Chronic Conditions. 2010. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE Clinical Guideline 95**

Bibliographic reference	***CG95 Model 2*** **National Clinical Guideline Centre for Acute and Chronic Conditions. 2010. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE Clinical Guideline 95**
Evaluation design	

Interventions	First line functional testing with MPS-SPECT
Comparators	First line anatomical testing with invasive coronary angiography
Base-line cohort characteristics	People presenting with stable chest pain with a moderate (20 to 60%) pre-test likelihood of CAD
Type of Analysis	Cost effectiveness analysis
Structure	Decision tree
Cycle length	Not applicable
Time horizon	Instantaneous
Perspective	NHS and PSS
Country	UK
Currency unit	£
Cost year	Not specified
Discounting	Not applicable
Other comments	Key assumptions: • Patients with an equivocal invasive coronary angiography are assumed to have a second line functional test using MPS-SPECT

Bibliographic reference	***CG95 Model 2*** **National Clinical Guideline Centre for Acute and Chronic Conditions. 2010. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE Clinical Guideline 95**
Results	

Comparison	MPS-SPECT vs. CA
Cost	Total cost for 1000 patients: • MPS-SPECT: £344,000 • CA: £850,000
Effects	Correct diagnosis: • MPS-SPECT: 76.5% • CA: 100%
Incremental cost effectiveness ratio	£21,549 per correct diagnosis
Conclusion	From study authors: Assuming a WTP threshold of £20,000, and given that we have presented an optimistic scenario for invasive coronary angiography our model indicates that it looks unlikely that use of first line coronary angiography for the modelled scenario is cost-effective with first line functional testing.

Data sources

Base-line data	Not applicable
Effectiveness data	MPS-SPECT • Indeterminate results: 6% (2008 HTA) • Death: 0% • Sensitivity: 86% • Specificity: 64% Coronary angiography • Sensitivity: 100% (assumed) • Specificity: 100% (assumed) • Death: 0.02% • Indeterminate result: 0%
Cost data	• MPS-SPECT: £293 (2008 HTA) • Invasive coronary angiography: £850 (2008 HTA)
Utility data	Not applicable

Bibliographic reference	***CG95 Model 2*** **National Clinical Guideline Centre for Acute and Chronic Conditions. 2010. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE Clinical Guideline 95**
Uncertainty	

One-way sensitivity analysis	• Assuming a threshold of £20,000 per correct diagnosis, the pre-test likelihood of CAD is varied from 20% to 50% to find the level of equivocal invasive coronary angiography results that results in indifference between strategies. Assuming a population prevalence of 40%, invasive coronary angiography would have to be 100% sensitive and specific and have an equivocal result rate of less than 0.6% before it is likely to be considered cost-effective compared with first line functional testing using MPS with SPECT. • Replacing CA with 64-slice CT angiography: ○ Based on the inputs from CG95 Model 1, 64-slice CT coronary angiography costs less than first line functional testing using MPS with SPECT and produces a great proportion of accurately diagnosed patients.
Probabilistic sensitivity analysis	Not undertaken

Applicability	**Partially Applicable** • Only two diagnostic pathways are compared in this analysis. CTCA replaced MPS-SPECT in a sensitivity analysis. • Health benefits are represented by the number of correctly diagnosed patients. There is no known threshold for cost effectiveness in terms of cost per correct diagnosis. This makes decision-making difficult compared to NICE's reference case of cost per QALY.
Limitations	**Very Serious Limitations** • Only the diagnostic timeframe has been modelled. No attempt has been made to extend the model to account for resource and health implications beyond this.
Conflicts	Please refer to the conflicts of interest in CG95.

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Bibliographic reference	**Hernandez,Rodolfo, Vale,Luke, The value of myocardial perfusion scintigraphy in the diagnosis and management of angina and myocardial infarction: a probabilistic economic analysis, Medical decision making : an international journal of the Society for Medical Decision Making, 27, 772-788, 2007**
Evaluation design	

Interventions	1. Stress ECG, followed by SPECT if stress ECG positive or indeterminate, followed by coronary angiography if SPECT positive-high risk-result or indeterminate 2. Stress ECG, followed by coronary angiography if stress ECG positive or indeterminate 3. SPECT, followed by coronary angiography if SPECT positive-high risk-result or indeterminate (SPECT) 4. Coronary angiography (invasive test as first option) (CA) Only the results for strategies that do not include stress ECG, strategies 3 and 4, are reported here because stress ECG was excluded from the clinical review protocol.
Base-line cohort characteristics	60 years old
Type of Analysis	Cost-utility analysis
Structure	Short term diagnostic decision tree; long term consequences Markov model
Cycle length	1 year
Time horizon	25 years
Perspective	NHS
Country	UK
Currency unit	£
Cost year	2002
Discounting	6% costs; 1.5% health outcomes
Other comments	Key assumptions: • All survivors are correctly diagnosed after a maximum of 10 years either as a result of additional diagnostic tests or a nonfatal MI. This assumption reflects the believe that at-risk individuals would face other opportunities over time, such as regular health checks, in which they may receive a correct diagnosis. Software: Excel for short term diagnostic decision tree; Data 4.0 for long term consequences Markov model

Bibliographic reference	**Hernandez,Rodolfo, Vale,Luke, The value of myocardial perfusion scintigraphy in the diagnosis and management of angina and myocardial infarction: a probabilistic economic analysis, Medical decision making : an international journal of the Society for Medical Decision Making, 27, 772-788, 2007**

Results

Bold indicates optimal strategy based on a cost-effectiveness threshold of £20,000/QALY.

Strategy	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
CAD Prevalence 10.5% (base case)					
SPECT-CA	5529	12.532	-	-	**-**
CA	5929	12.541	400	0.009	£44,444/QALY
CAD Prevalence 30%					
SPECT-CA	6155	11.798	-	-	-
CA	6484	11.84	329	0.042	**£7833/QALY**
CAD Prevalence 50%					
SPECT-CA	6797	11.045	-	-	-
CA	7053	11.121	256	0.076	**£3368/QALY**
CAD Prevalence 85%					
SPECT-CA	7921	9.726	-	-	-
CA	8049	9.862	128	0.136	**£941/QALY**

Study authors' conclusion: This analysis indicates that it is possible that the incremental cost per unit of QALY for the move from stress ECG-SPECT-CA to SPECT-CA might be considered worthwhile when the prevalence of CAD is below 30%. A combination of ECG-SPECT-CA and SPECT-CA strategies would be more efficient than reliance on a strategy of ECG-CA only at these levels of prevalence of disease. Probabilistic sensitivity analysis suggests that the CG-CA strategy is highly unlikely to be the most cost-effective and does not form part of the cost-effectiveness efficiency frontier described by the CEACs. The coronary angiography option is more likely to be considered optimal at high levels of prevalence of disease (>30%) but at lower levels of prevalence of disease, the SPECT-CA strategy is more likely to be considered optimal.

Bibliographic reference	**Hernandez,Rodolfo, Vale,Luke, The value of myocardial perfusion scintigraphy in the diagnosis and management of angina and myocardial infarction: a probabilistic economic analysis, Medical decision making : an international journal of the Society for Medical Decision Making, 27, 772-788, 2007**
Data sources	

Base-line data	• Prevalence of coronary heart disease from British Heart Foundation statistics
	• Risk of MI:
	  ○ Low risk and false positives: 2.5% (1999 study)
	  ○ Untreated medium risk and false-negative medium risk: 5% (1999 study)
	  ○ High risk and false-negative high risk: 9% (1999 study)
	• Proportion nonfatal MI: 55.16% (2000 study)

Effectiveness data	Transition probabilities, including sensitivity and specificity, from 2004 HTA / systematic review
	• SPECT:
	  ○ Sensitivity: 0.83
	  ○ Specificity: 0.59
	  ○ Indeterminacy: 0.09
	  ○ Mortality risk: 0.00005
	• Coronary angiography:
	  ○ Sensitivity: 1 (assumed)
	  ○ Specificity: 1 (assumed)
	  ○ Mortality risk: 0.0015

Cost data	• SPECT: £261.91 (1997 study from the literature) • Coronary angiography: £1309.55 (1997 study from the literature) • Medical management: £311 (2004 HTA) • Myocardial infarction: (£1122 NHS reference costs 2001-02) • Percutaneous transluminal coronary angiography: £1993.74 (study from literature) • Coronary artery bypass graft: £4397 (NHS reference costs 2001-02)

Utility data	• EQ-5D from 1999 study from the literature:
	  ○ Low risk: 0.87
	  ○ Medium risk: 0.81
	  ○ High risk: 0.67
	• Adjustment for revascularisation or MI: 0.1 (assumed)

Bibliographic reference	**Hernandez,Rodolfo, Vale,Luke, The value of myocardial perfusion scintigraphy in the diagnosis and management of angina and myocardial infarction: a probabilistic economic analysis, Medical decision making : an international journal of the Society for Medical Decision Making, 27, 772-788, 2007**
Uncertainty	

One-way sensitivity analysis	Nine different sensitivity analyses conducted but only narrative reporting of results provided.
	• SA1, reducing the time horizon:
	  ○ ICERs increase
	• SA2, modify the period in which false negatives are correctly rediagnosed:
	  ○ Not reported
	• SA3, higher values for ECG indeterminacy (30% vs. 18%) and lower values for SPECT indeterminacy (2% vs. 9%):
	  ○ SPECT strategies more likely to be considered cost effective
	• SA4 and SA6, using alternative costs
	  ○ Results of the analysis were insensitive to alternative cost data
	• SA5, subgroup analysis restricted to women
	  ○ More favourable to SPECT-based strategies
	• SA7, additional two strategies involving ECHO
	  ○ ECHO-SPECT-CA: at 10.5% CAD prevalence, it dominates ECG-SPECT and ECG-SPECT
	  ○ ECHO-CA: dominated both ECG-CA and SPECT-CA
	• SA8, lower levels of CAD prevalence
	  ○ up to 1%, ECG-SPECT-CA dominated all others
	  ○ 1-4%, SPECT-based strategies dominated non-SPECT-based strategies
	  ○ 5%: only SPECT-CA dominated CA
	• SA9, changes considered in the probability distributions for sensitivity and specificity

Probabilistic sensitivity analysis	Yes. Interpretation of CEACs: • At a CAD prevalence of 10.5%, SPECT-CA has a 90% likelihood of being the optimal strategy. • At 30% CAD prevalence, SPECT-CA is most optimal up to a threshold of £20,000 per QALY when CA takes over. • For higher levels of CAD prevalence and thresholds over £10,000 per QALY, coronary angiography is the optimal strategy.

Bibliographic reference	**Hernandez,Rodolfo, Vale,Luke, The value of myocardial perfusion scintigraphy in the diagnosis and management of angina and myocardial infarction: a probabilistic economic analysis, Medical decision making : an international journal of the Society for Medical Decision Making, 27, 772-788, 2007**
Applicability	**Partially Applicable** • 2002 costs are unlikely to accurately represent costs currently experienced in 2015 • Only two relevant diagnostic strategies are compared, SPECT vs. CA. Another two strategies involving stress ECG were compared in the study but exercise ECG was not included in the review protocol.
Limitations	**Potentially serious Limitations** • Missing relevant comparators • Different discount rate to the NICE reference case
Conflicts	No. Funded by NICE, NHS and the Scottish Executive Health Department

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

N.2 Review question 2

No economic evidence was identified for this review question.

Appendix O: Cost-effectiveness analysis of testing strategies to diagnose coronary artery disease (review question 1)

O.1 Introduction

Various tests are available to diagnose coronary artery disease in people with stable chest pain of suspected cardiac origin in whom coronary artery disease cannot be diagnosed or excluded by clinical assessment alone. The tests can be used alone or in combination and they vary in diagnostic accuracy, cost and risk of complications. A cost-effectiveness analysis was undertaken to determine the most cost-effective diagnostic strategy by combining evidence on these characteristics in a single decision-making framework.

Descriptions of individual tests are contained earlier in this document.

The clinical evidence review for review question1 identified a large amount of evidence on the included index tests. Meta-analyses were carried out for some of the tests and these have been used to inform the parameters on diagnostic accuracy used in the economic model.

O.2 Methods

O.2.1 Model overview

A decision tree was developed to compare the diagnostic outcomes of 16 strategies. The strategies were based on a single test or combination of tests. For each diagnostic strategy, the proportions of patients correctly identified with coronary artery disease (true positives (TP)), incorrectly diagnosed as having coronary artery disease (false positives (FP)), correctly diagnosed without coronary artery disease (true negatives (TN)), and incorrectly diagnosed as not having coronary artery disease (false negatives (FN)), were calculated. The model identified the proportion of people as TP, FN, TN, or FP depending on the sensitivity and specificity of the individual tests based on the results of the meta-analyses, combined with the pre-test likelihood of the person having coronary artery disease. In practice the pre-test likelihood of disease would be informed by clinician assessment of clinical history, including the use of a clinical prediction tool (as per review question 2). In the economic model, the pre-test likelihood was taken as given for each subpopulation. The risk of mortality and non-fatal complications as a result of testing was also included.

The committee had extensive discussions on the advantages, disadvantages and feasibility of long term modelling compared with short term modelling. The committee decided that a short term model was more appropriate for this update for the following reasons.

1. The original guideline, CG95, provides recommendations for the diagnosis of coronary artery disease. It does not cover symptom or risk management once the cause of chest pain is known. The effectiveness of alternative treatment options is critical to the structure and parameterisation of long term modelling. Therefore, non-systematic methods using evidence outside the update would need to be used. While this is often the case in economic models, it is one of the limitations to long term modelling in this instance.

2. The preliminary results of the short term model clearly favour CTCA as a first line test for all subpopulations of pre-test likelihood and long term modelling would not have altered this conclusion.
3. The committee could not clearly define the future treatment pathways that false positives would experience. It was determined that the uncertainty this would introduce to the model was greater than the uncertainty that remains by not undertaking long term modelling.
4. Similar uncertainty exists around the future treatment pathways for false negatives, true positives and true negatives.
5. The recommendations that result from long term modelling are not expected to be different from those that are derived from short term modelling. Because of the uncertainty involved, it is unlikely that the addition of long term modelling would have altered the recommendations the committee was able to make regarding second line testing.

This presented a number of challenges for the committee in interpreting the results of the economic model. The main challenge was that results were reported in terms of cost per correct diagnosis but NICE does not have a cost-effectiveness threshold for this measure.

O.2.2 Diagnostic strategies

The following diagnostic strategies were compared in the model. The '+' sign indicates that the second test follows a positive first test result. The '-' sign indicates the second test follows a negative first test result.

1. **ICA (ICA only)**

   This strategy involves invasive coronary angiography (ICA) only. Test results can either be positive and the person has CAD (TP) or negative and the person does not have CAD (TN). Regardless of whether the person has CAD, there is a risk of death or other complication due to ICA. FP and FN are not possible in this pathway because of the assumption that ICA has perfect sensitivity and specificity.

2. **CTCA (CTCA only)**

   Computed tomography coronary angiography (CTCA) yields positive or negative results. People with a positive result either do have CAD (TP) or do not (FP). People with negative CTCA results either do have CAD (FN) or do not have CAD (TN). Fatal and non-fatal adverse reactions are possible.

3. **CTCA+ICA (CTCA followed by ICA for positive CTCA results)**

   In this strategy, people with a positive CTCA result go on to have ICA to confirm their diagnosis and follow the same path as specified in strategy 1. FP CTCA results are subsequently correctly identified as not having CAD by ICA and there is no possibility of FP results by the end of this strategy. People with negative CTCA results undergo no further testing as they have been identified as not having CAD. However, some of these people will in fact have CAD and recorded by the model as FN. The potential for adverse events during testing are treated in a similar manner as strategy 1 and 2.

4. **CTCA+SPECT (CTCA followed by SPECT for positive CTCA results)**

   In this strategy, people with a positive CTCA result go on to have myocardial perfusion scintigraphy with single photon emission computed tomography (MPS SPECT). Some of these people will have CAD (TP) and MPS SPECT is used to confirm this diagnosis. Some people with a positive CTCA result will not have CAD and MPS SPECT will serve to correct the positive CTCA result. However, not all FP CTCA results will be picked up by MPS SPECT and there is the potential for FP results following MPS SPECT at the end of the pathway. That is, SPECT can incorrectly confirm the incorrect CTCA result. Fatal and non-fatal adverse reactions are possible during MPS SPECT as a result of inducing stress on the heart. People with negative CTCA results undergo no further testing. Some of these people will in fact have CAD that is missed (FN).

5. **CTCA+ECHO (CTCA followed by ECHO for positive CTCA results)**

   This strategy follows the same methodology as strategy 4 but with stress echocardiography (ECHO) used as the method of functional testing rather than MPS SPECT. Fatal and non-fatal adverse reactions are possible during ECHO as a result of inducing stress on the heart. Both FP and FN are possible with this strategy.

6. **CTCA+CMR (CTCA followed by CMR for positive CTCA results)**

   This strategy follows the same methodology as strategy 4 but with stress echocardiography (ECHO) used as the method of functional testing rather than MPS SPECT. Fatal and non-fatal adverse reactions are possible during CMR as a result of inducing stress on the heart. Both FP and FN are possible with this strategy.

7. **SPECT+ICA (SPECT followed by ICA for positive SPECT results)**

   People with a positive MPS SPECT result go on to have ICA to confirm their diagnosis. Because some of the positive MPS SPECT results will be FP, ICA will correctly diagnose these people as not having CAD and does so with 100% accuracy. People with negative MPS SPECT results undergo no further testing but some of these people will in fact have CAD (FN). FP results are not possible by the end of this strategy.

8. **ECHO+ICA (ECHO followed by ICA for positive ECHO results)**

   This strategy is the same as strategy 7 but with ECHO as the functional test rather than SPECT.

9. **CMR+ICA (CMR followed by ICA for positive CMR results)**

   This strategy is the same as strategy 7 but with CMR as the functional test rather than SPECT.

10. **SPECT+CTCA (SPECT followed by CTCA for positive CTCA results)**

    This strategy is similar to strategy 4 but with functional testing using MPS SPECT first and CTCA for any positive MPS SPECT results. Both FP and FN results are possible at the end of this strategy.

11. **ECHO+CTCA (ECHO followed by CTCA for positive ECHO results)**

    This strategy is the same as strategy 10 but with ECHO as the functional test rather than SPECT.

12. **CMR+CTCA (CMR followed by CTCA for positive CMR results)**

    This strategy is the same as strategy 10 but with CMR as the functional test rather than SPECT.

13. **CTCA-SPECT (CTCA followed by SPECT for negative CTCA results)**

    The purpose of strategies 13, 14 and 15 is to investigate whether conducting functional testing after negative CTCA results is a cost effective means of reducing the number false positive findings.

14. **CTCA-ECHO (CTCA followed by ECHO for negative CTCA results)**

    This strategy is the same as strategy 13 but with ECHO as the functional test.

15. **CTCA-CMR (CTCA followed by CMR for negative CTCA results)**

    This strategy is the same as strategy 13 but with CMR as the functional test.

16. **No testing**

There are no strategies that involve functional testing only as the topic experts advised this would not occur in practice. CT calcium scoring is not included in any strategies because the topic experts advised it is very rare this would be carried out in isolation from a full CTCA in practice.

O.2.3 Population

The target population consisted of people with a 10% to 90% pre-test likelihood of having coronary artery disease. CG95 recommends considering non-cardiac causes of chest pain for people with an estimated pre-test likelihood of less than 10%. For people with an estimated likelihood of CAD greater than 90%, treatment is administered according to CG126, Management of Stable Angina. These two populations are outside the scope of this guideline update.

Within the 10% to 90% pre-test likelihood target population, there are 3 subpopulations specified by the original guideline:

- 10-29% pre-test likelihood of CAD
- 30-60% pre-test likelihood of CAD
- 61-90% pre-test likelihood of CAD

The base case modelled 3 scenarios of pre-test likelihoods based on the midway points of 20%, 45% and 75%.

The age and sex of the population were inconsequential in the short term model because the diagnostic accuracies of the tests were the same regardless of age or sex.

O.2.4 Time horizon, perspective and discount rate

Due to reasons listed above, the time horizon of the short term model is effectively instantaneous. The length of time it takes to conduct each test was taken into account in the cost of each test.

An NHS & PSS perspective was adopted for costs. The perspective of the person with stable chest pain was adopted for health benefits.

Discounting was not applied due to the short time horizon.

O.2.5 Model structure

The decision tree structure calculates the overall probability of certain outcomes occurring (for example, a correct diagnosis) by multiplying the combined probabilities along each branch. The structure of the decision tree is provided in Figure 23 to Figure 29. Figure 23 shows the root node and the 16 strategies that are being compared in the model. Figure 24 is the subtree for the strategy based on ICA only. Figure 25 is the subtree for the strategy based on CTCA only. Figure 26 specifies the strategy that starts with CTCA and follows with ICA for any positive CTCA results. This structure serves as the basis for strategies 7, 8 and 9 that start with a non-invasive test followed by ICA for any positive non-invasive tests. Figure 27 presents the structure for strategy 4, CTCA+SPECT. This structure serves as the basis for any other strategy that involves two non-invasive tests with the second test followed a positive first test, namely strategies 5, 6, 10, 11 and 12. Figure 28 presents the structure of strategies with 2 tests where the second test occurs after a negative first test, strategies 13, 14 and 15. Please see section O.2.1 for an overview of the model and O.2.2 for a description of each of the diagnostic strategies.

O.2.6 Outcomes

The model calculated the following outcomes for each strategy:

- Proportion of correct diagnoses
- Expected cost
- True positives
- False negatives

- True negatives
- False positives
- Deaths
- Non-fatal complications (for example, myocardial infarction, ventricular arrhythmia, transient ischaemic attack, severe bronchospasm, severe chest pain)
- Number of times a second test correctly or incorrectly overrules the results of a first test

Due to the time horizon of the model, health benefits were not measured in terms of quality adjusted life years (QALYs). This was due to the limitations of long term modelling as noted above. Decision-making was based on cost per correct diagnosis but there is no threshold for cost per correct diagnosis. Preliminary model results suggested that the combined high sensitivity and low cost of CTCA helped to simplify decision-making under these circumstances.

The main metric used to assess cost effectiveness is the incremental cost-effectiveness ratio (ICER). The ICER is calculated by dividing the difference in costs by the difference in effectiveness. In this case effectiveness is measured by the proportion of correct diagnoses which means the ICER is reported in terms of cost per correct diagnosis. If costs are lower and effectiveness is higher, the option is said to dominate and an ICER is not calculated. If costs are higher and effectiveness is lower, the option is said to be dominated, an ICER is not calculated and an alternative should be recommended. When there are more than 2 comparators options must be ranked in order of increasing cost and options ruled out by dominance or extended dominance before calculating the ICERs excluding these options. An option is dominated and ruled out if another intervention is less costly and more effective. An option is extendedly dominated if a combination of two other options would prove to be less costly and more effective.

O.2.7 Uncertainty

One-way sensitivity analysis was carried out on the following parameters.

- SA1: Separate meta-analyses were carried out based on a stenosis threshold of 70%. These results were used in a sensitivity analysis in the economic model.
- SA2: The cost of CTCA was increased to determine the threshold level where CTCA was no longer the lowest cost per correct diagnosis.

Probabilistic sensitivity analysis, where the joint uncertainty of several parameters is taken into account concurrently, was conducted. This was applied to the parameters for sensitivity and specificity for all tests, and the cost of each test.

O.2.8 Validation

The model was developed in consultation with the standing committee core members and topic experts. Model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation. The model was peer reviewed by a second experienced health economist.

O.2.9 Assumptions

The following assumptions were made and validated by the committee.

- The sensitivity and specificity of the tests were independent of the pre-test likelihood of disease.
- Conditional independence was assumed due to a lack of data identified in the clinical review on conditional dependence of concurrent diagnostic tests. Conditional dependence of test sensitivities occurs when the second test has different sensitivities for people with

the condition that have a positive first test result compared with people that have a negative first test result.

- In diagnostic strategies with 2 tests the result of the second test had precedence over the first. Where the 2 tests disagreed, the diagnosis was made based on the results of the second test. The second test confirmed the correct result of the first, incorrectly confirmed the result of the first, correctly overruled the result of the first, or incorrectly overruled the result of the first. The number of times each occurred has been reported below.
- Any death or non-fatal complication resulted in no diagnosis regardless of whether it was the only, first or second test in the diagnostic pathway.
- Indeterminate test results were not possible. This assumption was made because insufficient data was identified in the clinical review to incorporate this as a separate pathway in the model. Topic experts advised that they try not to produce indeterminate results in clinical practice.
- Sensitivity and specificity of tests did not vary with age or sex.
- ICA had perfect diagnostic accuracy. That is, it had 100% sensitivity and 100% specificity. This was consistent with its use as a gold standard in the clinical evidence review and subsequent meta-analyses.
- People in the model were administered a clinical prediction tool as part of their clinical assessment prior to entering the model. The pre-test likelihood is given and fixed for each subpopulation.
- All people are eligible to undergo all types of testing.

Figure 23: Model structure, root node with 16 strategies, strategy subtrees collapsed

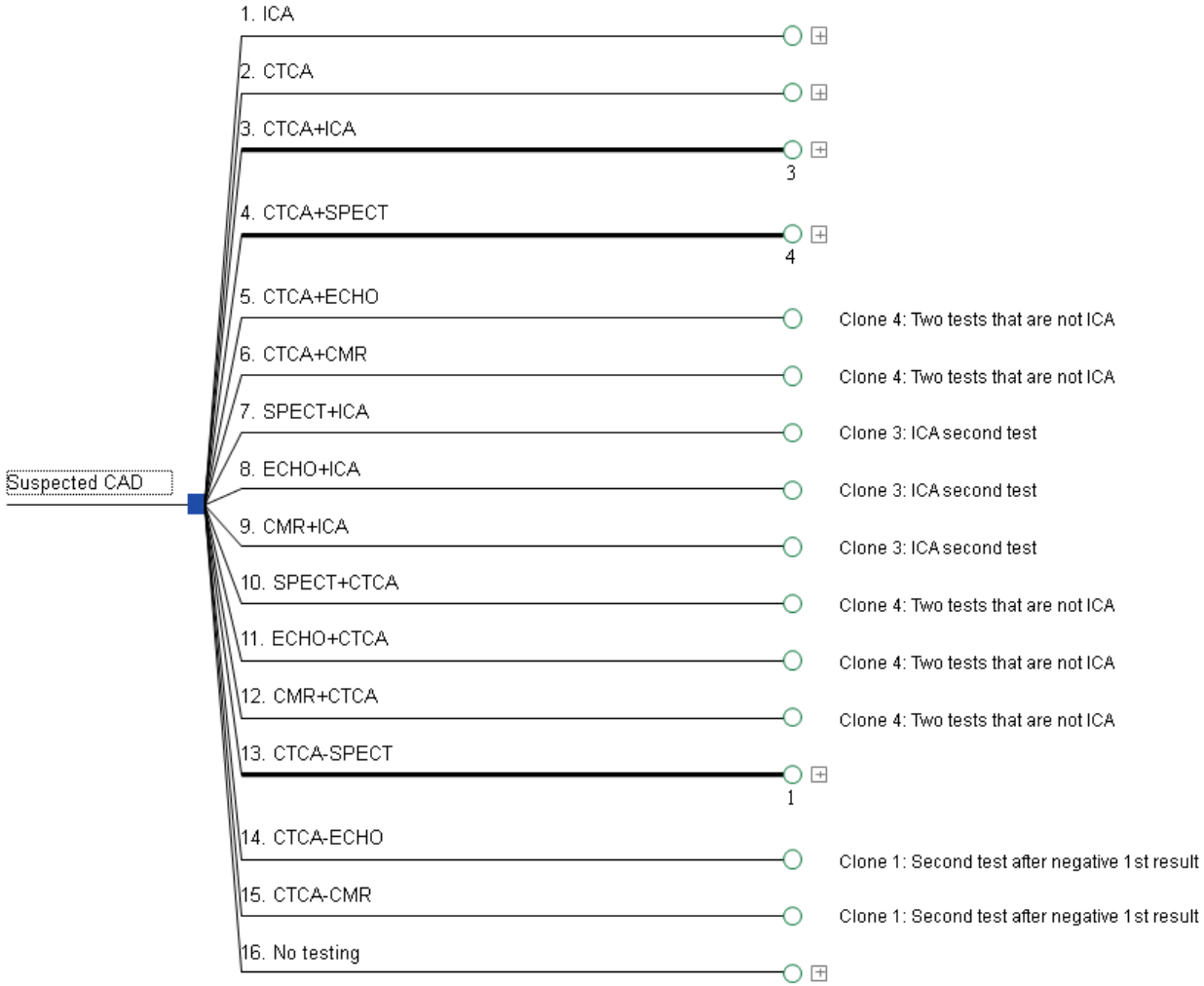


Figure 24: Model structure, strategy 1, ICA

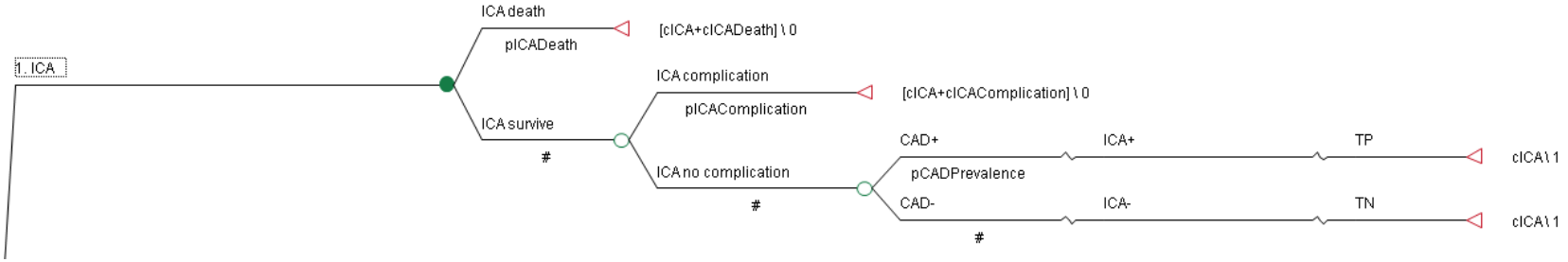


Figure 25: Model structure, strategy 2, CTCA

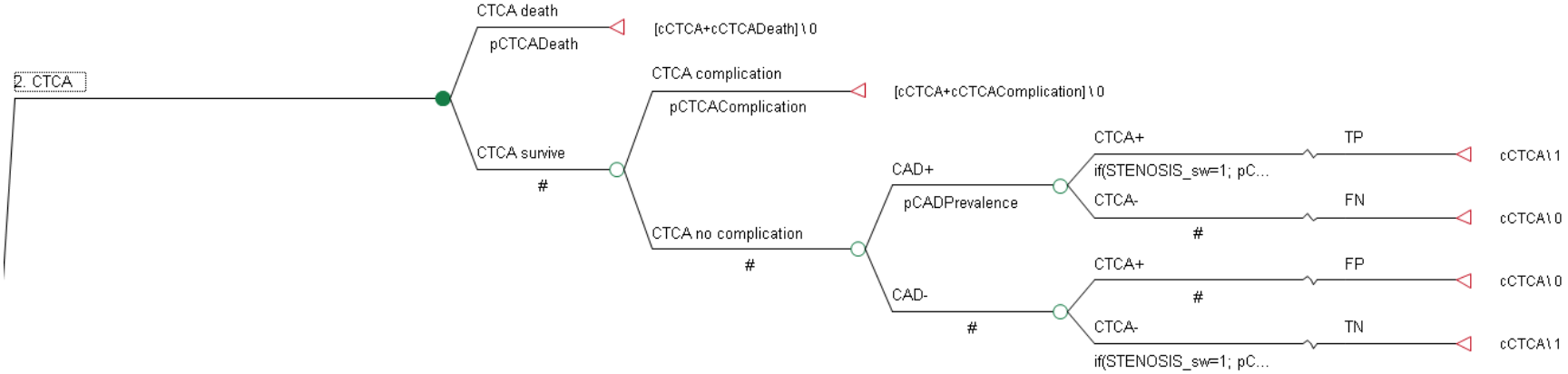


Figure 26: Model structure, strategy 3, CTCA+ICA

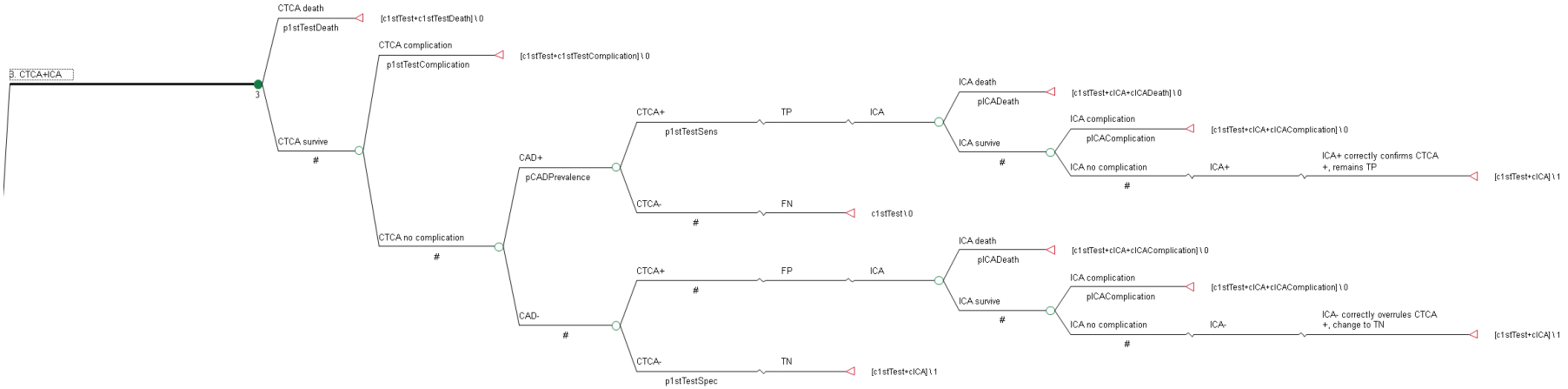


Figure 27: Model structure, strategy 4, CTCA+SPECT

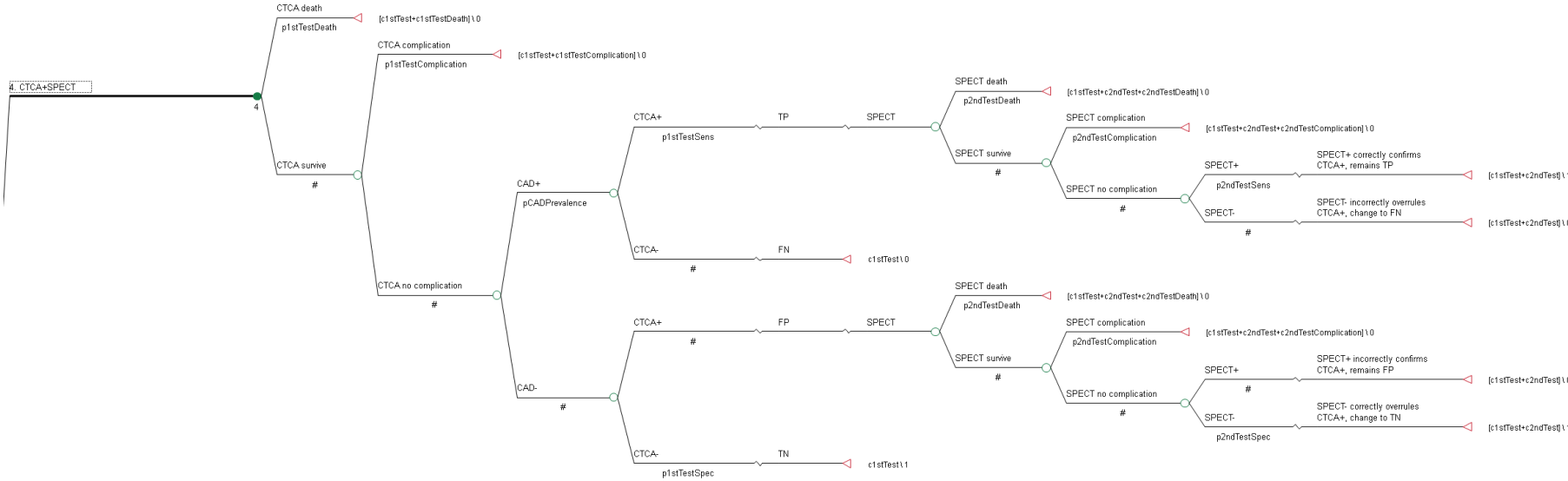


Figure 28: Model structure, strategy 13, CTCA-SPECT

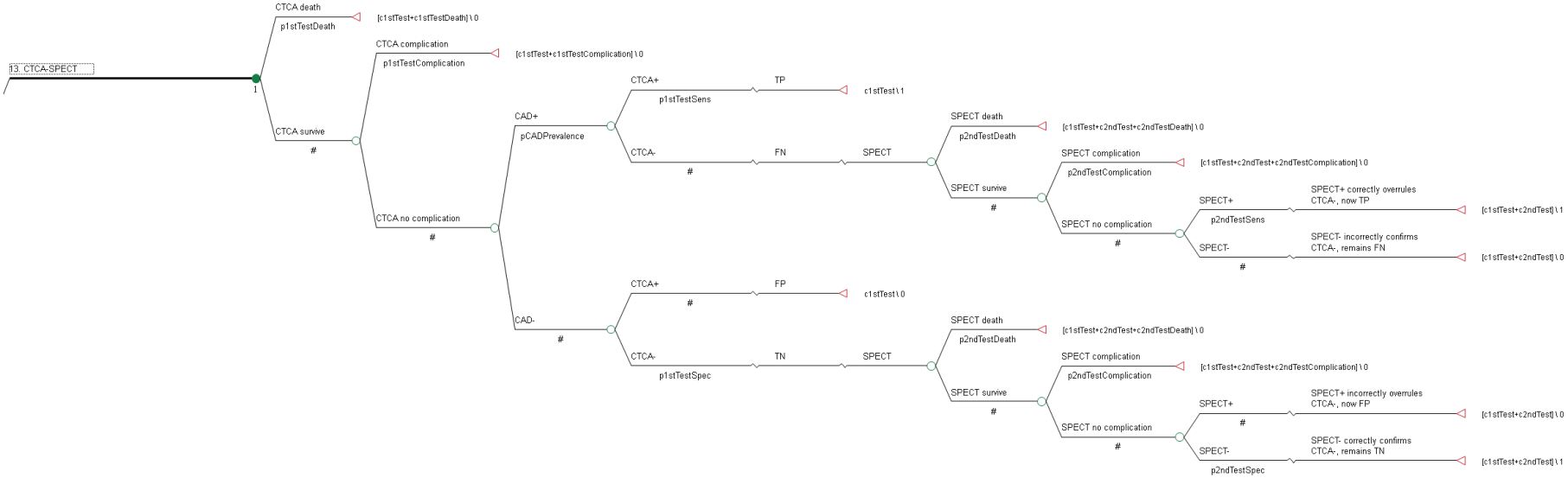


Figure 29: Model structure, strategy 16, no testing

O.3 Model inputs

O.3.1 Diagnostic accuracy

For the clinical evidence review, meta-analysis was conducted for some of the tests depending on the appropriateness of doing so on a case-by-case basis. The results of these meta-analyses were incorporated into the economic model. Coincidentally, meta-analysis was conducted for all tests that were included in the economic model. Table 86 details how evidence synthesis was conducted for each of the index tests in the clinical review and whether these results were incorporated into the economic model (light orange shading).

Table 86: Index test evidence synthesis methods and inclusion in economic model

Index test (number indicates index test number in clinical review, not economic model strategy)	**Subgroups for analysis**		**Number of studies**	**Synthesis method**	**Included in economic model**	**Diagnostic strategies in economic model this test appears in**
Index test 1. Invasive Coronary Angiography (ICA)	Not applicable		0	Not applicable	Yes	1. ICA 3. CTCA+ICA 7. SPECT+ICA 8. ECHO+ICA 9. CMR+ICA
Index test 2. Computed Tomography Coronary Angiography (CTCA)	50% sten.		25	Meta-analysis	Base case	2. CTCA 3. CTCA+ICA 4. CTCA+SPECT 5. CTCA+ECHO 6. CTCA+CMR 10. SPECT+CTCA 11. ECHO+CTCA 12. CMR+CTCA 13. CTCA-SPECT 14. CTCA-ECHO 15. CTCA-CMR
	70% sten.		3	Meta-analysis	Sensitivity analysis 1	
Index test 3. Calcium Score	50% sten.	Threshold: 0	2	Meta-analysis	No	Not applicable
		Threshold: 400	2	Meta-analysis	No	
	70% sten.	Threshold: 0	1	Single study	No	
		Threshold: 400	1	Single study	No	
Index test 4a. Stress Echocardiography (perfusion)	50% sten.		3	Meta-analysis	No	Not applicable
	70% sten.		1	Single study	No	
Index test 4b. Stress Echocardiography (Wall motion)	50% sten.	Stress method: vasodilatation	5	Meta-analysis	No	5. CTCA+ECHO 8. ECHO+ICA 11. ECHO+CTCA 14. CTCA-ECHO
		Stress	8	Meta-	Base case	

Index test (number indicates index test number in clinical review, not economic model strategy)	**Subgroups for analysis**		**Number of studies**	**Synthesis method**	**Included in economic model**	**Diagnostic strategies in economic model this test appears in**
		method: heart rate modification		analysis		
	70% sten.	Stress method: vasodilation	7	Meta-analysis	No	
		Stress method: heart rate modification	4	Meta-analysis	Sensitivity analysis 1	
Index test 5. Cardiac Magnetic Resonance (CMR) (Wall Motion)	50% sten.		1	Single study	No	Not applicable
	70% sten.		0	N/A	No	
Index test 6. CMR (perfusion)	50% sten.		5	Meta-analysis	Base case	6. CTCA+CMR 9. CMR+ICA 12. CMR+CTCA 15. CTCA-CMR
	70% sten.		3	Meta-analysis	Sensitivity analysis 1	
Index test 7a. Myocardial Perfusion Scintigraphy (MPS) (SPECT)	50% sten.		11	Meta-analysis	Base case	4. CTCA+SPECT 7. SPECT+ICA 10. SPECT+CTCA 13. CTCA-SPECT
	70% sten.		4	Meta-analysis	Sensitivity analysis 1	
Index test 7b. MPS (PET)	50% sten.		0	N/A	No	Not applicable
	70% sten.		1	Single study	No	
Index test 8. CT Fractional Flow Reserve			0	N/A	No	Not applicable
Index test 9. CT Perfusion	50% sten.		1	Single study	No	Not applicable
	70% sten.		1	Single study	No	

The parameters for sensitivity and specificity taken from the meta-analyses and used in the economic model are presented in Table 87.

Table 87: Sensitivity and specificity parameters, base case, 50% stenosis threshold

				Distribution parameters for probabilistic sensitivity analysis		
Test	**Mean sensitivity**	**Low 95% CI**	**High 95% CI**	**Distribution**	**alpha**	**beta**
Sensitivity						
ICA	1	n/a	n/a	n/a	n/a	n/a
CTCA	0.959	0.944	0.970	beta	856.171	36.604
ECHO	0.756	0.720	0.789	beta	449.342	145.026
CMR	0.840	0.764	0.895	beta	100.250	19.095
SPECT	0.806	0.735	0.861	beta	121.178	29.167
Specificity						
ICA	1	n/a	n/a	n/a	n/a	n/a
CTCA	0.785	0.717	0.840	beta	133.782	36.641
ECHO	0.804	0.706	0.876	beta	66.562	16.227
CMR	0.846	0.772	0.899	beta	104.163	18.961
SPECT	0.784	0.698	0.852	beta	85.239	23.484

O.3.2 Complications during testing

During a test there is a risk of death or non-fatal complication. Due to the variation in the type of complications that can occur, the model simply records the total probability of any non-fatal complication over the course of a strategy, rather than attempting to differentiate specific adverse effects. The effects of radiation exposure were not included due to the timeframe of the model.

Table 88: Probability of adverse effect due to testing

Test	Adverse effect	Probability per 10,000	Source
ICA	Death	7.20	West R, Ellis G, Brooks N (2006) Complications of diagnostic cardiac catheterisation: results from a confidential inquiry into cardiac catheter complications. Heart 92:810-814
	Non-fatal complication	74.00	
CTCA	Death	0.09	Caro JJ, Trindade E, McGregor M (1991) The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. American Journal of Roentgenology 156(4):825-32
	Non-fatal complication	3.10	
SPECT	Death	0.95	Lette J, Tatum JL, Fraser S et al. (1995) Safety of dipyridamole testing in 73,806 patients: the multicentre dipyridamole safety study. Journal of Nuclear Cardiology 2:3-17
	Non-fatal complication	5.01	
ECHO	Death	1.00	Expert advice
	Non-fatal complication	19.93	Secknus M, Marwick TH (1997) Evolution of dobutamine echocardiography protocols and indications: safety and side effects in 3,011 studies over 5 years. Journal of the American College of Cardiology 29:1234-40
CMR	Death	0.95	Lette J, Tatum JL, Fraser S et al. (1995) Safety of dipyridamole testing in 73,806 patients: the multicentre dipyridamole safety study. Journal of Nuclear Cardiology 2:3-17
	Non-fatal complication	5.01	

O.3.3 Costs

The costs of tests are presented in Table 89. NHS reference costs were used for all tests except for CMR. The committee determined that the reference cost for CMR was not representative of its true cost. The Payment by Results tariff has been used rather than the reference cost because it is believed to better represent the cost of CMR. Table 90 provides the cost of non-fatal complications. These costs were fixed and not altered in the probabilistic sensitivity analysis. They were approximated by calculating the weighted average of individual complications and combining this with the likelihood of them occurring relative to other complications.

Table 89: Cost of tests

				Gamma distribution parameters	
Test	**Code, description**	**Source**	**Amount**	**alpha**	**Lambda**
ICA	EY43A to EY43F, Standard cardiac catheterisation	NHS Reference Costs 2014-15, weighted average	£1684.71	16.000	0.009
CTCA	RD28Z, Complex computerised tomography scan	NHS Reference Costs 2014-15	£122.11	15.997	0.131
SPECT	RN21Z, Myocardial perfusion scan, stress only	NHS Reference Costs 2014-15	£367.29	16.001	0.044
ECHO	EY50Z, Complex echocardiogram	NHS Reference Costs 2014-15	£271.31	15.999	0.059
CMR	RA67Z, Cardiac magnetic resonance imaging scan, pre and post contrast	Enhanced Tariff Option 2015-16	£515.00	16.000	0.031

Table 90: Cost of non-fatal complications

Test	Amount	Source
ICA	£1,378.89	NHS reference costs 2014-15, weighted average of EB07A-E, AA22C-G, EY40A-D, EY41A-D, EB05A-C, AA29C-F, EB10A-E, EY42A-D, EY43A-F, with the cost of each proportioned according to how often complications occurred in West et al. 2006.
CTCA	£1,219.76	NHS reference costs 2014-15, weighted average of EB07A-E with the cost of each proportioned according to how often the complication occurred in Caro et al. 1991
SPECT	£1,554.18	NHS reference costs 2014-15, weighted average of EB10A-E, EB07A-E, with the cost of each proportioned according to how often the complications occurred in Lette et al. 1995
ECHO	£1,261.22	NHS reference costs 2014-15, weighted average of EB07A-E, EB04Z, EB08A-E, with the cost of each proportioned according to how often complications occurred in Secknus et al. 1997
CMR	£1,554.18	NHS reference costs 2014-15, weighted average of EB10A-E, EB07A-E, AA29C-F, DZ19H-K, with the cost of each proportioned according to how often the complications occurred in Lette et al. 1995

O.3.4 SA1: 70% stenosis threshold

For the first sensitivity analysis the mean sensitivities and specificities were replaced with those from the secondary meta-analysis results based on a 70% stenosis threshold. The

alternative sensitivities and specificities are provided in Table 91. The confidence intervals in this scenario are wider due to the smaller number of studies included in the meta-analyses.

Table 91: Sensitivity and specificity of tests, 70% stenosis threshold

				Distribution parameters for probabilistic sensitivity analysis		
Test	**Mean sensitivity**	**Low 95% CI**	**High 95% CI**	**Distribution**	**alpha**	**beta**
Sensitivity						
ICA	1	n/a	n/a	n/a	n/a	n/a
CTCA	0.960	0.884	0.987	beta	52.435	2.185
ECHO	0.752	0.617	0.851	beta	38.606	12.732
CMR	0.931	0.842	0.971	beta	54.295	4.024
SPECT	0.762	0.443	0.928	beta	8.266	2.582
Specificity						
ICA	1	n/a	n/a	n/a	n/a	n/a
CTCA	0.723	0.547	0.850	beta	23.512	9.008
ECHO	0.876	0.792	0.929	beta	77.028	10.904
CMR	0.809	0.559	0.934	beta	12.851	3.034
SPECT	0.758	0.583	0.876	beta	24.130	7.704

O.3.5 SA2: Cost of CTCA

The 2015-16 tariff for CTCA was similar to the NHS reference cost so the reference cost was used in the base case analysis. However, the committee expressed reservations about whether the reference cost for CTCA fully captured the true cost of the complex nature of CTCA so a threshold analysis was conducted to test the impact on results of varying the cost of CTCA.

O.3.6 SA3: Cost of CMR

The RA67Z tariff amount of £515 was used for CMR in the base case. This sensitivity analysis used the 2014-15 reference cost for RD10Z, Cardiac Magnetic Resonance Imaging Scan with pre and post contrast, £244.79, to match the source of the costs for other tests.

O.4 Results

The base case results are provided in Table 92. These are incremental results excluding dominated or extendedly dominated strategies (because dominated strategies have less correct diagnoses at a higher cost). CTCA has the lowest cost per correct diagnosis for all subgroups. For the 20% pre-test likelihood subgroup, the addition of ECHO for any positive CTCA result increases the proportion of correct diagnoses (defined as (true positives + true negatives) / total patients) by 9.09% at an additional cost of £1,096 per correct diagnosis. Alternatively, the addition of CMR for any positive CTCA result increases the proportion of correct diagnoses by 2.37% at a cost of £3,707 per correct diagnosis relative to CTCA+ECHO. The strategy of ICA only increases the proportion of correct diagnoses by 5.77% at an additional cost of £23,983 relative to CTCA+CMR. There is no cost-effectiveness threshold for cost per correct diagnosis so the optimal strategy cannot be clearly identified because we do not know at what point the additional cost exceeds an acceptable opportunity cost.

For the 45% pre-test likelihood subpopulation, the addition of CMR for any positive CTCA result increases the proportion of correct diagnoses by 3.07% at an additional cost of £9,232 per correct diagnosis relative to CTCA only.

For the 75% pre-test likelihood subpopulation, all combination strategies are dominated compared with CTCA and ICA. The ICA strategy only compared with the CTCA only strategy increases the proportion of correct diagnoses by 7.67% at a cost of £20,507 per correct diagnosis.

Cost effectiveness planes are provided in Figure 30, Figure 31 and Figure 32. These figures plot the average cost vs. the average proportion of correct diagnoses for each strategy. Undominated strategies included in incremental analysis (Table 92) are connected by a line representing the cost-effectiveness frontier with dominated and extendedly dominated options appearing to the north-west of this line.

The results for all strategies, including those that are dominated, are provided in Table 93. This table reports the average cost and effect for all strategies compared to a common baseline, no testing, and whether they are dominated or not. Undominated strategies appear in both Table 92 and Table 93.

The probabilistic sensitivity analysis results were the same as the deterministic results.

Table 92: Base case deterministic results, incremental cost effectiveness, undominated strategies only, 50% stenosis threshold

20% pre-test likelihood					
Strategy	**Cost**	**Proportion correctly diagnosed**	**Incremental cost**	**Incremental correct diagnosis**	**Incremental cost per correct diagnosis**
16. No testing	0.00	0.00%	-	-	-
2. CTCA	122.49	81.95%	122.49	81.95%	£149
5. CTCA+ECHO	222.07	91.04%	99.59	9.09%	£1,096
6. CTCA+CMR	310.07	93.41%	88.00	2.37%	£3,707
1. ICA	1,694.91	99.19%	1,384.84	5.77%	£23,983
45% pre-test likelihood					
Strategy	**Cost**	**Proportion correctly diagnosed**	**Incremental cost**	**Incremental correct diagnosis**	**Incremental cost per correct diagnosis**
16. No testing	0.00	0.00%	-	-	-
2. CTCA	122.49	86.30%	122.49	86.30%	£142
6. CTCA+CMR	405.97	89.37%	283.48	3.07%	£9,232
1. ICA	1,694.91	99.19%	1,288.93	9.82%	£13,132
75% pre-test likelihood					
Strategy	**Cost**	**Proportion correctly diagnosed**	**Incremental cost**	**Incremental correct diagnosis**	**Incremental cost per correct diagnosis**
16. No testing	0.00	0.00%	-	-	-
2. CTCA	122.49	91.52%	122.49	91.52%	£134
1. ICA	1,694.91	99.19%	1,572.42	7.67%	£20,507

Table 93: Base case results, all strategies compared with no testing

Strategy	Cost	Proportion correct diagnosis	Average cost per correct diagnosis	Dominance
20% pre-test likelihood				
16. No testing	0.00	0.00%	£0	undominated
2. CTCA	122.49	81.95%	£149	undominated
5. CTCA+ECHO	222.07	91.04%	£244	undominated
4. CTCA+SPECT	256.35	91.70%	£280	ext. dominated
14. CTCA-ECHO	296.64	70.16%	£423	abs. dominated
6. CTCA+CMR	310.07	93.41%	£332	undominated
11. ECHO+CTCA	311.47	90.93%	£343	abs. dominated
13. CTCA-SPECT	356.58	69.02%	£517	abs. dominated
10. SPECT+CTCA	408.96	91.68%	£446	abs. dominated
15. CTCA-CMR	450.52	72.94%	£618	abs. dominated
12. CMR+CTCA	550.91	93.40%	£590	abs. dominated
1. ICA	1,694.91	99.19%	£1,709	undominated
3. CTCA+ICA	1,796.73	98.85%	£1,818	abs. dominated
8. ECHO+ICA	1,876.42	94.68%	£1,982	abs. dominated
7. SPECT+ICA	1,990.02	95.79%	£2,077	abs. dominated
9. CMR+ICA	2,148.70	96.51%	£2,226	abs. dominated
45% pre-test likelihood				
16. No testing	0.00	0.00%	£0	undominated
2. CTCA	122.49	86.30%	£142	undominated
14. CTCA-ECHO	245.72	79.16%	£310	abs. dominated
5. CTCA+ECHO	272.99	85.19%	£320	abs. dominated
13. CTCA-SPECT	288.14	78.45%	£367	abs. dominated
4. CTCA+SPECT	324.79	87.18%	£373	ext. dominated
11. ECHO+CTCA	328.58	85.12%	£386	abs. dominated
15. CTCA-CMR	354.62	81.18%	£437	abs. dominated
6. CTCA+CMR	405.97	89.37%	£454	undominated
10. SPECT+CTCA	427.01	87.16%	£490	abs. dominated
12. CMR+CTCA	571.90	89.36%	£640	abs. dominated
1. ICA	1,694.91	99.19%	£1,709	undominated
8. ECHO+ICA	1,775.23	88.48%	£2,006	abs. dominated
3. CTCA+ICA	1,781.31	97.68%	£1,824	abs. dominated
7. SPECT+ICA	1,909.81	90.83%	£2,103	abs. dominated
9. CMR+ICA	2,083.06	92.37%	£2,255	abs. dominated
75% pre-test likelihood				
16. No testing	0.00	0.00%	£0	undominated
2. CTCA	122.49	91.52%	£134	undominated
14. CTCA-ECHO	184.63	89.96%	£205	abs. dominated
13. CTCA-SPECT	206.01	89.75%	£230	abs. dominated
15. CTCA-CMR	239.53	91.07%	£263	abs. dominated
5. CTCA+ECHO	334.09	78.17%	£427	abs. dominated
11. ECHO+CTCA	349.12	78.14%	£447	abs. dominated
4. CTCA+SPECT	406.91	81.75%	£498	abs. dominated
10. SPECT+CTCA	448.68	81.74%	£549	abs. dominated
6. CTCA+CMR	521.06	84.52%	£616	abs. dominated
12. CMR+CTCA	597.09	84.52%	£706	abs. dominated
8. ECHO+ICA	1,653.81	81.04%	£2,041	abs. dominated
1. ICA	1,694.91	99.19%	£1,709	undominated
3. CTCA+ICA	1,762.81	96.27%	£1,831	abs. dominated
7. SPECT+ICA	1,813.56	84.87%	£2,137	abs. dominated
9. CMR+ICA	2,004.29	87.41%	£2,293	abs. dominated

Figure 30: Cost-effectiveness plane, base case analysis, 20% pre-test likelihood, 50% stenosis threshold

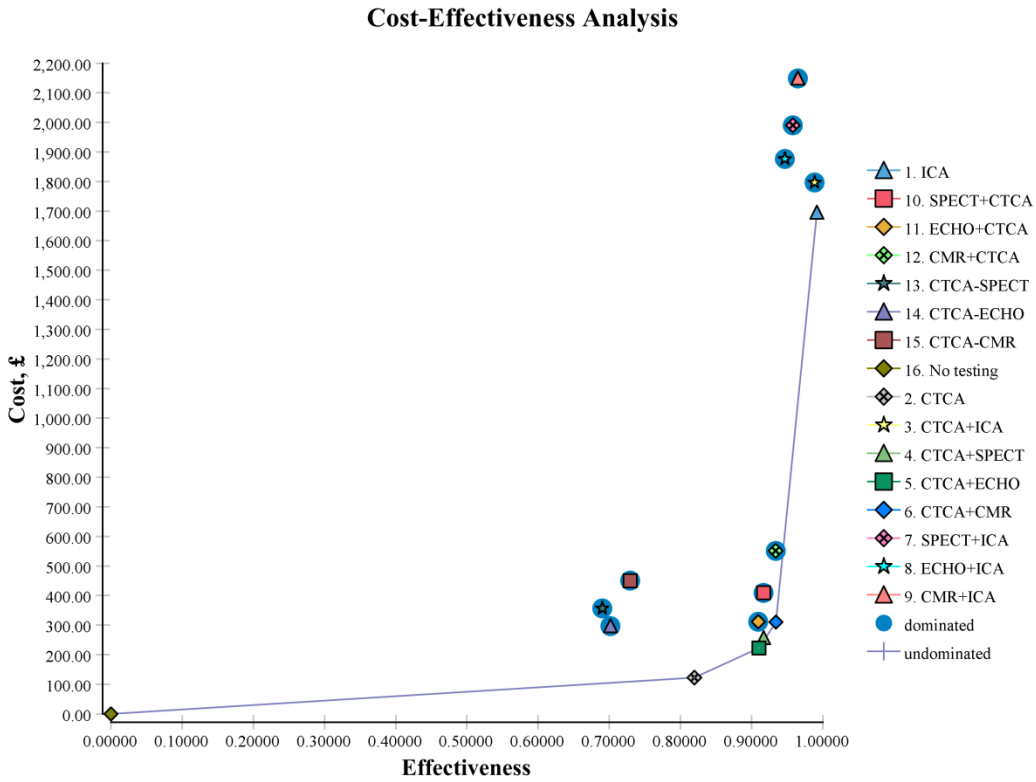


Figure 31: Cost-effectiveness plane, base case analysis, 45% pre-test likelihood, 50% stenosis threshold

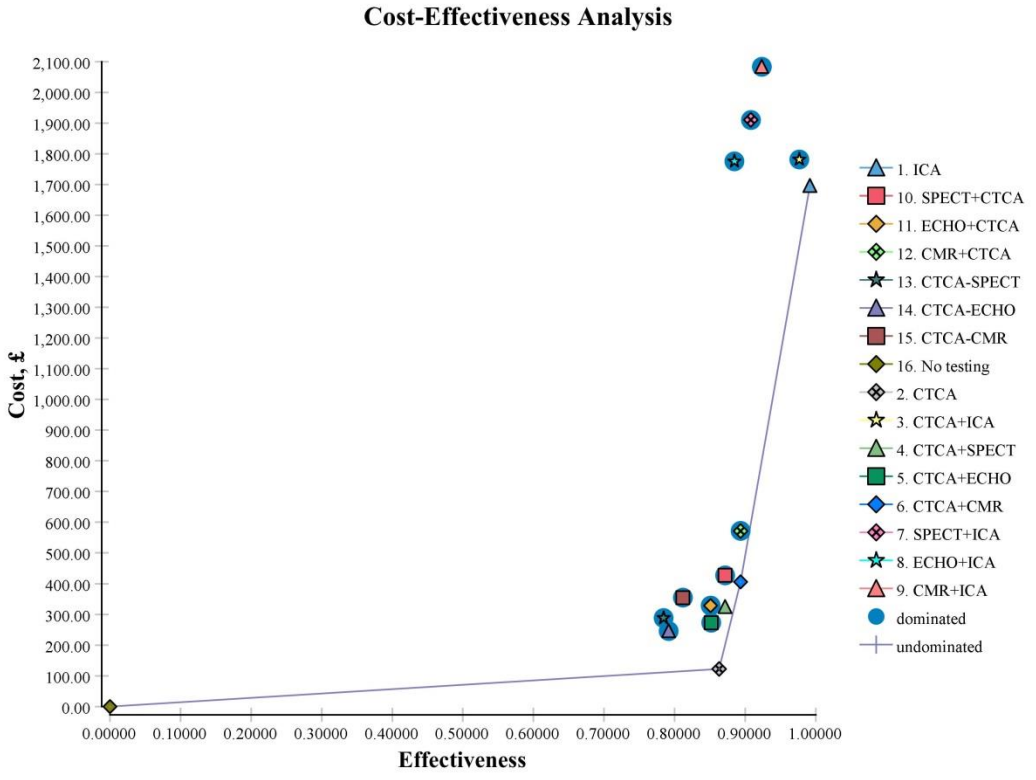
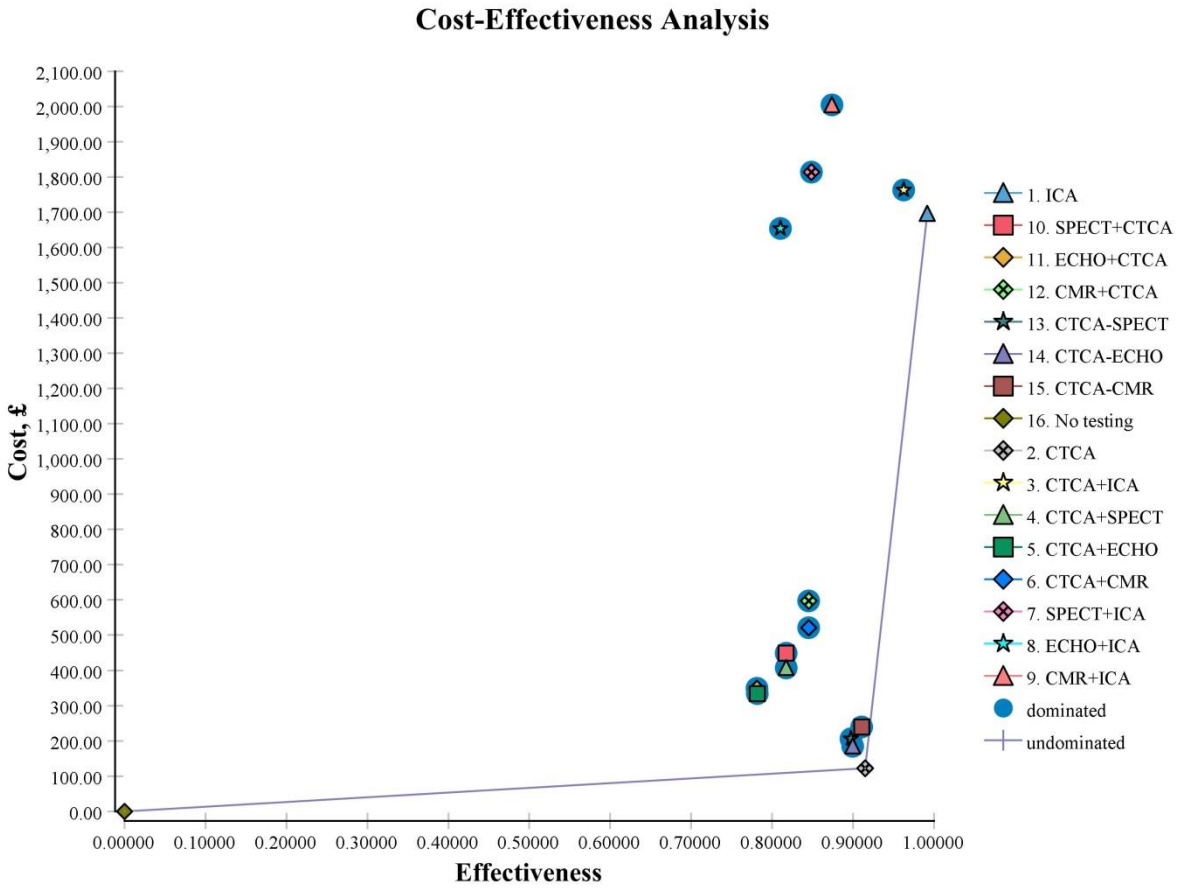


Figure 32: Cost-effectiveness plane, base case analysis, 75% pre-test likelihood, 50% stenosis threshold



O.4.14 Sensitivity analysis results

O.4.1.15 SA1: 70% stenosis threshold

Sensitivity analysis 1, where sensitivity and specificity are based on the 70% stenosis threshold, showed similar results to the base case.

Table 94: SA1, 70% stenosis threshold, incremental cost effectiveness results excluding dominated and extendedly dominated strategies

20% pre-test likelihood					
Strategy	**Cost**	**Proportion correctly diagnosed**	**Incremental cost**	**Incremental correct diagnosis**	**Incremental cost per correct diagnosis**
16. No testing	0.00	0.00%	-	-	-
2. CTCA	122.49	77.02%	122.49	77.02%	£159
5. CTCA+ECHO	235.71	91.59%	113.22	14.58%	£777
6. CTCA+CMR	335.75	93.59%	100.04	2.00%	£5,000
1. ICA	1,694.91	99.19%	1,359.16	5.60%	£24,283
45% pre-test likelihood					
Strategy	**Cost**	**Proportion correctly diagnosed**	**Incremental cost**	**Incremental correct diagnosis**	**Incremental cost per correct diagnosis**

16. No testing	0.00	0.00%	-	-	-
2. CTCA	122.49	82.94%	122.49	82.94%	£148
6. CTCA+CMR	423.79	92.25%	301.30	9.31%	£3,236
1. ICA	1,694.91	99.19%	1,271.12	6.94%	£18,316
75% pre-test likelihood					
Strategy	**Cost**	**Proportion correctly diagnosed**	**Incremental cost**	**Incremental correct diagnosis**	**Incremental cost per correct diagnosis**
16. No testing	0.00	0.00%	-	-	-
2. CTCA	122.49	90.05%	122.49	90.05%	£136
1. ICA	1,694.91	99.19%	1,572.42	9.14%	£17,199

1 **Table 95: SA1, 70% stenosis threshold, all strategies compared with no testing**

20% pre-test likelihood				
Strategy	**Cost**	**Proportion correct diagnosis**	**Average cost per correct diagnosis**	**Dominance**
16. No testing	0.00	0.00%	£0	undominated
2. CTCA	122.49	77.02%	£159	undominated
5. CTCA+ECHO	235.71	91.59%	£257	undominated
4. CTCA+SPECT	274.67	89.22%	£308	abs. dominated
14. CTCA-ECHO	283.01	70.34%	£402	abs. dominated
11. ECHO+CTCA	304.33	91.49%	£333	abs. dominated
6. CTCA+CMR	335.75	93.59%	£359	undominated
13. CTCA-SPECT	338.25	63.61%	£532	abs. dominated
10. SPECT+CTCA	410.42	89.21%	£460	abs. dominated
15. CTCA-CMR	424.84	66.69%	£637	abs. dominated
12. CMR+CTCA	556.76	93.58%	£595	abs. dominated
1. ICA	1,694.91	99.19%	£1,709	undominated
3. CTCA+ICA	1,797.62	98.83%	£1,819	abs. dominated
8. ECHO+ICA	1,874.42	94.65%	£1,980	abs. dominated
7. SPECT+ICA	1,975.35	94.90%	£2,081	abs. dominated
9. CMR+ICA	2,179.86	98.29%	£2,218	abs. dominated
45% pre-test likelihood				
Strategy	**Cost**	**Proportion correct diagnosis**	**Average cost per correct diagnosis**	**Dominance**
16. No testing	0.00	0.00%	£0	undominated
2. CTCA	122.49	82.94%	£148	undominated
14. CTCA-ECHO	236.27	79.29%	£298	abs. dominated
13. CTCA-SPECT	275.43	74.67%	£369	abs. dominated
5. CTCA+ECHO	282.45	85.47%	£330	ext. dominated
11. ECHO+CTCA	323.52	85.41%	£379	abs. dominated
15. CTCA-CMR	336.80	77.00%	£437	abs. dominated
4. CTCA+SPECT	337.50	84.18%	£401	abs. dominated
6. CTCA+CMR	423.79	92.25%	£459	undominated
10. SPECT+CTCA	426.34	84.17%	£507	abs. dominated
12. CMR+CTCA	579.40	92.24%	£628	abs. dominated
1. ICA	1,694.91	99.19%	£1,709	undominated
8. ECHO+ICA	1,771.74	88.33%	£2,006	abs. dominated
3. CTCA+ICA	1,782.45	97.70%	£1,825	abs. dominated
7. SPECT+ICA	1,876.43	88.85%	£2,112	abs. dominated
9. CMR+ICA	2,152.65	96.41%	£2,233	abs. dominated
75% pre-test likelihood				
Strategy	**Cost**	**Proportion correct diagnosis**	**Average cost per correct diagnosis**	**Dominance**
16. No testing	0.00	0.00%	£0	undominated
2. CTCA	122.49	90.05%	£136	undominated
14. CTCA-ECHO	180.18	90.02%	£200	abs. dominated
13. CTCA-SPECT	200.03	87.95%	£227	abs. dominated
15. CTCA-CMR	231.15	89.38%	£259	abs. dominated
5. CTCA+ECHO	338.53	78.13%	£433	abs. dominated
11. ECHO+CTCA	346.55	78.10%	£444	abs. dominated
4. CTCA+SPECT	412.89	78.13%	£528	abs. dominated
10. SPECT+CTCA	445.43	78.12%	£570	abs. dominated

6. CTCA+CMR	529.44	90.64%	£584	ext. dominated
12. CMR+CTCA	606.58	90.63%	£669	abs. dominated
8. ECHO+ICA	1,648.53	80.76%	£2,041	abs. dominated
1. ICA	1,694.91	99.19%	£1,709	undominated
7. SPECT+ICA	1,757.73	81.59%	£2,154	abs. dominated
3. CTCA+ICA	1,764.25	96.33%	£1,831	abs. dominated
9. CMR+ICA	2,120.00	94.16%	£2,251	abs. dominated

O.4.1.21 SA2: Cost of CTCA

Threshold analysis was conducted to identify at what cost the CTCA only strategy ceased to be the least cost per correct diagnosis option. The cost of CTCA would need to be at least £395 (from £122.11) before it would not be considered the lowest cost per correct diagnosis. EHCO+CTCA became the strategy with the lowest cost per correct diagnosis at figures above this point.

Table 96: SA2 results, threshold analysis of cost of CTCA, 50% stenosis threshold

Subpopulation	Cost of CTCA at which CTCA only was no longer the least cost per correct diagnosis	Strategy that became the least cost per correct diagnosis
20%	£394.95	ECHO+CTCA
45%	£494.84	ECHO+CTCA
75%	£710.32	ECHO+CTCA

O.4.1.38 SA3: Cost of CMR

The results for the sensitivity analysis where the cost of CMR was reduced to £244.79 from £515 are provided in Table 97. For a 20% pre-test likelihood, CTCA+ECHO became a dominated strategy and was excluded from the incremental analysis. The average cost of CTCA+CMR decreased to £211.80 from £310.07 and the incremental cost per correct diagnosis for CTCA+CMR decreased to £779 from £3,707. For a 45% pre-test likelihood, CTCA+ECHO was dominated and the incremental cost per correct diagnosis for CTCA+CMR decreased to £4,396 from £9,232 in the base case. For a 75% pre-test likelihood, CTCA+CMR was dominated in both the base case and SA3.

Table 97: SA3, reduced cost for CMR, incremental results, undominated strategies only, 50% stenosis threshold

20% pre-test likelihood					
Strategy	**Cost**	**Proportion correctly diagnosed**	**Incremental cost**	**Incremental correct diagnosis**	**Incremental cost per correct diagnosis**
16. No testing	0.00	0.00%	-	-	-
2. CTCA	122.49	81.95%	122.49	81.95%	£149
6. CTCA+CMR	211.80	93.41%	89.31	11.46%	£779
1. ICA	1,694.91	99.19%	1,483.11	5.77%	£25,685
45% pre-test likelihood					
Strategy	**Cost**	**Proportion correctly diagnosed**	**Incremental cost**	**Incremental correct diagnosis**	**Incremental cost per correct diagnosis**
16. No testing	0.00	0.00%	-	-	-
2. CTCA	122.49	86.30%	122.49	86.30%	£142
6. CTCA+CMR	257.46	89.37%	134.97	3.07%	£4,396
1. ICA	1,694.91	99.19%	1,437.45	9.82%	£14,645

75% pre-test likelihood					
Strategy	**Cost**	**Proportion correctly diagnosed**	**Incremental cost**	**Incremental correct diagnosis**	**Incremental cost per correct diagnosis**
16. No testing	0.00	0.00%	-	-	-
2. CTCA	122.49	91.52%	122.49	91.52%	£134
1. ICA	1,694.91	99.19%	1,572.42	7.67%	£20,507

Table 98: SA3, reduced cost of CMR, all strategies compared with no testing, 50% stenosis threshold

20% pre-test likelihood				
Strategy	**Cost**	**Proportion correct diagnosis**	**Average cost per correct diagnosis**	**Dominance**
16. No testing	0.00	0.00%	£0	undominated
2. CTCA	122.49	81.95%	£149	undominated
6. CTCA+CMR	211.80	93.41%	£227	undominated
5. CTCA+ECHO	222.07	91.04%	£244	abs. dominated
4. CTCA+SPECT	256.35	91.70%	£280	abs. dominated
15. CTCA-CMR	278.67	72.94%	£382	abs. dominated
12. CMR+CTCA	280.56	93.40%	£300	abs. dominated
14. CTCA-ECHO	296.64	70.16%	£423	abs. dominated
11. ECHO+CTCA	311.47	90.93%	£343	abs. dominated
13. CTCA-SPECT	356.58	69.02%	£517	abs. dominated
10. SPECT+CTCA	408.96	91.68%	£446	abs. dominated
1. ICA	1,694.91	99.19%	£1,709	undominated
3. CTCA+ICA	1,796.73	98.85%	£1,818	abs. dominated
8. ECHO+ICA	1,876.42	94.68%	£1,982	abs. dominated
9. CMR+ICA	1,878.49	96.51%	£1,946	abs. dominated
7. SPECT+ICA	1,990.02	95.79%	£2,077	abs. dominated
45% pre-test likelihood				
Strategy	**Cost**	**Proportion correct diagnosis**	**Average cost per correct diagnosis**	**Dominance**
16. No testing	0.00	0.00%	£0	undominated
2. CTCA	122.49	86.30%	£142	undominated
15. CTCA-CMR	233.01	81.18%	£287	abs. dominated
14. CTCA-ECHO	245.72	79.16%	£310	abs. dominated
6. CTCA+CMR	257.46	89.37%	£288	undominated
5. CTCA+ECHO	272.99	85.19%	£320	abs. dominated
13. CTCA-SPECT	288.14	78.45%	£367	abs. dominated
12. CMR+CTCA	301.55	89.36%	£337	abs. dominated
4. CTCA+SPECT	324.79	87.18%	£373	abs. dominated
11. ECHO+CTCA	328.58	85.12%	£386	abs. dominated
10. SPECT+CTCA	427.01	87.16%	£490	abs. dominated
1. ICA	1,694.91	99.19%	£1,709	undominated
8. ECHO+ICA	1,775.23	88.48%	£2,006	abs. dominated
3. CTCA+ICA	1,781.31	97.68%	£1,824	abs. dominated
9. CMR+ICA	1,812.85	92.37%	£1,963	abs. dominated
7. SPECT+ICA	1,909.81	90.83%	£2,103	abs. dominated
75% pre-test likelihood				
Strategy	**Cost**	**Proportion correct diagnosis**	**Average cost per correct diagnosis**	**Dominance**
16. No testing	0.00	0.00%	£0	undominated
2. CTCA	122.49	91.52%	£134	undominated
15. CTCA-CMR	178.21	91.07%	£196	abs. dominated
14. CTCA-ECHO	184.63	89.96%	£205	abs. dominated
13. CTCA-SPECT	206.01	89.75%	£230	abs. dominated
6. CTCA+CMR	312.25	84.52%	£369	abs. dominated
12. CMR+CTCA	326.75	84.52%	£387	abs. dominated
5. CTCA+ECHO	334.09	78.17%	£427	abs. dominated
11. ECHO+CTCA	349.12	78.14%	£447	abs. dominated
4. CTCA+SPECT	406.91	81.75%	£498	abs. dominated
10. SPECT+CTCA	448.68	81.74%	£549	abs. dominated
8. ECHO+ICA	1,653.81	81.04%	£2,041	abs. dominated
1. ICA	1,694.91	99.19%	£1,709	undominated
9. CMR+ICA	1,734.08	87.41%	£1,984	abs. dominated
3. CTCA+ICA	1,762.81	96.27%	£1,831	abs. dominated

7. SPECT+ICA	1,813.56	84.87%	£2,137	abs. dominated

O.4.1.41 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted to take into account the joint uncertainty of multiple parameters at once using Monte Carlo simulation. Cost-effectiveness acceptability curves show the proportion of microsimulations that favour a particular strategy at varying values of the cost-effectiveness threshold in terms of cost per correct diagnosis. Figure 33, Figure 34 and Figure 35, present cost-effectiveness acceptability curves for the undominated strategies in the base case analysis. The ability of these graphs to contribute to decision making is limited because there is no threshold for cost per correct diagnosis. However, they do yield some usable information. For example, in Figure 33 for people with a 20% pre-test likelihood of disease, the likelihood that CTCA, CTCA+ECHO or CTCA+CMR are the most cost-effective strategies changes depending on the threshold within a band of £500 to £4,000 per correct diagnosis, highlighting the uncertainty and how close these strategies are for this subpopulation. In contrast, CTCA is clearly favoured for the 75% pre-test likelihood (Figure 35).

For the 20% pre-test likelihood subpopulation, CTCA accounted for the majority of lowest cost per correct diagnosis simulations up until around £1,250 per correct diagnosis when CTCA+ECHO became the most likely to be the lowest cost per correct diagnosis. CTCA+CMR was most likely to be the least cost per correct diagnosis at a cost effectiveness threshold above around £3,800.

For a 45% pre-test likelihood, CTCA remained the most likely to be the lowest cost per correct diagnosis up until a relatively high value around £9,000 when CTCA+CMR became the lowest cost per correct diagnosis.

For the 75% pre-test likelihood, CTCA remained 100% likely to be the lowest cost per correct diagnosis up to £10,000.

The probabilistic sensitivity analysis found that CTCA had the least cost per correct diagnosis for 100% of the simulations for all 3 subpopulations.

The scatterplots showing 1,000 microsimulations for each subpopulation are presented in Figure 36, Figure 37, and Figure 38.

Figure 33: Cost effectiveness acceptability curve, 20% pre-test likelihood, 50% stenosis threshold

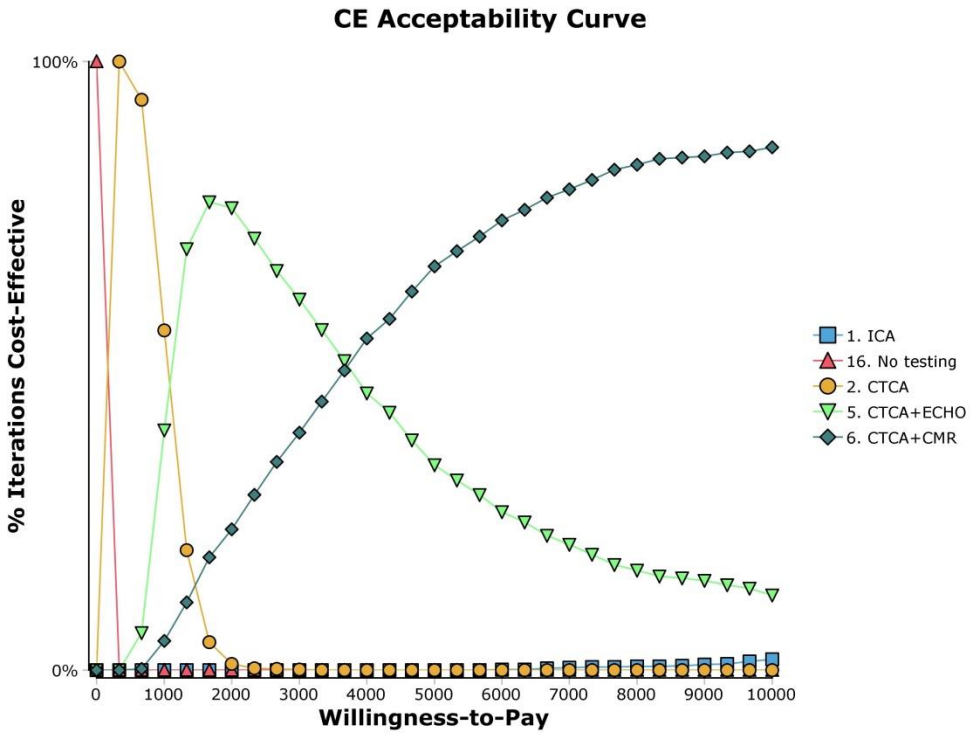


Figure 34: Cost-effectiveness acceptability curve, 45% pre-test likelihood, 50% stenosis threshold

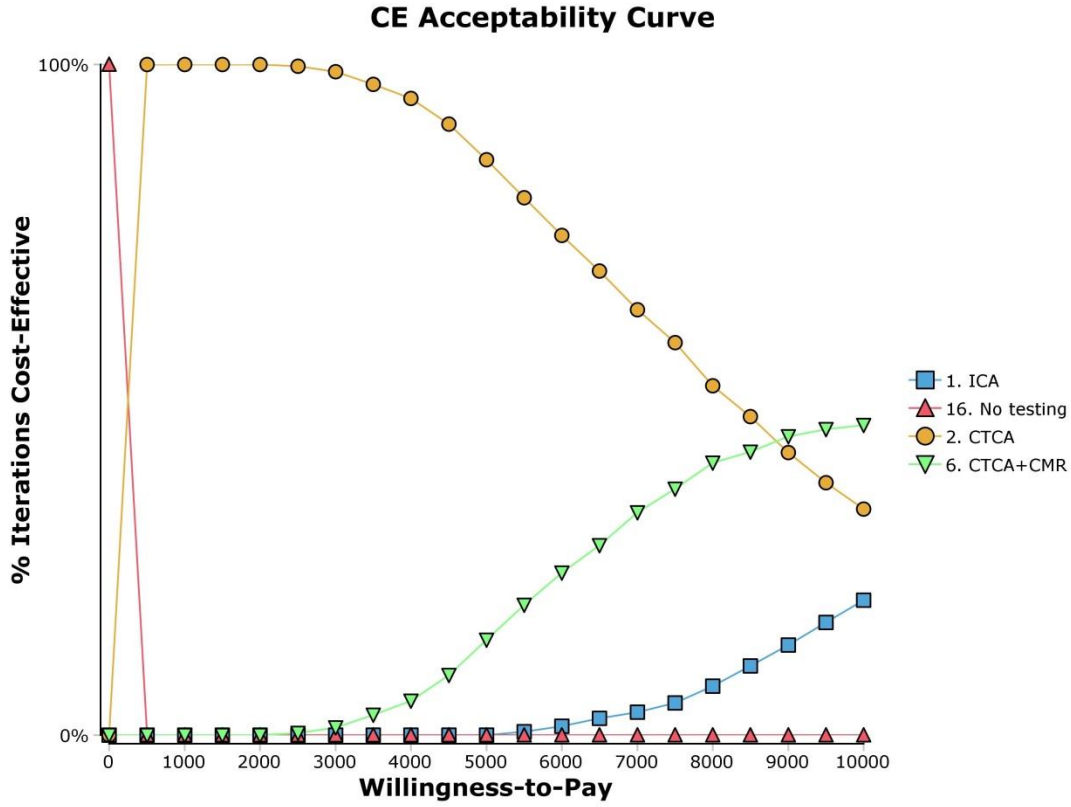


Figure 35: Cost-effectiveness acceptability curve, 75% pre-test likelihood, 50% stenosis threshold

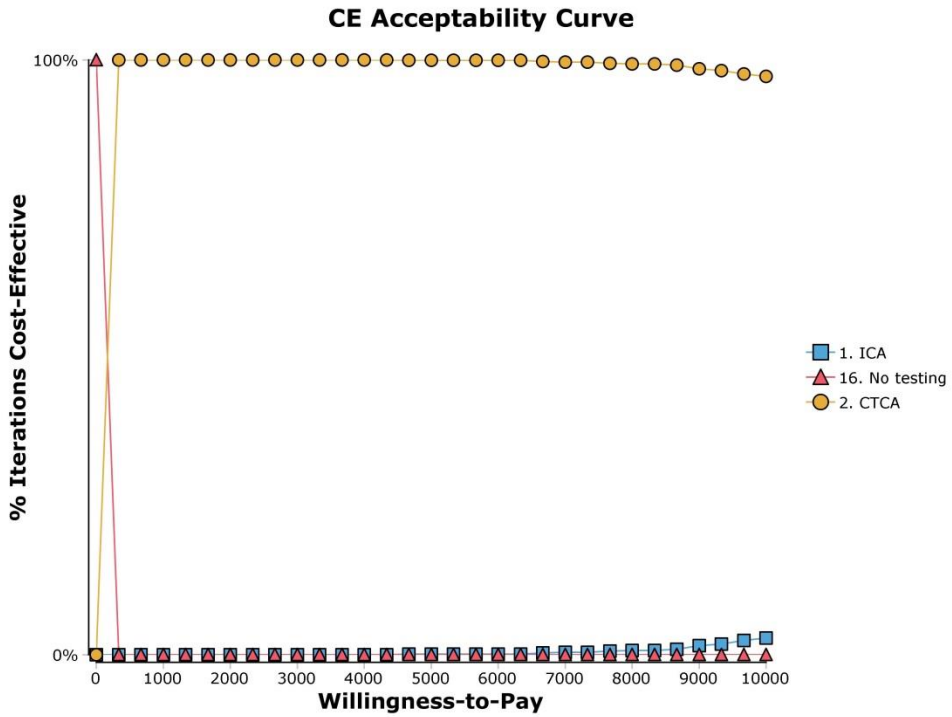


Figure 36: Cost-effectiveness scatterplot, 20% pre-test likelihood of CAD, 50% stenosis threshold

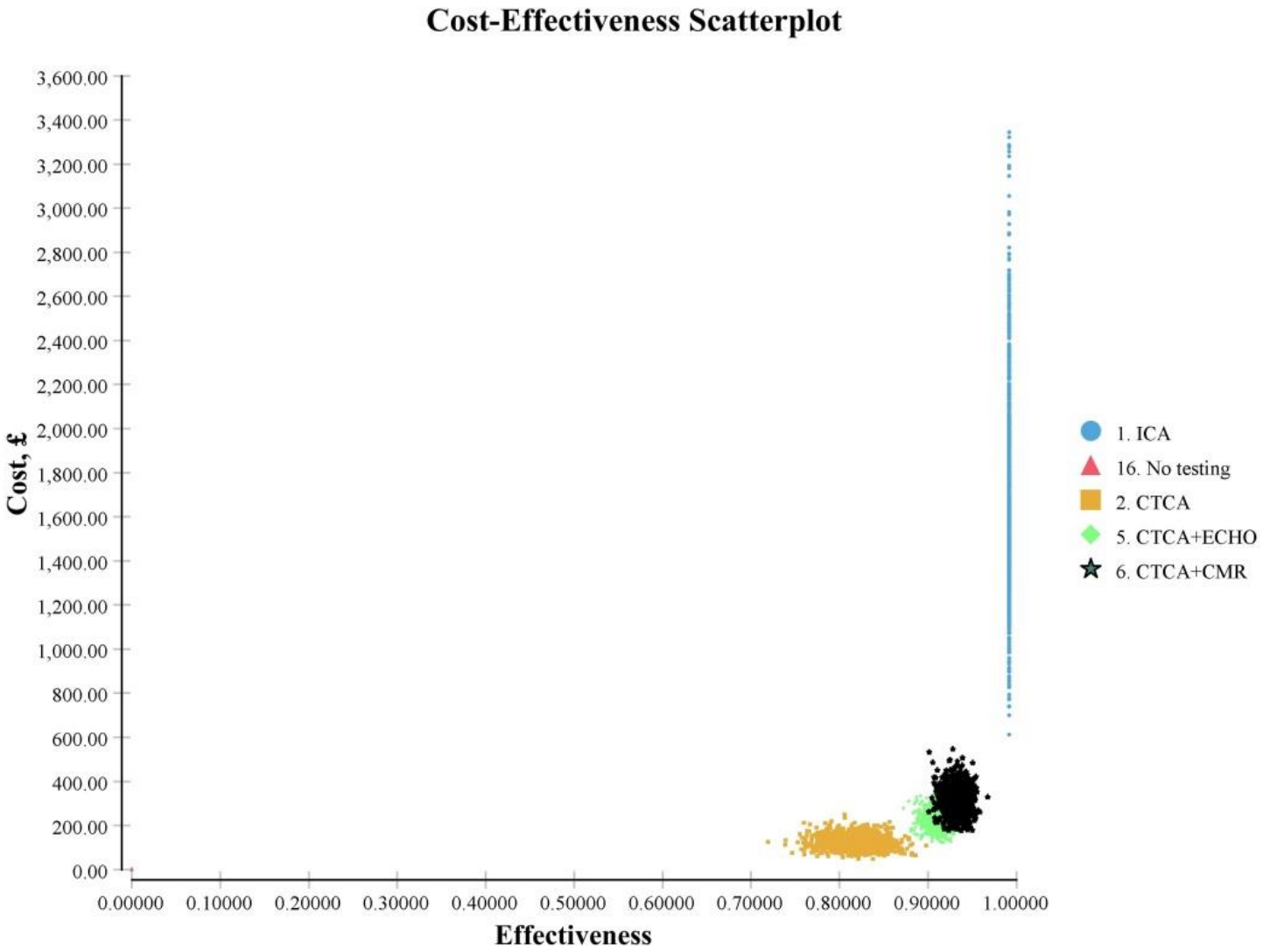


Figure 37: Cost-effectiveness scatterplot, 45% pre-test likelihood, 50% stenosis threshold

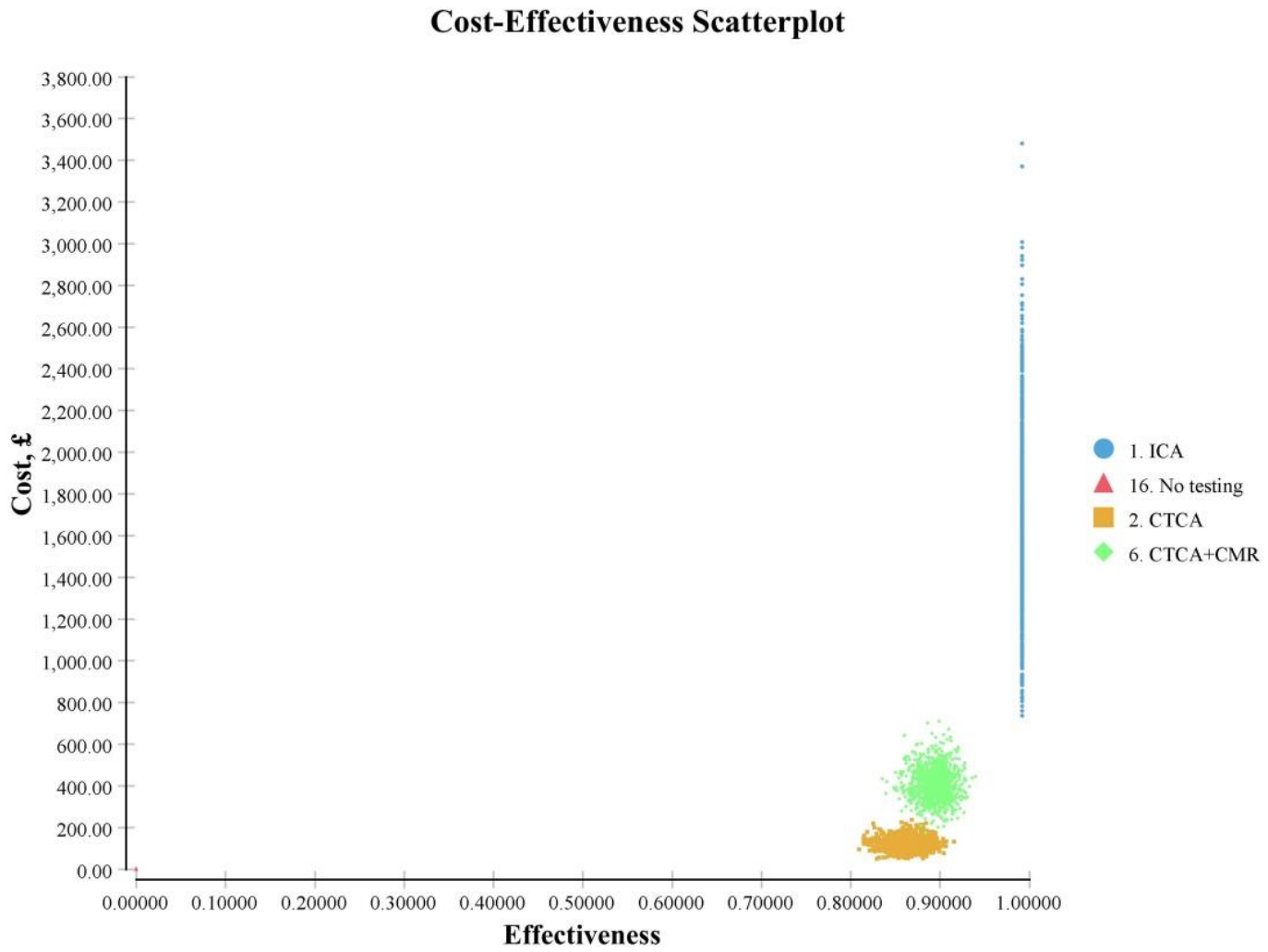
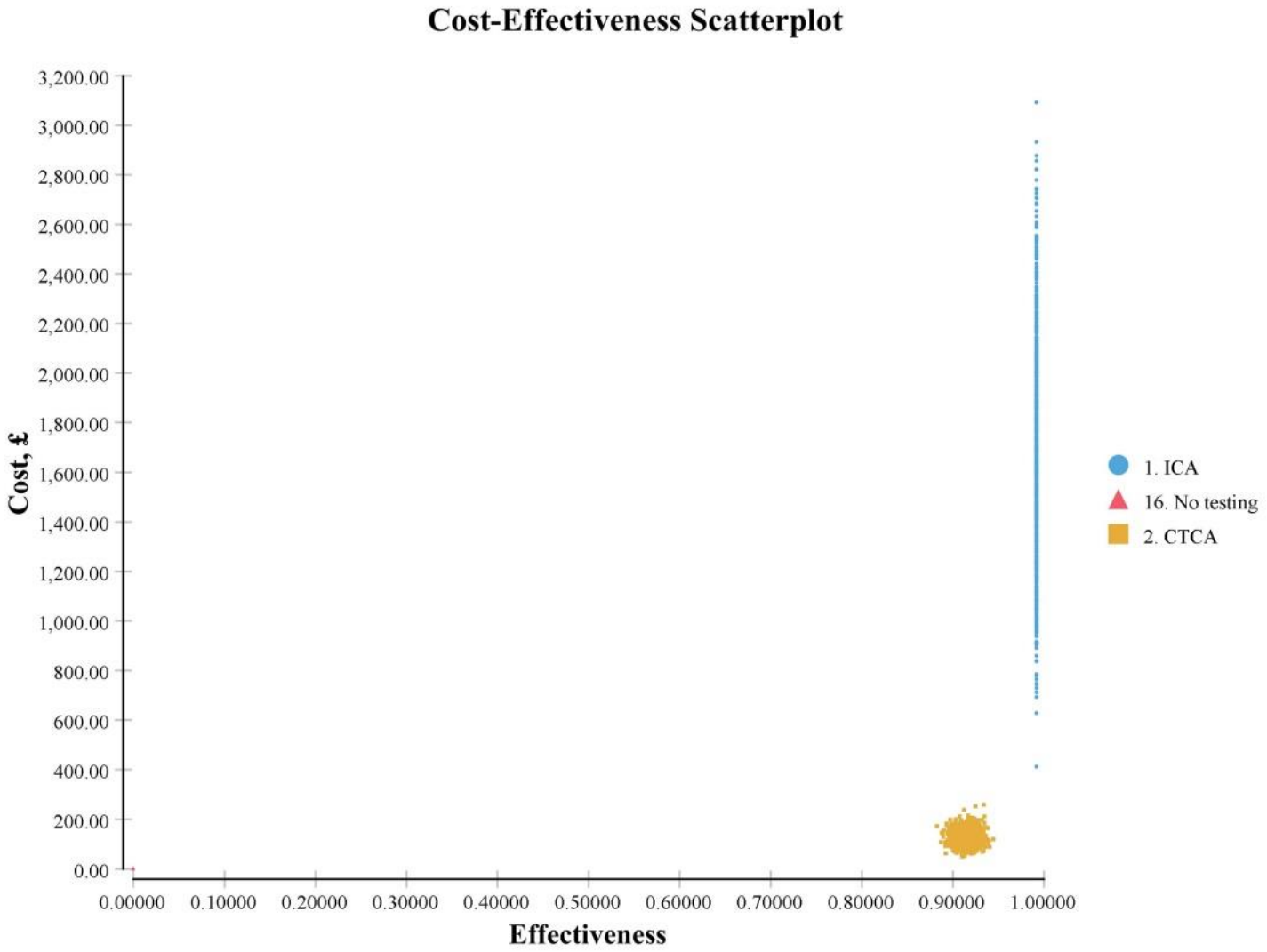


Figure 38: Cost-effectiveness scatterplot, 75% pre-test likelihood, 50% stenosis threshold



O.4.1.51 Additional model outcomes

The number of deaths, non-fatal complications, false positives, false negatives, number of times the second test correctly overruled the first, number of times the second test incorrectly overruled the first, number of times the second test correctly confirmed the first, and number of times the second test incorrectly confirmed the first are provided in Table 99, Table 100, and Table 101 for each of the pre-test likelihood subgroups.

Strategies with ICA are the only ones that register a death. Deaths do occur in other strategies but at a probability less than 0.5 per 1,000.

The highest number of non-fatal complications occurred with ICA, followed by ECHO+ICA.

The number of true positives and true negatives are reflected in the summary results in terms of cost per correct diagnosis.

The number of false positive results was 0 for the ICA strategy and strategies ending with ICA due to the assumption of perfect diagnostic accuracy of ICA. Excluding strategies that involve a second test after negative CTCA results (13, 14 and 15), CTCA had the highest number of false positive results. Strategies that involved a combination of CTCA and functional testing had similar numbers of false positive results. The number of false positive results decreased for all strategies as the pre-test likelihood increased, as expected.

CTCA+ECHO and ECHO+CTCA had the highest number of false negative results closely followed by SPECT+CTCA and CTCA+SPECT. Apart from ICA, CTCA-SPECT and CTCA-ECHO had the lowest number of false negatives.

The number of times the second test correctly overruled the first occurred the most with the CTCA+ICA and SPECT+ICA strategies. Apart from single test strategies, the least number of times the second test overruled the first occurred with the strategies where functional testing was undertaken following negative CTCA results.

The number of times the second test incorrectly overruled the first occurred the most in the strategies where functional testing followed negative CTCA results (13, 14 and 15). Apart from the strategies involving ICA, this occurred the least in strategies where CTCA followed positive functional tests (10, 11 and 12).

Table 99: Additional model outcomes, 20% pre-test likelihood, 50% stenosis threshold, all figures per 1,000

Strategy	Undominated	Deaths	Complications	True positives	False positives	True negatives	False negatives	Second test correctly overrules first	Second test incorrectly overrules first	Second test correctly confirms first	Second test incorrectly confirms first
1. ICA	yes	1	7	198	0	794	0	0	0	0	0
10. SPECT+CTCA		0	1	154	37	762	45	136	7	154	37
13. CTCA-SPECT		0	1	198	307	492	2	7	136	492	2
12. CMR+CTCA		0	1	161	26	773	39	97	7	161	26
11. ECHO+CTCA		0	2	145	34	765	55	123	6	145	34
6. CTCA+CMR	yes	0	0	161	26	773	39	145	31	161	26
15. CTCA-CMR		0	1	199	269	531	1	7	97	531	1
16. No testing	yes	0	0	0	0	0	0	0	0	0	0
2. CTCA	yes	0	0	192	172	628	8	0	0	0	0
3. CTCA+ICA		0	3	190	0	798	8	171	0	190	0
4. CTCA+SPECT		0	0	154	37	763	45	135	37	154	37
5. CTCA+ECHO	yes	0	1	145	34	766	55	138	47	145	34
14. CTCA-ECHO		0	2	198	295	504	2	6	123	504	2
7. SPECT+ICA		0	3	160	0	798	39	171	0	160	0
8. ECHO+ICA		0	4	150	0	797	49	155	0	150	0
9. CMR+ICA		0	3	167	0	799	32	122	0	167	0

Table 100: Additional model outcomes, 45% pre-test likelihood, 50% stenosis threshold, all figures per 1,000

Strategy	Undominated	Deaths	Complications	True positives	False positives	True negatives	False negatives	Second test correctly overrules first	Second test incorrectly overrules first	Second test correctly confirms first	Second test incorrectly confirms first
1. ICA	yes	1	7	446	0	546	0	0	0	0	0
10. SPECT+CTCA		0	1	348	26	524	102	93	15	348	26
15. CTCA-CMR		0	1	447	185	365	3	15	66	365	3
12. CMR+CTCA		0	1	362	18	531	87	66	15	362	18
5. CTCA+ECHO		0	1	325	23	526	123	95	105	325	23
14. CTCA-ECHO		0	1	445	203	346	4	14	84	346	4
11. ECHO+CTCA		0	2	325	23	526	123	84	14	325	23
16. No testing	yes	0	0	0	0	0	0	0	0	0	0
2. CTCA	yes	0	0	431	118	432	18	0	0	0	0
3. CTCA+ICA		0	4	428	0	549	18	117	0	428	0
4. CTCA+SPECT		0	1	348	26	524	102	93	84	348	26
13. CTCA-SPECT		0	1	446	211	338	4	15	93	338	4
6. CTCA+CMR	yes	0	1	362	18	532	87	100	69	362	18
7. SPECT+ICA		0	4	360	0	549	87	118	0	360	0
8. ECHO+ICA		0	5	337	0	548	110	107	0	337	0
9. CMR+ICA		0	4	375	0	549	72	84	0	375	0

Table 101: Additional model outcomes, 75% pre-test likelihood, 50% stenosis threshold, all figures per 1,000

Strategy	Undominated	Deaths	Complications	True positives	False positives	True negatives	False negatives	Second test correctly overrules first	Second test incorrectly overrules first	Second test correctly confirms first	Second test incorrectly confirms first
1. ICA	yes	1	7	744	0	248	0	0	0	0	0
10. SPECT+CTCA		0	1	579	12	238	170	42	25	579	12
11. ECHO+CTCA		0	2	542	11	239	206	38	23	542	11
12. CMR+CTCA		0	1	604	8	242	146	30	26	604	8
13. CTCA-SPECT		0	0	744	96	154	6	25	42	154	6
14. CTCA-ECHO		0	1	742	92	157	7	23	38	157	7
15. CTCA-CMR		0	0	745	84	166	5	26	30	166	5
16. No testing	yes	0	0	0	0	0	0	0	0	0	0
2. CTCA	yes	0	0	719	54	196	31	0	0	0	0
3. CTCA+ICA		1	6	713	0	249	31	53	0	713	0
4. CTCA+SPECT		0	1	579	12	238	170	42	139	579	12
5. CTCA+ECHO		0	2	542	11	239	206	43	175	542	11
6. CTCA+CMR		0	1	604	8	242	146	45	115	604	8
7. SPECT+ICA		1	5	599	0	249	145	54	0	599	0
8. ECHO+ICA		0	7	561	0	249	183	49	0	561	0
9. CMR+ICA		1	5	625	0	250	120	38	0	625	0

O.5 Discussion

The testing strategy of CTCA only had the lowest cost per correct diagnosis for all population subgroups in both the base case and the sensitivity analysis based on a 70% stenosis threshold. The addition of functional testing following a positive CTCA result may be cost effective for lower pre-test likelihoods, but which specific functional test would be the most cost-effective cannot be determined without a cost-effectiveness threshold.

Functional testing following a positive CTCA is only beneficial in reducing the number of false positives at the expense of slightly increasing the rate of false negative results.

Although it is difficult to quantify (and therefore not explicitly included in the form of long term modelling), these results should be interpreted within the context of the implications for false negatives and false positives. The potential implications for false negatives include remaining symptomatic with stable chest pain, returning for additional appointments with their GP or cardiologist, further testing with the same or alternative tests which may include ICA, and the costs involved for each of these elements. Due to the ongoing chest pain symptoms, most people with false negative results would be expected to be correctly diagnosed within 12 months although this may take 2 to 3 years. The potential implications and costs for people with false positive test results are varied. Some people will be treated with medication and, because their symptoms were due to a non-cardiac, transient cause, their chest pain alleviates and the medication is assumed to have worked. Therefore, even though they don't have disease, they continue on taking this medication for many years. It is unclear whether this would have negative or positive health effects because most people of this age group have some level of atheroma. In other words, although a person may not have clinically significant CAD, the medicine may have a protective effect, benefit to both health and costs. Alternatively, the medicines may cause side effects, and a cost to the NHS, that otherwise did not need to occur because they don't have disease. Some people treated with medication would continue to experience chest pain because it is caused by something other than CAD. This could be gastrointestinal reflux or a musculoskeletal problem, for example. Because their symptoms continue, they would usually be correctly diagnosed within the space of a year. This may be via an ICA, but not necessarily. In addition to the ICA or other test, people would incur the cost of additional GP and cardiologist visits. There would be a small proportion of people that would experience complications during the ICA or other test. There could also be further complications of whatever it is they do have but this canot be defined. Some people with false positive results would be sent for treatment with PCI or CABG. However, because ICA is always conducted prior to revascularisation, the only cost incurred would be the cost of an ICA, not the incorrect treatment with PCI or CABG. There would be a small proportion of people who experience complications during the ICA.

The analysis shows that functional testing is unlikely to be cost effective in the higher pre-test likelihood subpopulations. The committee advised that false negative outcomes are more important to avoid than false positives.

One of the strengths of this analysis is that the sensitivity and specificity parameters are based on the latest meta-analyses of all included tests conducted for the clinical evidence review for this update.

O.6 Limitations

The main limitation of this analysis is the lack of long term modelling. This would have provided an explicit trade-off between false positives and false negatives for each strategy and a cost per QALY enabling decision-makers to use NICE's cost-effectiveness threshold. However, the committee determined that the future treatment pathways, particularly for false

positives, were unclear and that given this uncertainty, the results of a long term model would be no less than the uncertainty inherent in the short term model. In addition, the short term model provides somewhat clear results that CTCA is the preferred first line test for all subpopulations.

Calculating results in terms of cost per correct diagnosis implies that false positives and false negatives are of equal value. However, the committee determined that false negative results were more important to prevent because it is important to identify and correctly diagnose disease where it exists. This limitation should be kept in mind when interpreting results.

The long term impacts of radiation exposure have not been included in the model. This is due to the time horizon and also topic expert advice that modern CT scanning uses such low levels of radiation that it would be inconsequential in the older age population to which this analysis applies.

The model assumed conditional independence for the second test. In clinical practice the results of the first test, and indeed the overall clinical history of the patient, would be taken into account when making a diagnosis. The clinical evidence review did not identify data that would have provided inputs for the model without this assumption.

O.7 Conclusion

This short term model shows that CTCA has the lowest cost per correct diagnosis for diagnosing coronary artery disease in people with stable chest pain of suspected cardiac origin. The strategies that involve the addition of functional testing after positive CTCA results may be cost effective in lower levels of pre-test likelihood. Clinicians should be aware that the utility of functional testing is to rule out false positive results in cases where doubt remains about a positive diagnosis following a CTCA.