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Title: 64-slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis

Short running head: 64-slice CT angiography for detecting CAD

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ABSTRACT

Objective
To assess whether 64-slice computed tomography (CT) angiography might replace some coronary angiography (CA) for diagnosis and assessment of coronary artery disease (CAD).

Methods
We searched electronic databases, conference proceedings and scanned reference lists of included studies. Eligible studies compared 64-slice CT with a reference standard of CA in adults with suspected/known CAD, reporting sensitivity and specificity or true and false positives and negatives. Data were pooled using the hierarchical summary receiver operating characteristic model.

Results
Forty studies were included; 28 provided sufficient data for inclusion in the meta-analyses, all using a cutoff of ≥ 50% stenosis to define significant CAD. In patient-based detection (n=1286) 64-slice CT pooled sensitivity was 99% (95% credible interval (CrI) 97 to 99%), specificity 89% (95% CrI 83 to 94%), median positive predictive value (PPV) across studies 93% (range 64 to 100%) and negative predictive value (NPV) 100% (range 86 to 100%). In segment-based detection (n=14,199) 64-slice CT pooled sensitivity was 90% (95% CrI 85 to 94%), specificity 97% (95% CrI 95 to 98%), median positive predictive value (PPV) across studies 76% (range 44 to 93%) and negative predictive value (NPV) 99% (range 95 to 100%).

Conclusions
64-slice CT is highly sensitive for patient-based detection of CAD and has high NPV. An ability to rule out significant CAD means that it may have a role in the assessment of chest pain, particularly when the diagnosis remains uncertain despite clinical evaluation and simple non-invasive testing.

INTRODUCTION

Coronary artery disease (CAD) is a major cause of mortality and ill health, causing an estimated 7.6 million deaths globally in 2005.[1] In the United Kingdom it causes around 101,000 deaths each year[2] and is the most common cause of death. Currently, invasive coronary angiography (CA) is regarded as the 'gold standard' for the assessment of coronary anatomy. However, conventional CA has limitations. It is an invasive procedure with a small (0.1 to 0.2%) risk of major complications[3] and affords information only on the site and degree of luminal narrowing – providing no data on the extent of atherosclerotic change within the vessel wall. Images are obtained in only two dimensions – though the use of multiple projections enables a more comprehensive assessment of any individual lesion. Finally, there are constraints on the amount of CA that can be undertaken, both in terms of infrastructure and cardiologist time. An accurate non-invasive test for diagnosing CAD that could potentially avoid the need for some CA is, therefore, highly desirable.

Multislice computed tomography (MSCT) has been developing rapidly in recent years. Four-slice machines appeared in 1998, 16-slice in 2001 and 64-slice in 2004. This has resulted in greatly increased temporal and spatial resolution[4] – facilitating the rapid identification and assessment of atherosclerosis within the moving coronary arteries[5,6] and generating considerable interest in the concept that MSCT might potentially reduce the need for invasive CA. The aim of this systematic review was to assess the accuracy of 64-slice CT angiography compared with conventional CA in the diagnosis and assessment of CAD.

METHODS

Search strategy

Highly sensitive search strategies were developed using both appropriate subject headings and text word terms. Full details of the search strategies used are available from the authors. We searched the following electronic databases: Medline (2002 – November Week 3 2006), Embase (2002 to December 2006), Biosis (2002 to December 2006), Science Citation Index (2002 – December 2006), Medline In-Process (14th December 2005), Cochrane Controlled Trials Register (The Cochrane Library, Issue 4 2006), Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 4, 2006), Database of Abstracts of Reviews of Effectiveness (December 2006), HTA Database (December 2006) and Health Management Information Consortium (2002 – May 2006). In addition, recent conference proceedings and reference lists of all included studies were scanned to identify additional potentially relevant studies. Searches were from 2002 onwards and restricted to English language reports.

Inclusion criteria

We included randomised controlled trials (RCTs), non-randomised comparative studies or case series involving adults with suspected or known CAD. The index test was 64-slice CT angiography compared with conventional CA as the reference standard. Studies had to report sensitivity and specificity or true and false positives and negatives.

Data extraction

One reviewer screened the titles (and abstracts if available) of all reports identified by the search strategy. Full copies of potentially relevant reports were obtained and two reviewers independently assessed them for inclusion. Data were extracted independently by two reviewers. Disagreements were resolved by consensus or arbitration by a third reviewer.

Quality assessment

Two reviewers independently assessed the methodological quality of full text studies using QUADAS[7] which was modified to make it more applicable to studies for diagnosing and assessing CAD. Three questions in the original QUADAS tool that related to the quality of reporting rather than methodological quality were excluded (questions 2, 8 and 9). Three questions were added on (a) whether an established cutoff point was used (question 12), (b) whether data on observer variation were reported and within an acceptable range (question 13) and (c) whether data were presented for appropriate subgroups of patients (question 14). Disagreements were resolved by consensus or arbitration by a third reviewer.

Statistical analysis

Where three or more studies reported data, summary receiver operating characteristic (SROC) curves were derived for the following levels of analysis: patient, segment, artery (left main, proximal left anterior descending (LAD), any LAD, left circumflex (LCX), right coronary artery (RCA)), stent and coronary artery bypass graft (CABG). The meta-analysis method used was the hierarchical summary receiver operating characteristic (HSROC) model,[8] fitted using WinBUGS 1.4.[9] A symmetric SROC model was used to address the lack of numerical convergence of the full SROC model. Pooled estimates for sensitivity and specificity were reported as medians and 95% credible intervals (CrIs), the Bayesian equivalent of confidence intervals (CIs).

If numerical difficulties were encountered with the symmetric HSROC model and there was also no evidence of heterogeneity, sensitivity and specificity were pooled using the weighted average method.[10] These analyses were carried out using Metadisc software[11] and corresponding 95% confidence intervals (CIs) (rather than CrIs) were reported. This approach was required for the left main artery analysis. Heterogeneity was assessed using the I^2 statistic in Metadisc software,[11] with a value greater than 50% considered to represent substantial heterogeneity.[12]

RESULTS

Figure 1 shows the flow of studies through the review. Out of a total of 1211 titles/abstracts screened, 275 were selected as potentially relevant and full papers obtained where possible. Forty studies (21 full text, [13-33] 19 abstracts [34-52]), published in 67 reports, met the inclusion criteria. All were non-randomised studies comparing 64-slice CT with a reference standard of invasive CA.

[**Figure 1** Flow of studies through review process]

The characteristics of the included studies are available as online content, linked to the online manuscript. The 40 studies involved more than 2400 people. In 25 studies reporting gender 67% (n=1184) of participants were men. Across 27 studies reporting mean age this ranged from 54 to 69 years (median 61 years). Most studies reported elective assessment for CAD, with study populations including those with suspected CAD, known CAD, or both. In addition the following specific groups were studied: patients with previous PCI or CABG and those with a suspected acute coronary syndrome.

All studies used 64-slice CT angiography. Most studies (n=28) used Siemens Sensation 64 machines; other types of equipment used included GE Healthcare Light-Speed VCT (n=2), Philips Brilliance 64 (n=2) and Toshiba Multi-Slice Aquilion 64 (n=1).

The quality assessment for the 21 full text studies is summarised in Figure 2. In all studies conventional CA was the reference standard, results were abstracted only if patients received both 64-slice CT angiography and the reference standard (partial verification bias avoided), patients received the same reference standard (differential verification bias avoided) and the index test did not form part of the reference standard (incorporation bias avoided). In 85% of studies those interpreting 64-slice CT data were blinded to the results of the reference standard test (test review bias avoided) and in 71% of studies vice versa (diagnostic review bias avoided). In 48% of studies the participants belonged to specific groups (spectrum bias), for example those with previous revascularisation.

[**Figure 2** Results of the quality assessment of the 21 full text studies]

Twenty-eight studies provided sufficient data (true positives, false positives, false negatives, true negatives) to allow their inclusion in the meta-analyses, although the number of studies included for each level of analysis varied (see Table 1). The pooled estimates for the sensitivity and specificity of 64-slice CT angiography for detecting significant CAD for each level of analysis are shown in Figure 3 (also available in a table as online content linked to the online manuscript). Across studies the median PPV and NPV along with their ranges for each level of analysis are shown in Figure 4 (also available in a table as online content linked to the online manuscript). All studies used a cut-off of > 50% or ≥ 50% stenosis to define significant CAD.

Table 1 Studies included in the pooled estimates for different levels of analysis

Study id	Level of analysis Patient	Segment	Left main artery	LAD artery	Proximal LAD artery	LCX artery	RCA	Stent	CABG
	Full text studies								
Ehara 2006a[13]	✓	✓	✓	✓	✓	✓	✓		
Ghostine 2006[15]	✓	✓	✓	✓	✓	✓	✓		
Hoffmann 2006[16]	✓								
Leber 2005[18]		✓						✓	
Leschka 2005[19]		✓	✓	✓	✓	✓	✓		
Meijboom 2006[20]	✓	✓		✓		✓	✓		
Mollet 2005[21]	✓	✓							
Nikolaou 2006[22]	✓	✓	✓	✓		✓	✓		
Ong 2006[23]		✓	✓	✓	✓	✓	✓		
Pache 2006[24]	✓								✓
Plass 2006[25]	✓	✓							
Pugliese 2006a[26]	✓	✓		✓	✓	✓	✓		
Raff 2005[27]	✓	✓							
Rist 2006[28]								✓	
Rixe 2006[29]								✓	
Ropers 2006a[30]	✓	✓							

	Level of analysis								
Study id	**Patient**	**Segment**	**Left main artery**	**LAD artery**	**Proximal LAD artery**	**LCX artery**	**RCA**	**Stent**	**CABG**
Ropers 2006b[31]	✓	✓							✓
Schuijf 2006[32]	✓	✓						✓	
	Abstracts								
Becker 2006[35]	✓								
Ehara 2006b[36]								✓	
Hausleiter 2005[38]									✓
Malagutti 2006[41]	✓								✓
Oncel 2006[42]								✓	
Onuma 2006[43]		✓							
Rubinshtein 2006a[47]	✓								
Rubinshtein 2006b[48]	✓								
Savino 2006[49]	✓	✓							
Schlosser 2006[50]		✓							

Notes:
1. LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; CABG, coronary artery bypass graft.

[**Figure 3** Pooled estimates (95% CrI) for different levels of analysis]
[**Figure 4** Median positive and negative predictive values across studies (range)]

Patient and segment based analyses

In 18 studies (n=1286) 64-slice CT was extremely sensitive in patient-based detection of CAD, with a pooled sensitivity of 99% (95% CrI 97 to 99%). Specificity was lower at 89% (95% CrI 83 to 94%). The median NPV across studies was very high at 100% (range 86 to 100%), while PPV was 93% (range 64 to 100%). The wide range of PPVs is probably due to the studies being heterogeneous in terms of their populations and the prevalence of significant CAD (median across studies 58%, range 23 to 96%). The median false positive rate across studies was 10% (range 0 to 50%), representing an overestimation of the presence of non-significant stenosis as significant, as opposed to finding CAD where none existed. There was very low statistical heterogeneity in terms of sensitivity (I^2=0.1%) and moderate statistical heterogeneity in terms of specificity (I^2=31.7%). In 17 studies reporting coronary artery segment-based detection (n=14,199), compared with patient-based detection, pooled sensitivity was lower (90%, 95% CrI 85 to 94%), specificity higher (97%, 95% CrI 95 to 98%), median PPV lower (76%, range 44 to 93%) and NPV similar (99%, range 95 to 100%).

Five of 18 studies in the pooled estimates for patient-based detection of CAD, and three of 17 for segment-based detection, were abstracts. A sensitivity analysis undertaken to examine the effect of removing abstracts from the pooled estimates found that this did not affect the results. For patient-based detection sensitivity (95% CrI) remained unchanged at 99% (97 to 99%), while specificity increased slightly to 91% (84 to 95%). For segment-based detection sensitivity also remained unchanged at 90% (84 to 94%), while specificity decreased slightly to 96% (95% CrI 94 to 98%).

Artery level analyses

At artery level pooled sensitivity and specificity were both highest for the left main artery (95% (95% CI 84 to 99%); 100% (95% CI 99 to 100%) respectively). Pooled sensitivity was lowest for the LCX at 85% (95% CrI 69 to 94%). Pooled specificity estimates for all of the arteries were very high at ≥ 96%. Across studies the median PPV and NPV were also both highest for the left main artery (100%, range 90 to 100%; 100% (all five studies) respectively). The median NPVs for all of the arteries were very high at ≥ 98% (ranges: LAD 95 to 100%; LCX 93 to 100%; RCA 94 to 100%). The median PPV was lowest for the LCX (81%, range 56 to 100%).

Specific subgroups

In six studies reporting patency of stents (n=317), with a cutoff > or ≥ 50% in-stent restenosis defining a positive test result, sensitivity was 89% (95% CrI 68 to 97%) and specificity 94% (95% CrI 83 to 98%), while across studies the median PPV was 77% (range 33 to 100%) and NPV was 96% (range 71 to 100%). Stents caused some problems for 64-slice CT. Leber and colleagues[18] reported that, of nine stents without any restenosis on conventional CA, four were false positives on 64-slice CT due to artifacts caused by the dense stent material. Importantly, the utility of CT angiography appears to be greatly influenced by the diameter and strut-thickness of the stent.[29] In three studies[28,29,36] 21% (59/276) of stents were classed as unevaluable and excluded from analysis, while the remaining three studies did not report this information.

Four studies reported patency of bypass grafts (n=543). Both sensitivity and specificity were very high (99%, 95% CrI 95 to 100%; 96%, 95% CrI 86 to 99% respectively), while across studies the median PPV was 93% (range 90 to 95%) and NPV was very high at 99% (range 98 to 100%).

Only three studies[16,35,46] assessed the diagnostic performance of 64-slice CT in patients admitted to hospital with suspected acute coronary syndromes (n=232). Across these studies the median (range) values were 100% (97 to 100%) for sensitivity, 100% (79 to 100%) for specificity, 100% (87 to 100%) for PPV and 100% (94 to 100%) for NPV.

Technical limitations

Scans could not be adequately evaluated in 2% (11/718) of patients (n=13 studies), 8% (997/12,476) of all arterial segments, 21% (59/276) of stented segments (n=3 studies) and 0% (0/231) of bypass grafts (n=2 studies). Three percent (11/404) of scans of the left main artery, 5% (74/1641) of the RCA and 6% of both the LAD (104/1789) and the LCX (93/1444) could not be evaluated. Studies reported that poor image quality was caused by factors including irregular heart rhythm, sinus tachycardia > 90/min, calcification, vessel motion or small vessel calibre in distal segments.

It is unclear to what extent the exclusion or otherwise of small diameter vessels affected 64-slice CT performance as only seven studies provided this information, with five[19,23,25,30,31] excluding segments < 1.5 mm in diameter from analysis and two[20,27] analysing all vessels regardless of size. Across the five studies excluding segments < 1.5 mm the median sensitivity was 87% (range 85 – 94%) and specificity 96% (range 76 – 97%) compared with median sensitivity of 90% (range 86 – 94%) and specificity of 96.5% (range 95 – 98%) for the two studies analysing all segments.

Coronary artery calcification may make scans more difficult to interpret. Ghostine and colleagues[15] noted that heavily calcified segments accounted for 21 (81%) of 26 false negative results. In the study by Raff and colleagues[27] the false positive rate increased as calcification became more severe, with a 2% (14/709) false positive rate in segments rated as 'no calcification', 6% (5/89) in those rated as 'mild', 13% (6/48) in those rated as 'moderate' and 18% (16/88) in those segments rated as 'severe'.

DISCUSSION

The current study suggests that 64-slice CT angiography is highly sensitive for patient-based detection of significant CAD (≥ 50% stenosis), with a very high NPV. This high NPV was also apparent in analyses based on individual coronary arteries and segments. At artery level the best results for 64-slice CT were in those arteries such as left main and LAD where significant CAD carries the poorest prognosis. Based on a few small studies, broadly similar results were demonstrated in patients who had undergone prior coronary artery stenting, CABG and those with a suspected acute coronary syndrome.

Prior studies

We did not identify any other published systematic reviews focusing on 64-slice CT. Several systematic reviews of MSCT[5,6,53-55] included 64-slice CT studies, all of which are included in our review. A systematic review by Stein and colleagues[5] of multidetector (4-slice and higher) CT for the diagnosis of CAD identified one 64-slice CT study by Leschka and colleagues.[19] The authors concluded that the preliminary data with 64-slice CT suggested that it was more sensitive and specific than 16-slice CT, and that multidetector CT had the potential to be used as a screening test in appropriate patients. The USA Technology Evaluation Center[6] (a subsidiary of the private providers Blue Cross and Blue Shield), in a review of CT angiography (32-slice or higher) identified six 64-slice CT studies.[18,19,21,26,27,30] The authors reported that in patient-based analysis the 64-slice CT studies showed high sensitivities and specificities compared with the reference standard of conventional coronary angiography.[6] A technology assessment by Patel and colleagues,[54] undertaken for the USA Medicare Coverage Advisory Commission included CT angiography (16-slice or higher) and identified six 64-slice CT studies.[18,19,21,26,27,30,37] The authors concluded that the sensitivity and specificity of 64-slice CT in patient-based analysis looked promising.[54] Systematic reviews and meta-analyses by Sun and colleagues[55] (4-slice or higher) and Hamon and colleagues[53] (16-slice or higher) identified seven[18,19,21,26,27,30,37] and nine[13,18,19,21,22,26,27,30,32] 64-slice CT studies respectively. Both reviews undertook meta-analyses at patient, vessel and segment level, although neither presented separate pooled estimates for the group of 64-slice CT studies. In patient-based analysis Sun and colleagues[55] reported pooled estimates (95%

confidence interval (CI)) of 91% (88 to 95%) sensitivity and 86% (81 to 92%) specificity. The authors concluded that diagnostic accuracy was significantly improved with 64-slice scanners compared with 4- and 16-slice scanners.[55] In patient-based analysis Hamon and colleagues[53] reported pooled estimates (95% CI) of 96% (94 to 98%) sensitivity and 74% (65 to 84%) specificity. The authors concluded that MSCT had shortcomings difficult to overcome in daily practice, with continuing moderate specificity in patient-based analysis in patients with high prevalence of CAD. They stated that studies evaluating the diagnostic performance of the newest-generation MSCT, including patients with low to moderate CAD prevalence, would be critical in establishing the clinical role of this emerging technology as an alternative to CA.[53]

Radiation doses

Although CT is regarded as non-invasive, it delivers a higher radiation dose than conventional CA and concerns have been raised about indiscriminate or repetitive use and, in particular, the risks in younger individuals or women of childbearing age.[56] Hausleiter and colleagues[57] reported an effective radiation dose of 11.0 (SD 4.1) mSv for 64-slice CT. By comparison estimates of mean effective doses for conventional CA include < 5 mSv by a British Cardiovascular Society Working Group,[58] and 4 to 8 mSv by the Technology Evaluation Center.[59] In this review six studies[15-18,22,28] reported 64-slice CT radiation dose for the patient population as a whole and six[20,21,26,27,30,31] reported it separately for men and women. The radiation dose for men ranged from 7.5 mSv[30] to 15.2 mSv[20,21] and for women from 10.2 mSv[31] to 21.4 mSv.[20,21] Two[30,31] of these studies using ECG-controlled dose modulation to reduce the tube current during systole reported the lowest radiation doses: 7.5 mSv[30] and 8.6 mSv[31] for men and 10.2 mSv[30] and 12.2 mSv[31] for women. One study[19] used an alternative technique, automatic exposure control,[60] to reduce radiation dose exposure but did not report the actual dosage values that the patients received. With the development of more modern technologies and methods, it may be possible to reduce the radiation dose further. Einstein and colleagues[61] have estimated that a single 64-slice CT study would result in an increase in lung cancer and breast cancer risk, especially if used in younger patients (for example a lifetime attributable cancer risk of 1 in 114 after a combined heart and aortic scan in a 20-year old woman, compared to 1 in 715 for a 60-year old woman, with risks reduced by ECG controlled modulation).

Strengths and limitations

The current review included both full text studies and conference abstracts in an attempt to obtain the latest available data. All studies used the same reference standard of conventional CA and only data for those who received both index test and reference standard were included in the meta-analyses. A limitation was that non-English language studies were excluded. No adjustment was made for studies which used multiple samples from each participant for some levels of analysis.

Implications for practice

Given the high sensitivity and negative predictive value, the main role of MSCT may be to rule out significant CAD, and thereby reduce the need for invasive CA. There are several clinical situations where this may be particularly useful. In patients with a very low probability of CAD it is unlikely that MSCT would be recommended, particularly given the radiation doses involved. Likewise, when the probability of CAD is high conventional angiography is likely to remain the investigation of choice in the majority of patients. However, very many patients fall into an intermediate category where the diagnosis of CAD remains uncertain following clinical assessment and simple non-invasive testing. Currently, this may necessitate either myocardial perfusion scanning or invasive CA. It seems likely that MSCT may have an increasing role in this setting.

There are other specific settings where MSCT may be of particular value. For example, in patients with acute chest pain a test with the capacity to rapidly and effectively rule out significant CAD – or provide a definitive diagnosis - has obvious potential. The limited data currently available suggest that this may indeed be the case.[62] In patients with a history of CABG invasive angiography may be more technically difficult, time-consuming and associated with higher radiation doses. MSCT may, therefore, have some advantages in selected patients following surgical revascularisation. Likewise, many patients who are scheduled to undergo surgery for valvular heart disease and other non-coronary cardiac conditions currently undergo 'routine' invasive angiography – much of which might be replaced by MSCT.[20,63]

Conclusion

Although further work is required to determine the prognostic utility of MSCT and to clarify its precise clinical role, the currently available data suggest that it will play an increasing role in the evaluation of patients with known or suspected CAD. The technology continues to evolve and data are awaited on the marginal costs and benefits of the next generation of MSCT, the 256 and higher-slice CT machines.

CONTRIBUTORS

NW designed the study. CF developed the search strategies, obtained papers and formatted the references. GM screened the search results. GM and XJ undertook data extraction and quality assessment. JC and GM analysed and interpreted data. GM drafted the manuscript. GH, SW and NW provided expert advice. All authors commented on drafts and approved the final manuscript. GM is guarantor.

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COMPETING INTERESTS

All authors declare that the answers to the questions on your competing interests form [http://bmj.com/cgi/content/full/317/7154/291/DC1] are all No and therefore have nothing to declare.

ETHICAL APPROVAL

Not required.

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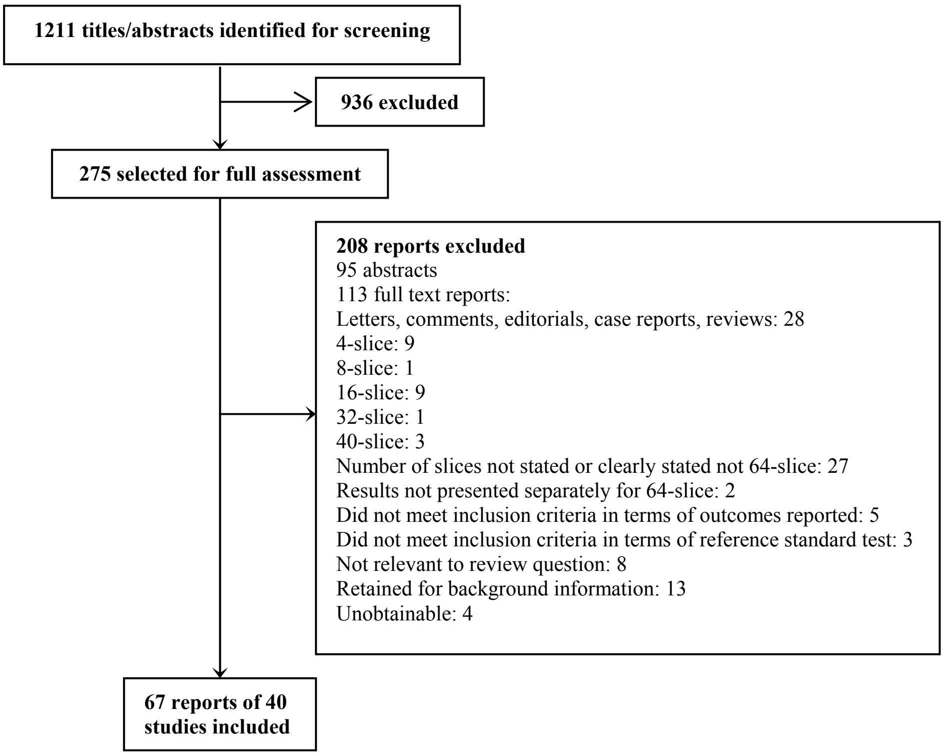


Figure 1 Flow of studies through review process

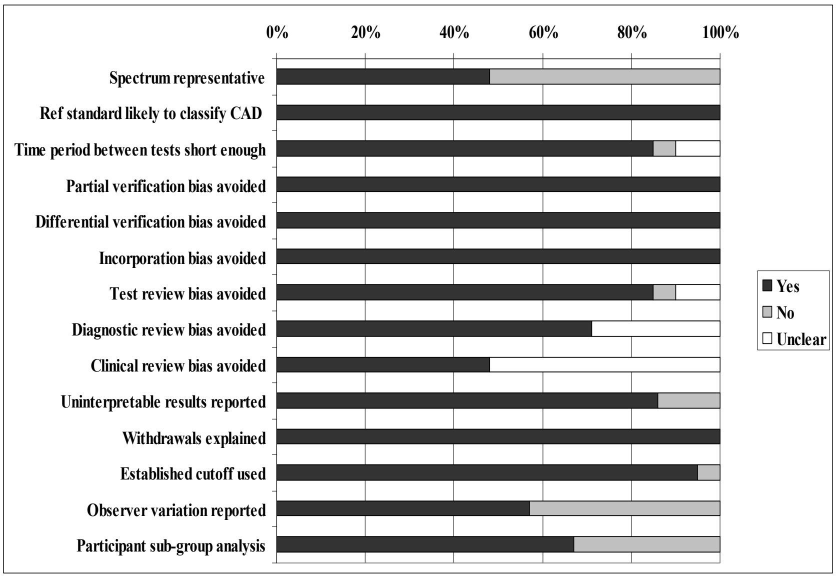
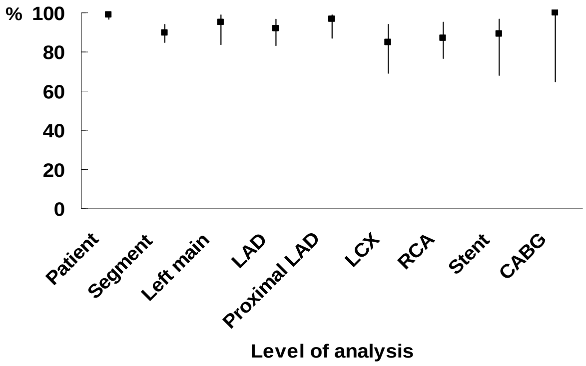


Figure 2 Results of the quality assessment of the 21 full text studies

Notes:

1. The question on 'partial verification bias avoided' was checked 'Yes' for two studies (16,17) in which only some patients received both index and reference standard tests. For these two studies only the results for the patients who received both tests were included in the review.

(a) Sensitivity



(b) Specificity

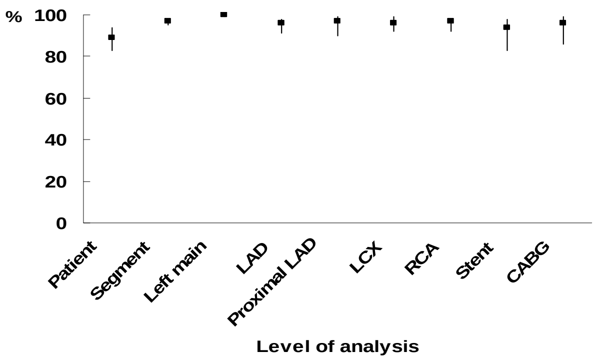
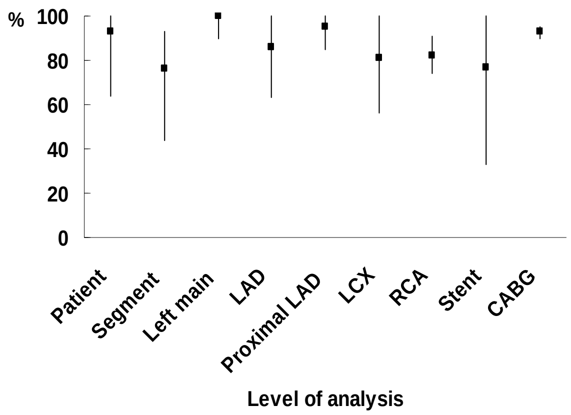


Figure 3 Pooled estimates (95% CrI) for different levels of analysis

Notes:

1. Left main artery: due to numerical difficulties with the HSROC symmetric model, sensitivity and specificity were pooled using the weighted average method and confidence intervals rather than credible intervals were reported.

(a) Positive predictive value



(b) Negative predictive value

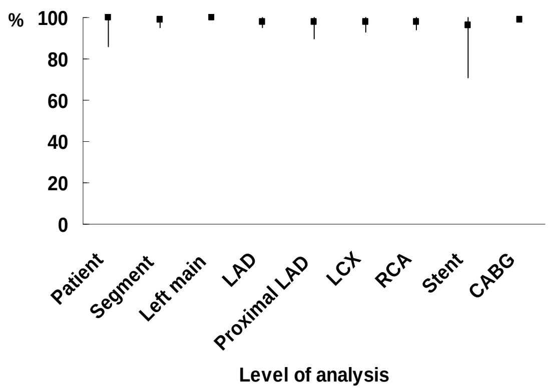


Figure 4 Median positive and negative predictive values across studies (range)

Supplementary material Table 1 Characteristics of the included studies

(a) Full text

Study id, country	Participants	64-slice CT	Outcomes summary
Ehara 2006a[13]	**Enrolled:** 69	**Machine:** Sensation 64, Siemens	**Segments** (n=884), **patients** (n=67)
	Analysed: 67	**Radiation dose:** N/S	**Cutoff:** > 50% stenosis
Country: Japan	**Age (years):** Mean 67, SD 11	**Dose modulation used:** N/S	**Sensitivity:** 90%, 98%
	Sex: M 52; F 17		**Specificity:** 94%, 86%
	Prevalence of significant CAD: 88% (61/69)		**PPV:** 89%, 98%
			NPV: 95%, 86%
Fine 2006a[14]	**Enrolled:** 66	**Machine:** Sensation 64, Siemens	**Arteries** (n=245)
	Analysed: 66	**Radiation dose:** N/S	**Cutoff:** > 50% stenosis
Country: USA	**Age (years):** Mean 62, SD 7	**Dose modulation used:** N/S	**Sensitivity:** 95%
	Sex: M 32; F 34		**Specificity:** 96%
	Prevalence of significant CAD: N/S		**PPV:** 97%
			NPV: 92%
Ghostine 2006[15]	**Enrolled:** 66	**Machine:** Sensation 64, Siemens	**Segments** (n=94), **patients** (n=29)
	Analysed: 66	**Radiation dose:** 7 (SD 2) mSv	**Cutoff:** > 50% stenosis
Country: France	**Age (years):** Mean 69, SD 13	**Dose modulation used:** Yes	**Sensitivity:** 97%, 72%

Study id, country	Participants	64-slice CT	Outcomes summary
	Sex: M 40; F 26 **Prevalence of significant CAD:** 44% (29/66)		**Specificity:** 95%, 99% **PPV:** 93%, 91% **NPV:** 97%, 97%
Hoffmann 2006[16] **Country:** USA	**Enrolled:** 106 **Analysed:** 103 (8 received both MSCT and invasive CA) **Age (years):** Mean 54, SD 12 (whole group) **Sex:** M 62; F 41 (whole group) **Prevalence of significant CAD:** 63% (5/8)	**Machine:** Sensation 64, Siemens **Radiation dose:** 6 – 11 mSv **Dose modulation used:** Yes	**Patients** (n=8) **Cutoff:** > 50% stenosis **Sensitivity:** 100% **Specificity:** 100% **PPV:** 100% **NPV:** 100%
Johnson 2007[17] **Country:** Germany	**Enrolled:** 55 **Analysed:** 55 (20 received both CT and invasive CA) **Age (years):** N/S **Sex:** N/S **Prevalence of significant CAD:** 85% (17/20)	**Machine:** Sensation 64, Siemens **Radiation dose:** approximately 6.9 mSv **Dose modulation used:** Yes	**Patients** (n=20) **Cutoff:** > 50% stenosis **Sensitivity:** 94% **PPV:** 84% **Specificity and NPV:** Not calculable (no true negatives)

Study id, country	Participants	64-slice CT	Outcomes summary
Leber 2005[18] **Country:** Germany	**Enrolled:** 59 **Analysed:** 59 **Age (years):** Mean 64, SD 10 **Sex:** N/S **Prevalence of significant CAD:** 42% (25/59)	**Machine:** Sensation 64, Siemens **Radiation dose:** Mean 10 to 14 mSv **Dose modulation used:** Yes	**Segments** (n=697), **patients** (n=55) **Cutoff:** > 50% stenosis **Sensitivity:** 73%, 88% **Specificity:** 97%, N/S **PPV:** 60%, N/S **NPV:** 98%, N/S
Leschka 2005[19] **Country:** Switzerland	**Enrolled:** 67 **Analysed:** 67 **Age (years):** Mean 60.1, SD 10.5, range 34-82 **Sex:** M 50; F 17 **Prevalence of significant CAD:** 70% (47/67)	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** No	**Segments** (n=1005) **Cutoff:** > 50% stenosis **Sensitivity:** 94% **Specificity:** 97% **PPV:** 87% **NPV:** 99%
Meijboom 2006[20] **Country:** The Netherlands	**Enrolled:** 70 **Analysed:** 70 **Age (years):** Mean 63, SD 11 **Sex:** M 49; F 21 **Prevalence of significant CAD:** 26% (18/70)	**Machine:** Sensation 64, Siemens **Radiation dose:** 15.2 to 21.4 mSv for men and women, respectively **Dose modulation used:** No	**Segments** (n=1003), **patients** (n=70) **Cutoff:** ≥ 50% stenosis **Sensitivity:** 94%, 100% **Specificity:** 98%, 92% **PPV:** 65%, 82% **NPV:** 100%, 100%

Study id, country	Participants	64-slice CT	Outcomes summary
Mollet 2005[21] **Country:** The Netherlands	**Enrolled:** 70 **Analysed:** 52 **Age (years):** Mean 59.6, SD 12.1 **Sex:** M 34; F 18 **Prevalence of significant CAD:** 75% (39/52)	**Machine:** Sensation 64, Siemens **Radiation dose:** 15.2 to 21.4 mSv for men and women, respectively **Dose modulation used:** No	**Segments** (n=725), **patients** (n=51) **Cutoff:** ≥ 50% stenosis **Sensitivity:** 99%, 100% **Specificity:** 95%, 92% **PPV:** 76%, 97% **NPV:** 100%, 100%
Nikolaou 2006[22] **Country:** Germany	**Enrolled:** 72 **Analysed:** 68 **Age (years):** Mean 64, SD 10, range 38 to 89 **Sex:** M 59; F 13 **Prevalence of significant CAD:** 57% (39/68)	**Machine:** Sensation 64, Siemens **Radiation dose:** approximately 8 to 10 mSv **Dose modulation used:** Yes	**Segments** (n=923), **patients** (n=68) **Cutoff:** > 50% stenosis **Sensitivity:** 82%, 97% **Specificity:** 95%, 79% **PPV:** 69%, 86% **NPV:** 97%, 96%
Ong 2006[23] **Country:** Malaysia	**Enrolled:** 134 **Analysed:** 134 **Age (years):** Mean 54.5, SD 8.8 **Sex:** M 98; F 36 **Prevalence of significant CAD:** 73% (98/134)	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** Yes	**Segments** (n=68, group A), (n=66, group B) **Cutoff:** ≥ 50% stenosis **Sensitivity:** 85%, 80% **Specificity:** 98%, 93% **PPV:** 83%, 77%

Study id, country	Participants	64-slice CT	Outcomes summary
			NPV: 98%, 94%
Pache 2006[24] **Country:** Germany	**Enrolled:** 31 **Analysed:** 31 **Age (years):** Mean 68.4, SD 8.4, range 45 to 83 **Sex:** M 26; F 5 **Prevalence of significant CAD:** 60% (24/31)	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** Yes	**Grafts** (n=93), **patients** (n=31) **Cutoff:** > 50% stenosis **Sensitivity:** 98%, 100% **Specificity:** 89%, 71% **PPV:** 90%, 92% **NPV:** 98%, 100%
Plass 2006[25] **Country:** Switzerland	**Enrolled:** 50 **Analysed:** 50 **Age (years):** Mean 66, SD 8 **Sex:** M 39; F 11 **Prevalence of significant CAD:** 80% (40/50)	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** N/S	**Segments** (n=550), **patients (**n=50) **Cutoff:** > 50% stenosis **Sensitivity:** 87%, 100% **Specificity:** 96%, 90% **PPV:** 86%, 98% **NPV:** 96%, 100%
Pugliese 2006a[26] **Country:** Italy	**Enrolled:** 35 **Analysed:** 35 **Age (years):** Mean 61, SD 10, range 46 to 80 **Sex:** M 21; F 14	**Machine:** Sensation 64, Siemens **Radiation dose:** 15:20 mSv (male:female, respectively) **Dose modulation used:** No	**Segments** (n=494), **patients (**n=35) **Cutoff:** ≥ 50% stenosis **Sensitivity:** 99%, 100% **Specificity:** 96%, 90%

Study id, country	Participants	64-slice CT	Outcomes summary
	Prevalence of significant CAD: 71% (25/35)		**PPV:** 78%, 96% **NPV:** 100%, 100%
Raff 2005[27] **Country:** USA	**Enrolled:** 70 **Analysed:** 70 **Age (years):** Mean 59, SD 11, range 22 to 81 **Sex:** M 53; F 17 **Prevalence of significant CAD:** 57% (40/70)	**Machine:** Sensation 64, Siemens **Radiation dose:** 13:18 mSv (men:women, respectively) **Dose modulation used:** No	**Segments** (n=935), **patients** (n=70) **Cutoff:** ≥ 50% stenosis **Sensitivity:** 86%, 95% **Specificity:** 95%, 90% **PPV:** 66%, 93% **NPV:** 98%, 93%
Rist 2006[28] **Country:** Germany	**Enrolled:** 25 **Analysed:** 25 **Age (years):** Mean 59.4, SD 12, range 40 to 83 **Sex:** M 23; F 2 **Prevalence of significant CAD:** N/S	**Machine:** Sensation 64, Siemens **Radiation dose:** 8-10 mSv **Dose modulation used:** Yes	**Stents** (n=45) **Cutoff:** ≥ 50% stenosis **Sensitivity:** 75% **Specificity:** 92% **PPV:** 67% **NPV:** 94%
Rixe 2006[29] **Country:** Germany	**Enrolled:** 64 **Analysed:** 64 **Age (years):** Mean 58, SD 10	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** Yes	**Stents** (n=59) **Cutoff:** > 50% stenosis **Sensitivity:** 86%

Study id, country	Participants	64-slice CT	Outcomes summary
	Sex: M 41; F 23 **Prevalence of significant CAD:** N/S		**Specificity:** 98% **PPV:** 86% **NPV:** 98%
Ropers 2006a[30] **Country:** Germany	**Enrolled:** 84 **Analysed:** 81 **Age (years):** Mean 58, SD 10, range 35 to 77 **Sex:** N/S **Prevalence of significant CAD:** 32% (26/81)	**Machine:** Sensation 64, Siemens **Radiation dose:** average 7.45:10.24 mSv (men:women, respectively) **Dose modulation used:** Yes	**Segments** (n=1083), **patients** (n=81) **Cutoff:** ≥ 50% stenosis **Sensitivity:** 93%, 96% **Specificity:** 97%, 91% **PPV:** 56%, 83% **NPV:** 100%, 98%
Ropers 2006b[31] **Country:** Germany	**Enrolled:** 50 **Analysed:** 50 **Age (years):** Mean 67, range 44 to 82 **Sex:** M 38; F 12 **Prevalence of significant CAD:** N/S	**Machine:** Sensation 64, Siemens **Radiation dose:** average 8.55:12.24 mSv (men:women, respectively) **Dose modulation used:** Yes	**Native segments** (n=566), **grafts** (n=138) **Cutoff:** ≥ 50% stenosis **Sensitivity:** 86%; 100% **Specificity:** 76%; 94% **PPV:** 44%; 92% **NPV:** 96%; 100%
Schuijf 2006[32]	**Enrolled:** 61	**Machine:** Aquilion 64, Toshiba	**Segments** (n=842), **patients** (n=60)

Study id, country	Participants	64-slice CT	Outcomes summary
Country: The Netherlands	**Analysed:** 60 **Age (years):** Mean 60, SD 11 **Sex:** M 46; F 14 **Prevalence of significant CAD:** 52% (31/60)	**Radiation dose:** N/S **Dose modulation used:** N/S	**Cutoff:** ≥ 50% stenosis **Sensitivity:** 85%; 94% **Specificity:** 98%; 97% **PPV:** 82%; 97% **NPV:** 99%; 93%
Sheth 2006[33] **Country:** USA	**Enrolled:** 29 **Analysed:** 29 **Age (years):** Mean 60.3 **Sex:** M 24; F 5 **Prevalence of significant CAD:** N/S	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** N/S	**Segments, ≥1 feature of complexity** (n=55) **Cutoff:** ≥ 1 criteria of complexity **Sensitivity:** 89% **Specificity:** 83% **PPV:** 82% **NPV:** 89%

(b) Abstracts

Study id, country	Participants	Tests	Outcomes summary
Beck 2006[34] **Country:** Germany	**Enrolled:** N/S **Analysed:** 102 **Age (years):** 62, SD 10 **Sex:** M 82; F 20 **Prevalence of significant CAD:** N/S	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** N/S	**Segments** (n=1326) **Cutoff:** > 50% stenosis **Sensitivity:** 90% **Specificity:** 99% **PPV:** 95% **NPV:** 98%
Becker 2006[35] **Country:** Germany	**Enrolled:** N/S **Analysed:** 199 **Age (years):** 61.3, SD 12.6 **Sex:** M 82; F 117 **Prevalence of significant CAD:** 59% (117/199)	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** N/S	**Patients** (n=199) **Cutoff:** significant CAD **Sensitivity:** 97% **Specificity:** 79% **PPV:** 87% **NPV:** 94%
Ehara 2006b[36] **Country:** Japan	**Enrolled:** N/S **Analysed:** 80 **Age (years):** 68 **Sex:** M 62; F 18	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** N/S	**Stents** (n=113) **Cutoff:** > 50% stenosis **Sensitivity:** 95% **Specificity:** 90%

Study id, country	Participants	Tests	Outcomes summary
	Prevalence of significant CAD: N/S		**PPV:** 70% **NPV:** 99%
Fine 2006b[37] **Country:** USA	**Enrolled:** N/S **Analysed:** 101 **Age (years):** N/S **Sex:** N/S **Prevalence of > 70% CAD:** 41% (diabetes group), 33% (metabolic syndrome group), 15% (comparator group)	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** N/S	**Segments** (n=N/S) **Cutoff:** > 70% stenosis **Diabetes group, metabolic syndrome group, comparator group** **Sensitivity:** 87%, 91%, 91% **Specificity:** 94%, 94%, 98% **PPV:** 87%, 87%, 93% **NPV:** 94%, 94%, 98%
Hausleiter 2005[38] **Country:** Germany	**Enrolled:** N/S **Analysed:** 43 **Age (years):** N/S **Sex:** N/S **Prevalence of significant CAD:** N/S	**Machine:** N/S **Radiation dose:** N/S **Dose modulation used:** N/S	**Bypass grafts** (n=130) **Cutoff:** ≥ 50% stenosis **Sensitivity:** 97% **Specificity:** 98% **PPV:** 95% **NPV:** 99%
Makaryus 2006a[39] **Country:** USA	**Enrolled:** 374 **Analysed:** N/S	**Machine:** GE Light-Speed VCT, GE Healthcare	**Unit of analysis:** unclear **Cutoff:** > 50% stenosis

Study id, country	Participants	Tests	Outcomes summary
	Age (years): N/S **Sex:** N/S **Prevalence of significant CAD:** N/S	**Radiation dose:** N/S **Dose modulation used:** N/S	**Sensitivity:** 88% **Specificity:** 97% **PPV:** N/S **NPV:** N/S
Makaryus 2006b[40] **Country:** USA	**Enrolled:** 18 **Analysed:** 18 **Age (years):** N/S **Sex:** N/S **Prevalence of significant CAD:** N/S	**Machine:** GE Light-Speed VCT, GE Healthcare **Radiation dose:** N/S **Dose modulation used:** N/S	**Bypass grafts** (n=43) **Cutoff:** > 50% stenosis **Sensitivity:** 90% **Specificity:** 97% **PPV:** N/S **NPV:** N/S
Malagutti 2006[41] **Country:** The Netherlands	**Enrolled:** N/S **Analysed:** 52 **Age (years):** N/S **Sex:** N/S **Prevalence of significant CAD:** 96% (50/52)	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** N/S	**Segments** (n=182), **patients** (n=52) **Cutoff:** > 50% stenosis **Sensitivity:** 99%, 100% **Specificity:** 96%, 50% **PPV:** 95%, 98% **NPV:** 99%, 100%
Oncel 2006[42]	**Enrolled:** N/S	**Machine:** Sensation 64, Siemens	**Stents** (n=43)

Study id, country	Participants	Tests	Outcomes summary
 Country: Turkey	**Analysed:** 43 **Age (years):** N/S **Sex:** N/S **Prevalence of significant CAD:** N/S	**Radiation dose:** N/S **Dose modulation used:** N/S	**Cutoff:** > 50% stenosis **Sensitivity:** 92% **Specificity:** 94% **PPV:** 96% **NPV:** 89%
Onuma 2006[43] **Country:** Japan	**Enrolled:** N/S **Analysed:** 29 **Age (years):** N/S **Sex:** N/S **Prevalence of significant CAD:** N/S	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** N/S	**Segments** (n=430) **Cutoff:** > 50% stenosis **Sensitivity:** 94% **Specificity:** 99% **PPV:** 93% **NPV:** 99%
Pinto 2006[44] **Country:** Brazil	**Enrolled:** N/S **Analysed:** 30 **Age (years):** N/S **Sex:** N/S **Prevalence of significant CAD:** 10% (3/30)	**Machine:** N/S **Radiation dose:** N/S **Dose modulation used:** N/S	**Stents** (n=30) **Cutoff:** in-stent restenosis **Sensitivity:** 100% **Specificity:** N/S **PPV:** N/S **NPV:** N/S
Pugliese 2006b[45]	**Enrolled:** 51 **Analysed:** 51	**Machine:** N/S **Radiation dose:** N/S	**>2mm segments** (n=N/S), **all segments** (n=N/S)

Study id, country	Participants	Tests	Outcomes summary
Country: The Netherlands	**Age (years):** N/S **Sex:** N/S **Prevalence of significant CAD:** N/S	**Dose modulation used:** N/S	**Cutoff:** N/S **Sensitivity:** 99%, 99% **Specificity:** 96%, 95% **PPV:** 80%, 76% **NPV:** 99%, 99%
Pugliese 2006c[46] **Country:** The Netherlands	**Enrolled:** N/S **Analysed:** 25 **Age (years):** N/S **Sex:** N/S **Prevalence of significant CAD:** 96% (24/25)	**Machine:** N/S **Radiation dose:** N/S **Dose modulation used:** N/S	**Patients** (n=25) **Cutoff:** ≥ 1 vessel disease **Sensitivity:** 100% **Specificity:** 100% **PPV:** 100% **NPV:** 100%
Rubinshtein 2006a[47] **Country:** Israel	**Enrolled:** N/S **Analysed:** 133 **Age (years):** 58.2, SD 11.8 **Sex:** M 88; F 45 **Prevalence of significant CAD:** 30% (40/133)	**Machine:** Brilliance 64, Philips **Radiation dose:** N/S **Dose modulation used:** N/S	**Patients** (n=133) **Cutoff:** ≥ 50% stenosis **Sensitivity:** 100% **Specificity:** 96% **PPV:** 91% **NPV:** 100%

Study id, country	Participants	Tests	Outcomes summary
Rubinshtein 2006b[48] **Country:** Israel	**Enrolled:** N/S **Analysed:** 40 **Age (years):** 59, SD 11 **Sex:** M 24; F 16 **Prevalence of significant CAD:** 23% (9/40)	**Machine:** Brilliance 64, Philips **Radiation dose:** N/S **Dose modulation used:** N/S	**Stents** (n=51), **patients** (n=40) **Cutoff:** > 50% stenosis **Sensitivity:** 100%, 100% **Specificity:** 88%, 84% **PPV:** 67%, 64% **NPV:** 100%, 100%
Savino 2006[49] **Country:** USA	**Enrolled:** N/S **Analysed:** 55 **Age (years):** N/S **Sex:** N/S **Prevalence of significant CAD:**35% (19/55)	**Machine:** N/S **Radiation dose:** N/S **Dose modulation used:** N/S	**Segments** (n=826), **patients** (n=55) **Cutoff:** > 50% stenosis **Sensitivity:** 82%, 100% **Specificity:** 97%, 83% **PPV:** 69%, 76% **NPV:** 99%, 100%
Schlosser 2006[50] **Country:** Germany	**Enrolled:** 179 **Analysed:** 61 **Age (years):** N/S **Sex:** N/S **Prevalence of significant CAD:** N/S	**Machine:** N/S **Radiation dose:** N/S **Dose modulation used:** N/S	**Segments** (n=915) **Cutoff:** ≥ 50% stenosis **Sensitivity:** 100% **Specificity:** 97% **PPV:** 55% **NPV:** 100%

Study id, country	Participants	Tests	Outcomes summary
Sirol 2006[51] **Country:** Germany	**Enrolled:** N/S **Analysed:** 38 **Age (years):** 59, SD 14 **Sex:** M 24, F 14 **Prevalence of significant CAD:** N/S	**Machine:** N/S **Radiation dose:** N/S **Dose modulation used:** N/S	**Segments** (n=521), **patients** (n=N/S) **Cutoff:** > 50% stenosis **Sensitivity:** 75%; 75% **Specificity:** 77%; 89% **PPV:** 88%; 88% **NPV:** 94%; 76%
Wang 2006[52] **Country:** China	**Enrolled:** 100 **Analysed:** 48 **Age (years):** N/S **Sex:** N/S **Prevalence of significant CAD:** N/S	**Machine:** Sensation 64, Siemens **Radiation dose:** N/S **Dose modulation used:** N/S	**Arteries** (n=192) **Cutoff:** > 50% stenosis **Sensitivity:** 95% **Specificity:** 93% **PPV:** 86% **NPV:** 98%

Notes:
1. N/S, not stated.

Supplementary material Table 2 Summary of diagnostic accuracy results for different levels of analysis

Level of analysis	Number of studies	Number analysed	Pooled sensitivity % (95% CrI)	Pooled specificity % (95% CrI)	PPV median % (range)	NPV median % (range)
Patient	18	1286	99 (97 to 99)	89 (83 to 94)	93 (64 to 100)	100 (86 to 100)
Segment	17	14199	90 (85 to 94)	97 (95 to 98)	76 (44 to 93)	99 (95 to 100)
Left main artery	5	393	95 (84 to 99)	100 (99 to 100)	100 (90 to 100)	100
LAD overall	7	1685	92 (83 to 97)	96 (91 to 98)	86 (63 to 100)	98 (95 to 100)
LAD proximal	5	358	97 (87 to 99)	97 (90 to 99)	95 (85 to 100)	98 (90 to 100)
LCX overall	7	1351	85 (69 to 94)	96 (92 to 99)	81 (56 to 100)	98 (93 to 100)
RCA overall	7	1567	87 (77 to 95)	97 (92 to 98)	82 (74 to 91)	98 (94 to 100)
Stents	6	317	89 (68 to 97)	94 (83 to 98)	77 (33 to 100)	96 (71 to 100)
CABGs	4	543	99 (95 to 100)	96 (86 to 99)	93 (90 to 95)	99 (98 to 100)

Notes:
1. PPV, positive predictive value; NPV, negative predictive value; LAD, left anterior descending; LCX, left circumflex; CABG, coronary artery bypass graft.
2. For left main artery analysis the 95% intervals around the pooled sensitivity and specificity estimates are confidence intervals (CIs) rather than credible intervals (CrIs).
3. All five studies reporting left main artery analysis had an NPV of 100%