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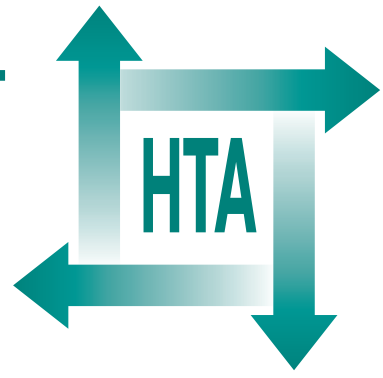

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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 06/15/01. The contractual start date was in July 2006. The draft report began editorial review in October 2007 and was accepted for publication in November 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

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Abstract

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Objectives: To assess the clinical effectiveness and cost-effectiveness, in different patient groups, of the use of 64-slice or higher computed tomography (CT) angiography, instead of invasive coronary angiography (CA), for diagnosing people with suspected coronary artery disease (CAD) and assessing people with known CAD.

Data sources: Electronic databases were searched from 2002 to December 2006.

Review methods: Included studies were tabulated and sensitivity, specificity, positive and negative predictive values calculated. Meta-analysis models were fitted using hierarchical summary receiver operating characteristic curves. Summary sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios for each model were reported as a median and 95% credible interval (CrI). Searches were also carried out for studies on the cost-effectiveness of 64-slice CT in the assessment of CAD.

Results: The diagnostic accuracy and prognostic studies enrolled over 2500 and 1700 people, respectively. The overall quality of the studies was reasonably good. In the pooled estimates, 64-slice CT angiography was highly sensitive (99%, 95% CrI 97 to 99%) for patient-based detection of significant CAD (defined as 50% or more stenosis), while across studies the negative predictive value (NPV) was very high (median 100%, range 86 to 100%). In segment-level analysis compared with patient-based detection, sensitivity was lower (90%, 95% CrI 85 to 94%, versus 99%, 95% CrI 97 to 99%) and specificity higher (97%, 95% CrI 95 to 98%, versus 89%, 95% CrI 83 to 94%), while across studies the median NPV was similar (99%, range 95 to 100%, versus 100%, range 86 to 100%). At individual coronary artery level the pooled estimates for sensitivity ranged from 85% for the left circumflex (LCX) artery to 95% for the left main artery, specificity ranged from 96% for both the left anterior descending (LAD) artery and LCX to 100% for the left main artery, while across studies the positive predictive value (PPV) ranged from 81% for the LCX to 100% for the left main artery and NPV was very high, ranging from 98% for the LAD (range 95 to 100%), LCX (range 93 to 100%) and right coronary artery (RCA) (range 94 to 100%) to 100% for the left main artery. The pooled estimates for bypass graft analysis were 99% (95% CrI 95 to 100%) sensitivity, 96% (95% CrI 86 to 99%) specificity, with median PPV and NPV values across studies of 93% (range 90 to 95%) and 99% (range 98 to 100%), respectively. This compares with, for stent analysis, a pooled sensitivity of 89% (95% CrI 68 to 97%), specificity 94% (95% CrI 83 to 98%), and median PPV and NPV values across studies of 77% (range 33 to 100%) and 96% (range 71 to 100%), respectively. Sixty-four-slice CT is almost as good as invasive CA in terms of detecting true positives. However, it is somewhat poorer in its rate of false positives. It seems likely that diagnostic strategies involving 64-slice CT will still require invasive CA for CT test positives, partly to identify CT false positives, but also because CA provides other information that CT currently does not, notably details of insertion site and distal run-off for possible coronary artery bypass graft (CABG). The high sensitivity of 64-slice CT avoids the costs of unnecessary

CA in those referred for investigation but who do not have CAD. Given the possible, although small, associated death rate, avoiding these unnecessary CAs through the use of 64-slice CT may also confer a small immediate survival advantage. This in itself may be sufficient to outweigh the very marginally inferior rates of detection of true positives by strategies involving 64-slice CT. The avoidance of unnecessary CA through the use of 64-slice CT also appears likely to result in overall cost savings in the diagnostic pathway. Only if both the cost of CA is relatively low and the prevalence of CAD in the presenting population is relatively high (so that most patients will go on to CA) will the use of 64-slice CT be likely to result in a higher overall diagnostic cost per patient.

Conclusions: The main value of 64-slice CT may at present be to rule out significant CAD. It is unlikely to replace CA in assessment for revascularisation of patients, particularly as angiography and angioplasty are often done on the same occasion. Further research is needed into the marginal advantages and costs of 256-slice machines compared with 64-slice CT, the usefulness of 64-slice CT in people with suspected acute coronary syndrome, the potential of multislice computed tomography to examine plaque morphology, the role of CT in identifying patients suitable for CABG, and the concerns raised about repetitive use, or use of 64-slice or higher CT angiography in younger individuals or women of childbearing age.

Contents

List of abbreviations

ACS	acute coronary syndrome
AHA	American Heart Association
AS	Agatston score
BMI	body mass index
bpm	beats per minute
CA	coronary angiography
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CI	confidence interval
CrI	credible interval
CT	computed tomography
DOR	diagnostic odds ratio
EBCT	electron-beam computed tomography
ECG	electrocardiogram
ED	emergency department
ETT	exercise tolerance test
FN	false negative
FP	false positive
HCHS	Hospital and Community Health Services
HSROC	hierarchical summary receiver operating characteristic
ICRP	International Commission on Radiological Protection
LAD	left anterior descending
LBBB	left bundle branch block
LCX	left circumflex
LR	likelihood ratio
MDCT	multidetector computed tomography
MI	myocardial infarction
MPI	myocardial perfusion imaging
MPS	myocardial perfusion scintigraphy
MRI	magnetic resonance imaging
MSAC	Medical Services Advisory Committee
MSCT	multislice computed tomography
NA	not applicable
NPV	negative predictive value
NR	not reported
NS	not stated
PA	posterior–anterior
PET	positron emission tomography
PCI	percutaneous coronary intervention
PPV	positive predictive value
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality-adjusted life-year

continued

List of abbreviations *continued*

QUADAS	Quality Assessment of Diagnostic Studies
RCA	right coronary artery
RCT	randomised controlled trial
SD	standard deviation
SPECT	single-photon emission computed tomography
SROC	summary receiver operating characteristic
TEC	Technology Evaluation Center
TN	true negative
TP	true positive
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Coronary artery disease (CAD) is a major cause of mortality and ill-health. Coronary angiography (CA) is the gold standard for diagnosing CAD. However, CA is an invasive and expensive procedure, with a small (0.1–0.2%) risk of major complications such as death, myocardial infarction and stroke. A primary non-invasive technique for the diagnosis of CAD is therefore highly desirable.

The emergence of multislice computed tomography (MSCT) in the past decade and the introduction of 64-slice systems in 2004 have overcome many of the image quality issues that affected conventional CT systems. The technical factors that enhance image quality in 64-slice CT also result in a higher radiation dose, although the use of electrocardiogram (ECG)-dependent dose modulation can reduce this by 30–50%.

Objectives

This review aims to assess the clinical effectiveness and cost-effectiveness, in different patient groups, of the use of 64-slice or higher CT angiography, instead of invasive CA, for diagnosing people with suspected CAD and assessing people with known CAD.

Methods

Electronic searches were undertaken to identify published and unpublished reports. Searches were restricted to the years 2002 onwards and to English-language reports. The date of the last searches was December 2006.

The types of studies considered were randomised controlled trials, non-randomised comparative studies or case series in which adults received 64-slice or higher CT angiography, with invasive CA or long-term follow-up as the reference standard. Myocardial perfusion scintigraphy (MPS) was considered as a comparator test. Diagnostic accuracy studies had to report the absolute numbers of true and false positives and negatives, or sensitivity and specificity. Prognostic studies had to provide information on the likelihood of future cardiac events.

One reviewer screened the titles (and abstracts if available) of all reports identified by the search strategy. Two reviewers independently extracted details from the included full-text studies and assessed their quality using a modified version of the QUADAS instrument.

The results of the individual studies were tabulated and sensitivity, specificity, positive and negative predictive values calculated. Separate summary receiver operating characteristic (SROC) curves were derived for various levels of analysis. Meta-analysis models were fitted using hierarchical summary receiver operating characteristic (HSROC) curves. A symmetric SROC model was used. Summary sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios (DORs) for each model were reported as a median and 95% credible interval (CrI).

Searches were also carried out for studies on the cost-effectiveness of 64-slice CT in the assessment of CAD.

Results

Twenty-one diagnostic accuracy studies reported as full-text papers and 20 reported as abstracts, along with one prognostic study reported as a full-text paper and four reported as abstracts, met the inclusion criteria for the review. The diagnostic accuracy and prognostic studies enrolled over 2500 and 1700 people, respectively. As measured by the modified QUADAS checklist, the overall quality of the full-text diagnostic accuracy studies was reasonably good.

In the pooled estimates, 64-slice CT angiography was highly sensitive (99%, 95% CrI 97 to 99%) for patient-based detection of significant CAD (defined as >50% or ⩾50% stenosis), while across studies the negative predictive value (NPV) was very high (median 100%, range 86 to 100%). In the 13 full-text studies included in the pooled estimates, in terms of patient-based detection, 11 (2%) of 718 patients could not be assessed owing

to unevaluable CT scans (median across studies 0%, range 0 to 6%). Three studies reported that all vessels smaller than 1.5 mm were excluded from analysis.

In segment-level analysis compared with patient-based detection, sensitivity was lower (90%, 95% CrI 85 to 94%, versus 99%, 95% CrI 97 to 99%) and specificity higher (97%, 95% CrI 95 to 98%, versus 89%, 95% CrI 83 to 94%), while across studies the median NPV was similar (99%, range 95 to 100%, versus 100%, range 86 to 100%). At individual coronary artery level the pooled estimates for sensitivity ranged from 85% (95% CrI 69 to 94%) for the left circumflex (LCX) artery to 95% (95% CI 84 to 99%) for the left main artery, specificity ranged from 96% for both the left anterior descending (LAD) artery (95% CrI 91 to 98%) and LCX (95% CrI 92 to 99%) to 100% (95% CrI 99 to 100%) for the left main artery, while across studies the positive predictive value (PPV) ranged from 81% (range 56 to 100%) for the LCX to 100% (range 90 to 100%) for the left main artery and NPV was very high, ranging from 98% for the LAD (range 95 to 100%), LCX (range 93 to 100%) and right coronary artery (range 94 to 100%) to 100% (all five studies) for the left main artery. The pooled estimates for bypass graft analysis were 99% (95% CrI 95 to 100%) sensitivity, 96% (95% CrI 86 to 99%) specificity, with median PPV and NPV values across studies of 93% (range 90 to 95%) and 99% (range 98 to 100%), respectively. This compares with, for stent analysis, a pooled sensitivity of 89% (95% CrI 68 to 97%), specificity 94% (95% CrI 83 to 98%), and median PPV and NPV values across studies of 77% (range 33 to 100%) and 96% (range 71 to 100%), respectively.

None of the studies reporting the diagnostic accuracy of 64-slice CT included MPS as a comparator. In two systematic reviews of single-photon emission computed tomography (SPECT) MPS, sensitivity was reported as a median of 81% across studies (range 63 to 93%) or pooled estimate of 87% [fixed-effect model, 95% confidence interval (CI) 86 to 88%], while specificity was reported as a median of 65% across studies (range 10 to 90%) or pooled estimate of 64% (fixed-effect model, 95% CI 60 to 68%).

Three of the five prognostic studies included low-risk patients with suspected acute coronary syndrome and all reported that 64-slice CT angiography had very good NPV in short-term (mostly 30-day) follow-up. Of the other two studies, one reported that in the year following the introduction of 64-slice CT the rates of increase in diagnostic catheterisation volume and percutaneous coronary interventions had not been significantly affected, while the other reported that in the 6 months following the introduction of 64-slice CT invasive CA was avoided in 398 (82%) of 486 patients who would have received the test.

Cost-effectiveness

No studies of the cost-effectiveness of 64-slice CT in assessing CAD were found. However, some of the reviews and previous health technology assessments did identify some of the cost-effectiveness issues that are likely to arise. Other studies examined the cost-effectiveness of other investigations against angiography, such as exercise testing and positron emission tomography scanning, and these provided useful background.

Sixty-four-slice CT appears to be as good as but cheaper than MPS for the diagnosis of CAD. Consequently, 64-slice CT is likely to be a cost-effective replacement for MPS in diagnosing CAD.

Sixty-four-slice CT is almost as good as invasive CA in terms of detecting true positives. However, it is somewhat poorer in its rate of false positives. Consequently, diagnostic strategies involving 64-slice CT angiography will result in a number of false positives (not in terms of whether CAD is present, but in terms of quantifying the degree of stenosis). It seems likely that diagnostic strategies involving 64-slice CT will still require invasive CA for CT test positives, partly to identify CT false positives, but also because CA provides other information that CT currently does not, notably details of insertion site and distal run-off for possible coronary artery bypass graft (CABG).

The high sensitivity of 64-slice CT avoids the costs of unnecessary CA in those referred for investigation but who do not have CAD. Given the possible although small associated death rate, avoiding these unnecessary CAs through the use of 64-slice CT may also confer a small immediate survival advantage on the presenting population. This in itself may be sufficient to outweigh the very marginally inferior rates of detection of true positives by strategies involving 64-slice CT.

The avoidance of unnecessary CA through the use of 64-slice CT also appears likely to result in overall cost savings in the diagnostic pathway. Only if both the cost of CA is relatively low and the prevalence of CAD in the presenting population is relatively high (so that most patients will go on to

CA) will the use of 64-slice CT be likely to result in a higher overall diagnostic cost per patient.

Conclusions

Implications for practice

The proportion of CA that could be replaced by 64-slice CT is currently uncertain. Reduction in CA would be mainly at the diagnostic end of the pathway, in both elective assessment of chest pain of possibly anginal origin, and assessment of suspected acute coronary syndromes in some patients with normal or equivocal ECGs and negative troponin tests. In the emergency situation, some hospital admissions might be avoided. However, to do so, 64-slice CT would need to be readily available, ideally on a 24-hour basis, which is unlikely to be the case in most hospitals. Some perfusion studies could also be replaced by 64-slice CT angiography.

In summary, the main value of 64-slice CT may at present be to rule out significant CAD. It is unlikely to replace CA in assessment for revascularisation of patients, particularly as angiography and angioplasty are often done on the same occasion.

One issue is whether to acquire 64-slice CT systems or wait until 256-slice systems become available. Evidence on 256-slice CT is currently sparse and mostly commercial in origin. However, it is unlikely that performance would be less good, and if the cost difference between 64- and 256-slice machines were small, it could be argued that the NHS should bypass 64-slice machines in favour of 256-slice ones. However, there must come a time when the extra data do not provide additional clinical benefit, although it is as yet unclear when that point will be reached.

Recommendations for research

The following areas should be addressed by further research.

- The marginal advantages and costs of 256-slice machines compared with 64-slice CT.
- The usefulness of 64-slice CT in people with suspected ACS. This review identified only a few studies, mostly reported as abstracts, containing small numbers of patients, most of whom were low risk and would be expected to have relatively low event rates.
- The potential of MSCT to examine plaque morphology.
- The role of CT in identifying patients suitable for CABG. CT can identify stenoses, but research is needed into its ability to identify distal insertion sites and adequacy of run-off. Such research could be done by conducting CT in a large group of patients before CABG (with preceding invasive CA), with assessment of suitability for CABG by observers unaware of the invasive CA results and arterial findings at CABG.
- Concerns raised about repetitive use, or use of 64-slice or higher CT angiography in younger individuals or women of childbearing age.

Chapter 1
Background

Aim of the review

The primary aim of this review is to assess the clinical effectiveness and cost-effectiveness, in different patient groups, of using 64-slice or higher computed tomography (CT) angiography, instead of invasive coronary angiography (CA), for diagnosing people with suspected coronary artery disease (CAD) and assessing people with known CAD. However, a further consideration is whether 64-slice CT could replace some myocardial perfusion scanning.

The disease

CAD is a major cause of mortality and ill-health in the UK. It presents in different ways, with the most common being angina and myocardial infarction (MI). The underlying cause is a process called atherosclerosis, which leads to narrowing of the coronary arteries, restricting the blood flow to the heart muscle. During exercise, if the blood flow to the heart muscle cannot increase enough, angina occurs. This leads to treatment and/or referral for cardiological assessment.

The diagnosis of angina is usually made on clinical history and simple examinations such as electrocardiogram (ECG) or exercise ECG testing.

Treatment options include:

- symptomatic measures such as nitrates, β-blockers and calcium antagonists
- antithrombotic drugs such as aspirin, dipyridamole and clopidrogel, to reduce the chance of a coronary thrombosis forming on the atheromatous plaque
- lipid-lowering drugs such as statins, to lower the risk of MI and reduce or prevent progression of atherosclerosis
- angioplasty with or without (but nowadays, usually with) stenting; angioplasty is now often referred to as percutaneous coronary intervention (PCI)
- coronary artery bypass graft (CABG) surgery
- general diet and lifestyle advice.

PCI and CABG may be used for two purposes: first, to relieve symptoms when medical therapy fails to achieve that and, secondly, in some groups, to reduce the chance of a heart attack (MI). About twice as many people now have angioplasty as CABG. Increasingly, angioplasty is done at the same time as the initial angiography.

Before either CABG or angioplasty, the state of the arteries is examined by coronary angiography. This involves passing a fine catheter into each artery in turn, injecting a dye and visualising the arteries by X-ray. A limiting factor in these processes is that angiography facilities (catheter laboratories) are limited.

Angiography is used to assess the extent of the CAD, identify significant stenoses (narrowings) that may be the culprit lesions causing angina and provide information on prognosis, in terms of likelihood of future infarction and its severity. Some patterns of disease such as left main or left anterior descending (LAD) artery stenosis carry a higher risk of death. The information from angiography is used to decide whether to proceed to angioplasty or CABG, and if the former, which stenoses to dilate.

One of the constraints on angiography is space in angiography rooms; another is cardiologist time. Both will be under greater pressure if immediate angioplasty becomes routine, as suggested by the findings of a previous HTA review.[1]

The technology

CT has been developing rapidly in recent years. Four-slice machines appeared in 1998, 16-slice in 2001 and 64-slice machines at the end of 2004. The newer multidetector machines can produce more images in less time, thereby increasing throughput and decreasing the cost per patient. A previous HTA review[2] is now well out of date. A recent HTA review[3] examined the role of electron-beam computed tomography (EBCT) in screening for CAD, but did not address the use of the newer forms of CT in investigation of suspected or symptomatic CAD.

Imaging of the heart is technically challenging because of continuous motion during the cardiac cycle. CA is the gold standard for the diagnosis of CAD owing to its high temporal and spatial resolution. However, it is an invasive and expensive procedure, with a small (0.1–0.2%) risk of major complications such as death, MI and stroke.[4] Previously, magnetic resonance imaging (MRI) and EBCT were considered non-invasive cardiac imaging modalities of choice, owing to their high temporal resolution, but neither has been used in routine clinical practice because of limited availability in specialist centres. A primary non-invasive technique for the diagnosis of CAD is therefore highly desirable.

The emergence of multislice computed tomography (MSCT) in the past decade and the introduction of 64-slice systems in 2004 have overcome many of the image quality issues that plagued conventional CT systems. This newest generation of CT systems acquires 64 × 0.6-mm slices in a single tube rotation of just 330 ms.[5] Coupled with hard and software advances, 64-slice CT has become a viable proposition in non-invasive imaging of cardiac vascular anatomy and pathology.

CT image quality depends on the patient's ability to suspend respiration. With 64-slice CT, the major benefit of the increased number of slices acquired and the improved temporal resolution (time required to acquire data for one image) is a shorter overall scan time. Currently, this has been reduced to 8 seconds.[6] Image acquisition is completed within a single breath-hold, which reduces respiratory motion and improves image quality. The spatial resolution (the number of pixels of information that make up a digital image) of 64-slice CT is also superior to conventional CT. This allows better assessment of smaller coronary arteries such as the distal LAD and left circumflex (LCX) arteries. In addition, there is less blooming artefact, the main cause of false-positive results where partial volume averaging effects of high-density calcific material overestimate the degree of stenosis, and therefore 64-slice CT allows better assessment of calcified or stented vessels.[7]

Following the acquisition of data the images are reconstructed with a slice thickness of 0.75 mm, a 50% overlap between slices and a pixel matrix of 512 × 512. Although the thinner slice improves the resolution of three-dimensional data sets and the quality of reformatted images, it comes at the cost of increased image noise, which can significantly limit the diagnostic assessment of the coronary arteries in patients with a body mass index (BMI) of greater than 30.

Heart rate also significantly influences the length of coronary artery visualised without motion artefact. Sixty-four-slice CT angiography uses ECG gating techniques to capture data at points in the cardiac cycle when cardiac motion is minimised, usually in the mid to late diastolic phase.[6] The ECG signal is monitored and used prospectively to trigger imaging or retrospectively to reconstruct data from continuous acquisitions. However, despite this technique motion artefact remains a major technical problem with heart rates above 70 beats per minute. In both studies and clinical practice β-blockers have been used to reduce the heart rate, lengthen the period of diastole and therefore minimise cardiac motion. In patients with a contraindication to β-blockade (e.g. chronic obstructive pulmonary disease), calcium channel blockers can be used as an alternative.

Image quality also depends on the volume of contrast material within the coronary tree at the time of imaging. CT angiography relies on the intravenous administration of iodinated contrast material, unlike conventional angiography in which contrast is administered directly into the coronary arterial tree. To ensure adequate contrast enhancement, the contrast material is injected intravenously and a bolus tracking technique used to synchronise its arrival in the coronary arteries with initiation of the examination. CT angiography is performed with less iodinated contrast material (average 80–100 ml) than conventional angiography; however, the absolute contraindication of hypersensitivity to iodinated contrast agent remains in addition to the relative contraindications of renal insufficiency, multiple myeloma and phaeochromocytoma. CT angiography, however, avoids the major complications associated with arterial puncture, plaque embolisation, serious bleeding and vessel dissection, and provides highly detailed information about the aorta, pulmonary artery and veins, lungs and mediastinum, which may prove useful in clinical practice for excluding other causes of chest pain such as pulmonary thromboembolism and thoracic aortic dissection.

The technical factors that enhance image quality in 64-slice CT, namely high spatial and temporal resolution, also affect the radiation dose received. To obtain diagnostic image quality with the narrow slice width and reduced scan time of 64-slice CT, the number of photons received by the detector

array must be increased. This occurs by increasing the tube current from 400–650 mAs typically used in 16-slice CT to 500–950 mAs in 64-slice CT. This results in an increased radiation exposure and increased effective dose. A recent study by Hausleiter and colleagues[8] estimated the effective dose to be 11.0 (SD 4.1) mSv for 64-slice CT. Use of ECG-dependent dose modulation can reduce the radiation dose by 30–50% during systole, when the acquired data add little to coronary imaging. This radiation exposure is comparable to 160 posterior–anterior (PA) chest films or three to four times the average yearly effective dose of natural background radiation (2.5 mSv). Alternative methods to reduce radiation dose include reducing tube kilovoltage; however, this is often to the detriment of image quality and the high radiation doses received remain an important consideration of this choice of imaging modality.

Previous reports

Reviews

There have been some recent reviews, but the pace of publication in this field means that they quickly become out of date.

Stein and colleagues,[9] in a high-quality review published in 2006, found only one study of 64-slice CT, because their literature search was up to March 2005. The conclusions of their review were that:

- MSCT had high sensitivity for detecting significant stenosis
- sensitivity increased with number of detectors
- specificity also increased with increasing number of detectors
- with a higher number of detectors, more segments could be examined
- there was higher sensitivity for stenoses in proximal and mid-segments of arteries.

Significant stenosis was defined as being 50% or greater narrowing of the artery. This definition is presumably based on assessment for revascularisation. However, CT may be used for other purposes. One could be to confirm or rule out the presence of CAD, in which case much lesser degrees of atherosclerosis and stenosis would be relevant. Another could be to identify high-risk plaques (i.e. those that are most likely to provide the focus for a coronary thrombosis). High-risk plaques may show little or no stenosis. Hence, the sensitivity required will vary according to the purpose of CT.

The term 'segments' refers to the part of the artery, and is based on definitions by the American Heart Association (AHA). Proximal includes the parts of the arteries from their origins to the first main branches, where the artery is widest. Distal includes the sections after the largest branches have come off, and where the artery is progressively narrowing. The higher up (or more proximal) a stenosis, the more dangerous it is, because blockage would deprive a large part of the heart muscle of its blood supply. Blockage of a distal artery is less dangerous, partly because a much smaller portion of muscle is affected, and partly because at that level, there may be collateral circulation from the distal branches of the other coronary arteries. Hence, sensitivity at the distal level could be seen as less important, but awareness of the extent of distal disease is still useful since it may predict the success of relieving or bypassing a proximal stenosis.

The Technology Evaluation Center (TEC), which is a joint service to Blue Cross/Blue Shield and Kaiser Permanente in the USA, published another high-quality review of cardiac CT in 2005.[10] Searches were up to April 2005, and no studies of CT with more than 16 slices were found. The review assumed that negative CT would avoid the need for invasive CA, and that positive CT would be followed by angiography. It is possible that the latter assumption may not apply with 64-slice CT. CT failed to meet the TEC criteria, and in particular criterion 2, which states that the technology should improve health outcomes. However, the report envisaged a more persuasive case once 64-slice CT arrived.

The TEC report notes some weaknesses of the literature. One is that results are often presented in terms of number of arteries or segments examined, rather than being based on patients. Clinical decisions need the whole picture for the patient. Secondly, results are often presented only for 'evaluable' segments of arteries, which can give a misleadingly good impression of the technology. Thirdly, studies were often done in high-risk patients, not representative of the groups in which it may be used in future, such as those with only suspected CAD.

The TEC report concluded that CT should not be recommended because the criteria were not yet met. One issue dealt with, albeit briefly, in the TEC report, was the potential of CT to examine plaques. As the report points out, plaque morphology is important and if CT can assess the composition of plaques and identify the lipid-rich unstable

plaques, it may provide information that CA does not.

A report from the Andalusian Agency for Healthcare Technology Assessment[11] drew on the TEC report, but added a review of some more recent papers on 16-slice CT. Using patient-based analysis (rather than artery-based), the 16-slice studies reviewed gave sensitivities ranging from 86 to 97%, specificities from 49 to 87%, positive predictive values (PPVs) of 84 to 90% and negative predictive values (NPVs) of 53 to 95%. If the main role of CT is to rule out the need for CA, then for 16-slice machines the low NPV is a problem.

CT is very quick, and faster than CA, and so probably much less expensive, as well as being less invasive, although the radiation dose is higher than the average 4–8-mSv exposure quoted by the TEC report[10] or the below 5% exposure quoted by a British Cardiovascular Society Working Group report[12] for invasive angiography. The radiation dose is also higher with 64-slice than 16-slice (about 11 versus 6 mSv)[8] but there are ways of reducing the dose such as ECG-dependent dose modulation and reduced tube voltage.[8]

Studies of 16-slice CT

While not strictly relevant to this review, which is more concerned with 64-slice CT, past reviews or studies of 16-slice can at least provide a baseline impression, on the assumption that 64-slice will be better.

Hoffman and colleagues[13] compared 16-slice CT with invasive CA in 103 patients with known or suspected CAD, and produced patient-based results for the sensitivity of detection of stenoses of 50% or more. Only 6% of images were not good enough for diagnosis, mainly because of fast heart rates. Segment-based sensitivity and specificity were high at 95% and 98%, and NPV was 99%. However, in the patient-based analysis, in 27% of cases there was incomplete coverage of the whole coronary tree. In those with complete coverage, CT identified 84% of those without significant stenosis, as judged by invasive CA, and identified 97% of those with stenoses suitable for revascularisation.

Kefer and colleagues[14] compared both 16-slice CT and MRI with CA in 52 patients with a high probability of significant arterial disease. CT was better than MRI, but both overestimated non-significant stenosis and underestimated significant (> 50%) stenosis. Sensitivity of CT was better in larger vessels such as the left main and LAD, but not so good in small branches of the LCX and right coronary artery (RCA).

Kuettner and colleagues[15] reported good results with a more modern 16-slice CT machine, but did not include CA, so there was no reference standard.

More useful background comes from a good Canadian Coordinating Office for Health Technology Assessment (CCOHTA) review[16] of the clinical effectiveness (economics reported separately). The review notes that there are several manufacturers of MSCT: GE Medical Systems in the USA, Philips in The Netherlands, Siemens in Germany, and Shimadzu and Toshiba in Japan. Much of the research comes from those countries.

The CCOHTA report was on all uses of CT. It noted the rapid growth of CT in Canada, from 200 scanners in 1991 to 338 in 2004; a growth rate of 70%. In January 2004, there were 11 CT machines (publicly funded) per million population.

The CCOHTA review[16] identified five existing reviews,[17–21] but none of these covered 64-slice CT (the latest references were from 2003), and most received low-quality scores using a modification of the Oxman and Guyatt criteria. The CCOHTA review concluded that MSCT was "promising but not yet superior to coronary angiography".

Another thorough review from Canada,[22] this time from the Ontario Health Technology Advisory Committee, in April 2005, was again a little too early to provide data on 64-slice CT, since only two abstracts could be found. It provides a good review of 16-slice studies, and concluded that 16-slice CT was not good enough to rule out the presence of CAD.

Gaspar and colleagues[23] provide both a brief review and the results of their own experience of using a variety of CT scanners in over 1000 patients. They provide one of the few accounts of using a 40-slice scanner, noting that it had high sensitivity of 95% on an arterial basis, but lower at 90% on a patient basis. Calcifications rendered some segments unevaluable. CT was useful in showing significant CAD in 29% of patients with a negative or non-diagnostic exercise tolerance test (ETT).

Gaspar and colleagues[23] also give details of their assessment of the value of CT in four specific applications:

- in plaque characterisation, where they concluded that MSCT was better than CA for detecting non-obstructive but high-risk plaques
- evaluation of in-stent restenosis with both 40-slice and 64-slice CT, where they reported that stent lumens were visible in 200 stents of 13 different designs, and that in-stent restenosis could be detected with 85% sensitivity, 97% specificity and 95% NPV
- CABG, where 64-slice is more useful than 16-slice CT
- acute chest pain diagnosis, where 64-slice CT changed diagnosis or management in almost half of 42 patients. Among those discharged because CT was low risk or negative, there were no adverse cardiac events in 30-day follow-up.

Berman and colleagues[24] provide a wide-ranging review of the place of non-invasive imaging tests. It is not a systematic review, and is a little out of date (it was submitted in July 2005) and hence does not include all the 64-slice studies now available; it relies mainly on 16-slice studies. However, it includes useful thinking about the place of the different technologies in a number of scenarios, including situations similar to both the diagnostic and assessment scenarios included in this review.

Among other things, Berman and colleagues[24] consider the relative places of single-photon emission computed tomography (SPECT), myocardial perfusion scintigraphy (MPS) and CT angiography (CTA). In patients being investigated for symptoms that may be due to CAD, they suggest that the choice of investigation should depend on the pretest likelihood of CAD. Very low-risk patients are not investigated further. High-risk patients are sent for MPS, looking for functional changes in myocardial muscle with a view to revascularisation. Intermediate risk patients go for CT angiography, and if abnormal for CA with a view to angioplasty. They argue that in the intermediate group (who on risk scoring might have from 10 to 20% risk of a cardiac event in the next 10 years), that,

> "Although existing guidelines recommend exercise testing without imaging for these patients, because CTA provides a far more sensitive test for CAD in this population, we consider it more useful than the exercise ECG in selecting patients for aggressive medical management and for additional testing. It is likely that the definitive ability to rule out CAD will become a principal driving force in the application of coronary CT."

One question that needs to be considered is the threshold for ruling out CAD. Most people being investigated for suspected angina will be middle aged. What proportion of such people in the UK will have entirely normal coronary arteries? However 'ruling out CAD' is short-hand for 'ruling out CAD as a cause of symptoms', which implies that it is not complete absence of CAD which is required, but rather absence of sufficient stenosis to cause angina. That then raises a need to define 'sufficient'. Whether a stenosis can cause angina will depend not just on the percentage narrowing of the lumen, but on other factors such as the length of the stenosis, the difference in pressure across it and the demands placed on the heart by the level of exercise.

Berman and colleagues[24] anticipate that CT angiography can replace some MPS, and that the rapid growth of MPS activity in the USA will slow considerably.

NHS Quality Improvement Scotland issued an evidence note in 2005,[25] in which it was concluded that 16-slice CT was not yet as good as CA for detecting stenosis, and that it was too early to pass judgement on 64-slice CT. The cost of a 64-slice scanner was estimated to be over £1 million, with annual maintenance, and perhaps cardiovascular imaging software, costs to be added. But it also concluded [probably based on the Medical Services Advisory Committee (MSAC) review] that the cost of the multislice procedure might be less than half that of CA.

More recently, a working group convened by the American College of Cardiology Foundation, with representatives from other relevant organisations, produced recommendations on appropriate uses of cardiac CT (and cardiac MRI).[26] The appropriate indications for CT angiography included:

- evaluation of chest pain where there was intermediate pretest probability of CAD and either an uninterpretable ECG or inability to exercise; or after an uninterpretable or equivocal stress test
- evaluation of suspected coronary anomalies in symptomatic CAD
- acute chest pain with intermediate pretest probability of CAD, no ECG changes and enzymes negative
- evaluation of coronary arteries in patients with new onset heart failure to assess aetiology.

At almost the same time, another statement on CT angiography was issued by a different group of American societies, led by the AHA.[27] There was only one author in common. The statement noted the rapid development of CT and commented

that: "As a result, the diagnostic capabilities at times have preceded the critical evaluation of clinical application."

The statement included the following recommendations or conclusions:

- CT angiography is useful for the assessment of obstructive coronary disease in symptomatic patients, perhaps especially for ruling out stenosis in patients with low or intermediate pretest likelihood of disease. "A 'normal' CT coronary angiogram allows the clinician to rule out the presence of haemodynamically relevant coronary artery stenosis with a high degree of reliability."
- There is insufficient evidence at present for its use in follow-up of stent placement.
- The use of CT to study non-calcified plaque is promising but premature.
- CT angiography is not recommended for detecting CAD in asymptomatic people.
- Serial imaging for assessment of progression of coronary calcification is not recommended.
- "The use of cardiac CT angiography for non-invasive assessment of lumen stenosis in symptomatic individuals has the potential to significantly alter the management of CAD and current diagnostic testing patterns."

The authors concluded that CT angiography could reduce the need for invasive CA.

Neither of the working group statements mentions the possible use of CT angiography to identify patients whose pattern of disease is such that they are not suitable for angioplasty, but should go straight to CABG. That might be another way of reducing CA needs.

There is great interest in the USA in 64-slice CT, as a recent commentator[28] noted:

> "The advent of the 64-slice scanner and its ability to spin an x-ray tube around a body at 30 mph, capturing the heart in a 10-second breath-hold, has clearly unleashed a surge of excitement and ambition. For radiology, this may well be the holy grail. For cardiology, it foretells tectonic change and the potential for some professional and technical obsolescence. Surely there are plenty of cardiologists out there who would like to vaporise the 64-slice."

Decision problem

Key question: Could CT be used to reduce CA requirements, for the diagnosis and assessment of CAD?

Subsidiary questions – technical:

- How well does 64-slice CT identify stenoses in coronary arteries?
- Can 64-slice CT identify vulnerable plaques which do not cause significant stenoses?

Can 64-slice CT replace some angiography by:

- Excluding significant CAD in people with symptoms suggestive of angina but where there is uncertainty about the diagnosis? The essential feature would be a high NPV.
- Excluding significant CAD in people with acute chest pain? Again this would require a high NPV.
- Identifying cases where CAD is present but does not require revascularisation (at present), i.e. to rule out further procedures, at least for the present? This might be followed by 'watchful waiting' with repeat CT angiography at intervals.
- Identifying cases where revascularisation by CABG rather than PCI is indicated, i.e. enabling some patients to go direct to CABG without prior angiography?

In both the last two cases, ability to detect non-stenotic but unstable plaques would also be of value, since these are more likely sites of coronary thrombosis than rigid calcified plaques.

An additional question is whether CT angiography could replace some perfusion studies. This is not within the original remit of this review, but since we need to consider the pathways by which people reach CT or CA, it can be dealt with in passing.

Possible patient subgroups include:

- Those with definite coronary heart disease being assessed with a view to revascularisation. The options for this group include medical treatment only, angioplasty or CABG. Given the trend to do angioplasty at the same time as CA, CT may not have a large role in this group, unless it could identify those in whom CABG is required.
- Those in whom there is diagnostic uncertainty after resting and exercise ECG testing. At present, people may be referred for MPS, and CT may replace some of this. One possibility could be that in those with a low pretest probability of heart disease, CT could be used, whereas in those with a high probability, CA would be used. If CT was negative, patients would not go for CA.

- Disease-specific groups: in people with diabetes, the pattern of atherosclerosis is different (more diffuse so often less amenable to angioplasty). There may be a role for CT in identifying patients who will require CABG rather than angioplasty. One possibility may be that people with diabetes would have CT to decide whether to proceed to CA with an intention of angioplasty, or to go directly to CABG.
- People admitted with chest pain, but who do not have convincing evidence of acute coronary syndrome (ACS) (and have normal ECG and troponins). This may represent quite a large group and there may be a place for CT. Exercise testing is another option.

One issue is what to use as the reference standard, and this may vary according to whether the purpose is to detect stenosis, in which case angiography would be the gold standard, or vulnerable plaques, when angiography may miss some lesions, and where the gold standard may be long-term follow-up. However, it is likely that people with vulnerable plaques will also have stenoses elsewhere, which would trigger intervention.

False positives could be defined as lesions not needing revascularisation but which are so treated; but once treated it would not be possible to identify which were false positives. So the use of a reference standard would be to identify false negatives; that is, those in whom CT or CA suggests that there is no disease requiring treatment, but who go on to suffer an event such as MI or angina. Long-term follow-up would be the best reference standard here, but the duration of follow-up requires thought. Too long a follow-up would make it difficult to distinguish false negatives from true negatives in whom disease has developed *de novo*.

False negatives could be divided into two groups:

- those in whom the severity of arterial disease is underestimated, and who are therefore not sent for revascularisation
- those in whom disease is missed altogether.

Sensitivity and specificity may differ for stenotic and non-stenotic lesions, and also perhaps for different arteries. CT may be better for detecting lesions in, for example, left main or LAD arteries than in LCX, because of their locations; or for proximal rather than distal lesions.

If CT could reveal vulnerable plaques, one problem would be knowing what treatments to use. The data on the benefits of revascularisation all relate to degrees of stenosis. So uncertainties about treatment of vulnerable plaques may reduce the value of CT information.

The analysis will focus on the diagnostic and prognostic assessment pathways (*Figures 1–5*). It is assumed that treatments such as revascularisation are of proven benefit, and that the key outcome for the review is allocation to appropriate treatment.

Figure 1 shows the investigation pathway for non-urgent investigation. A resting ECG may show

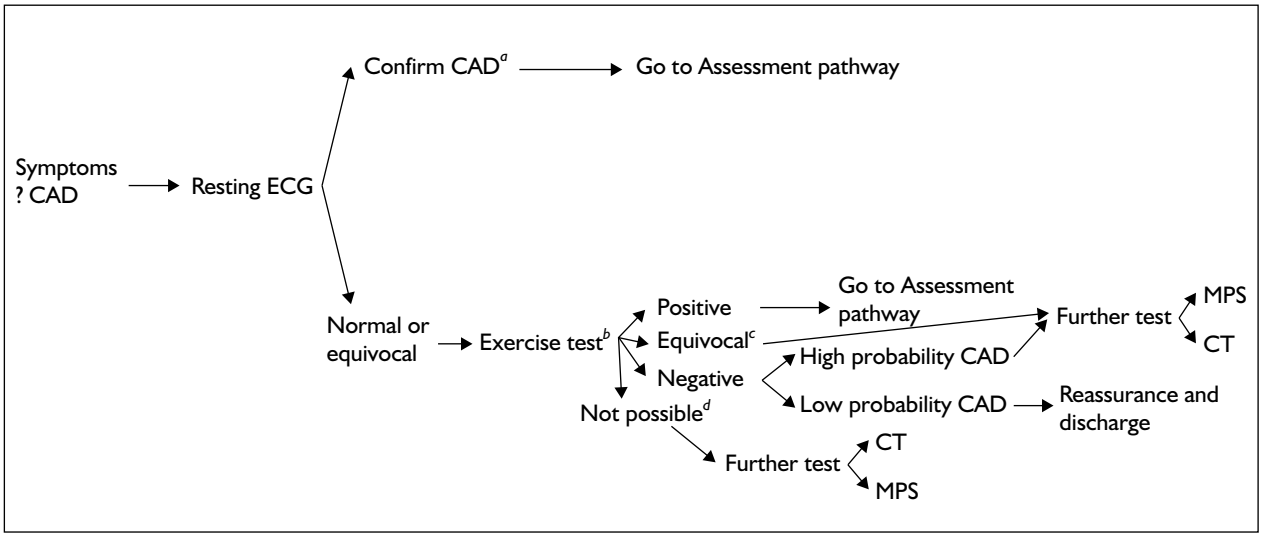


FIGURE 1 *Investigation pathway – non-acute.* [a] *For example, evidence of previous MI;* [b] *exercise test plus clinical finding;* [c] *includes unable to exercise enough, non-specific ECG changes;* [d] *e.g. left bundle branch block (LBBB).*

evidence of a previous infarction, but more often the patient will progress through the usual pathway of exercise testing on a treadmill. If the diagnosis is confirmed, patients go forward for prognostic assessment. If the exercise test is equivocal, or negative but with a high probability of CAD, then further testing may be carried out, and options include CT and MPS.

Figure 2 shows the pathway for urgent investigation when someone attends an emergency facility with acute chest pain of suspected cardiac origin. If clinical assessment suggests that the pain is cardiac, ECG and troponin testing will be done. If these confirm that the pain is cardiac in origin, appropriate care will follow. But with both tests, especially in the early hours after MI, false negatives can occur. The physicians have to decide whether patients should be admitted for observation and repeated tests, or reassured and discharged. After admission, some will be shown not to have pain of cardiac origin; these could be regarded as a form of 'false positives' in the assessment process. Conversely, some of those discharged may truly have had pain of cardiac origin: the 'false negatives'. Some may have a recurrence and be admitted, but others may die at home from an MI. If CT were available in the emergency situation, it might have a role in excluding CAD and avoiding the need for admission for observation. Conversely, it might also lead to some people being admitted who would otherwise have been incorrectly discharged.

Figure 3 starts with a positive diagnosis of CAD, following which treatment for angina will be given. If symptoms are not relieved, revascularisation will be considered for symptomatic relief. If symptoms are relieved, then revascularisation may still be considered if CABG would improve the prognosis. Good performance on an exercise test suggests a good prognosis, and that CABG is unlikely to be indicated.

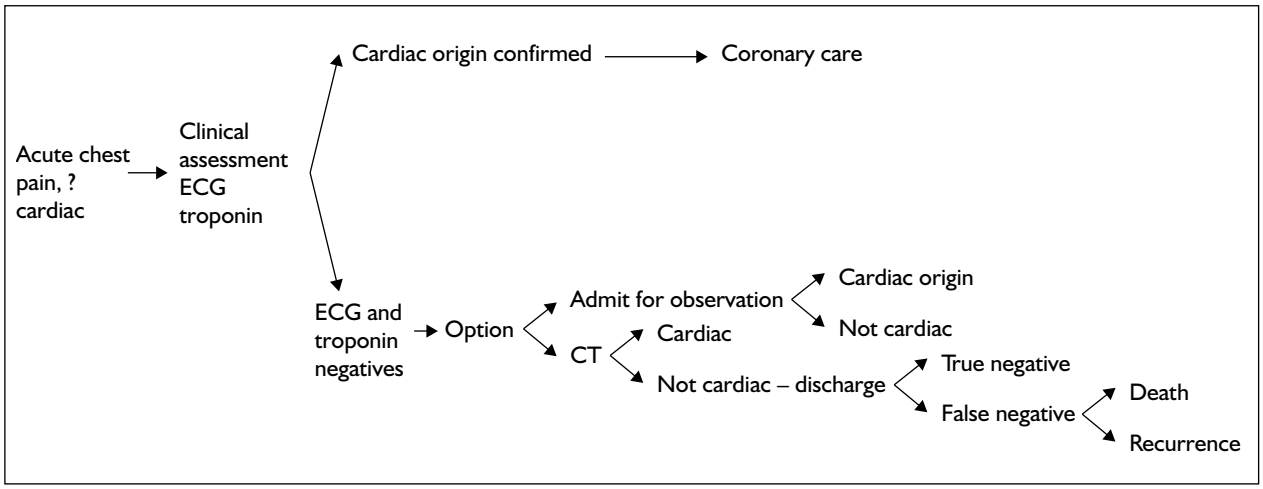


FIGURE 2 *Diagnosis of acute chest pain*

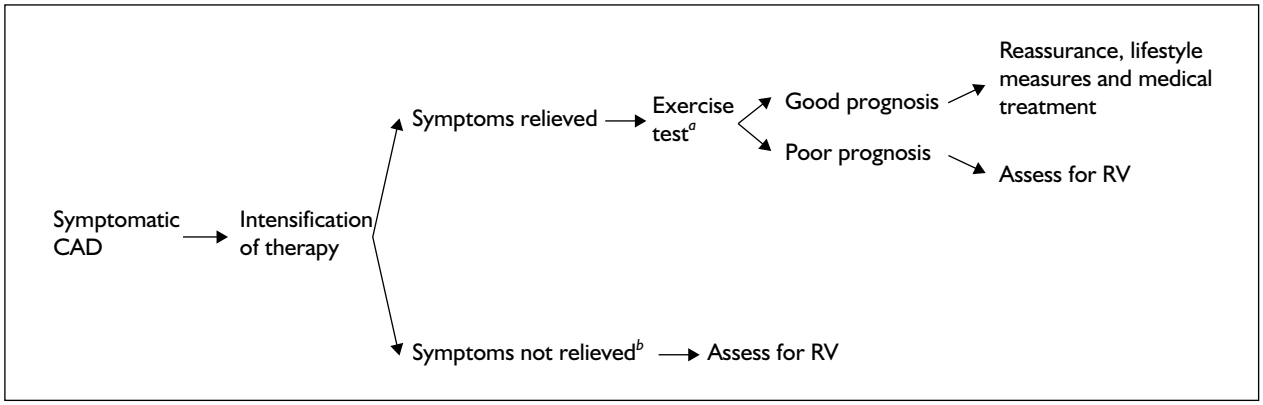


FIGURE 3 *Prognosis pathway.* [a] *Perfusion scanning would be another option; the aim is to assess for inducible ischaemia;* [b] *may include a few false positives who do not have CAD; RV, revascularisation.*

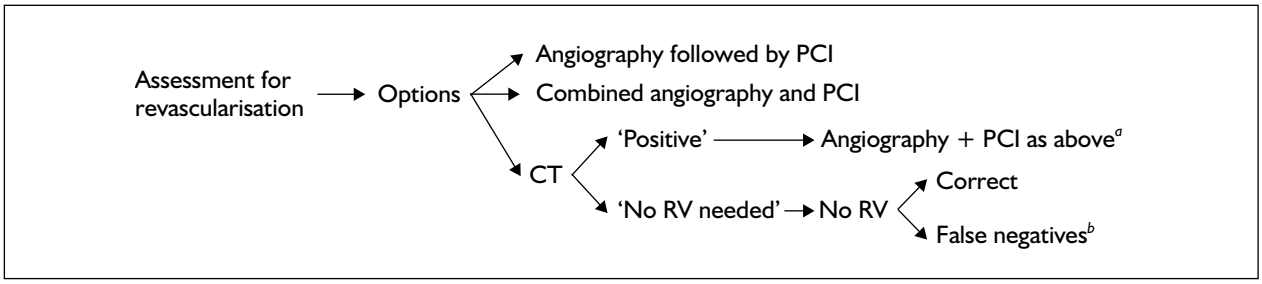


FIGURE 4 *Assessment for revascularisation.* [a] *In theory, there could be false positives if CT overestimated the degree of stenosis;* [b] *a false negative would be someone in whom CT underestimated stenosis sufficiently to rule out RV in a patient with over 50% stenosis.*

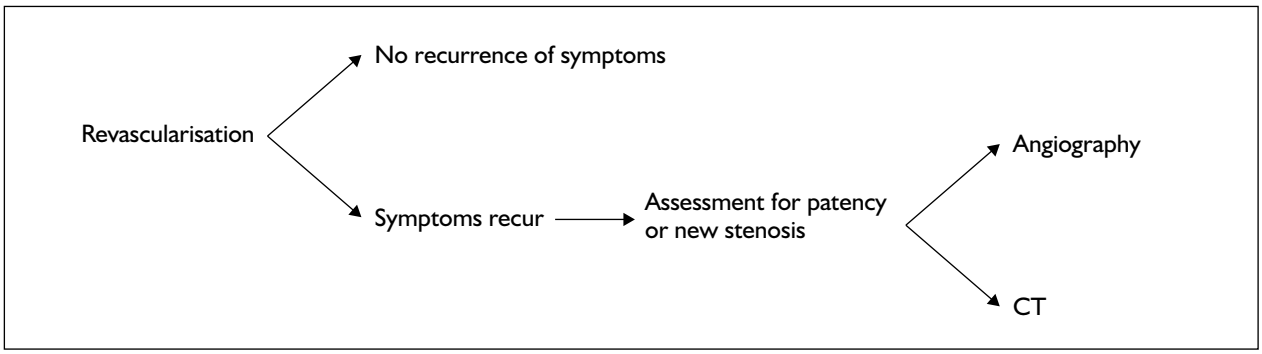


FIGURE 5 *Assessment following revascularisation*

Figure 4 concerns those patients in whom revascularisation is being considered, and the question here is whether CT could be used to rule out the need for CABG.

Figure 5 shows what happens after revascularisation. Symptoms may be permanently relieved, or may recur. If they recur, that could be due to a graft being narrowed or occluded, or a new lesion arising in another artery. CT may be an alternative to invasive angiography.

One aspect will be the degree of reassurance from negative results. Would negative CT provide the same level of reassurance as negative CA or perfusion studies? Answering that question would require data on (untreated) follow-up after each investigation.

A last question is whether CT could assist with the planning of angiography/PCI sessions by identifying which patients would need PCI as well as angiography. This may make planning of sessions easier and improve the efficiency of use of catheter laboratories.

Terminology

For the purposes of this review, confirming the diagnosis in people with symptoms that may be due to CAD means determining whether there is sufficient CAD to cause the symptoms. Most people of the age at which symptoms present may have some evidence of CAD, so 'sufficient CAD' means the presence of one or more stenoses that result in enough arterial narrowing to limit blood flow. The consensus among cardiologists is that stenosis has to be about 70% or more of the lumen to be flow limiting and cause symptoms. However, 50% is another accepted cut-off and errs on the side of not missing anything that may be flow limiting. CT angiography will often detect CAD with lesser degrees of narrowing, and while these patients will not be referred for revascularisation, they would be considered for lifestyle advice and statin therapy.

Screening for asymptomatic CAD

This review does not cover screening for asymptomatic disease. The patient groups included here are suspected of having coronary disease, or known to have it. Screening for asymptomatic disease by CT is usually done by looking for calcium deposits in the coronary arteries, and was the subject of a previous report by Waugh and colleagues.[3]

Chapter 2

Assessment of test performance for diagnosis and assessment of coronary artery disease

Methods for reviewing test performance

Search strategy

Electronic searches were undertaken to identify published and unpublished reports evaluating the performance of 64-slice or higher CT angiography for the diagnosis and assessment of CAD. Searches were restricted to the years 2002 onwards and to English-language reports. Abstracts from recent conference proceedings were also searched.

The main databases searched were: MEDLINE (2002 to November week 3 2006), EMBASE (2002 to week 49 2006), BIOSIS (2002 to December 2006), Science Citation Index (SCI, 2002 to December 2006), Medline In-Process (14 December 2005), Cochrane Controlled Trials Register (CCTR, The Cochrane Library, Issue 4, 2006), Cochrane Database of Systematic Reviews (CDSR, The Cochrane Library, Issue 4, 2006), Database of Abstracts of Reviews of Effects (DARE, December 2006), HTA Database (December 2006) and Health Management Information Consortium (HMIC, 2002 to May 2006). In addition, recent conference proceedings and reference lists of all included studies were scanned to identify additional potentially relevant studies. Full details of the search strategies used are documented in Appendix 1.

Inclusion and exclusion criteria

Types of studies

The types of studies considered were randomised controlled trials (RCTs) or prospective/retrospective non-randomised comparative studies or case series in which some or all patients received both MSCT angiography using 64-slice or higher machines and invasive CA.

Index and comparator tests

The index test was multislice CT angiography using 64-slice or higher machines. MPS was considered as a comparator test.

Reference standard

Two reference standards were considered, either invasive CA or long-term follow-up of participants. The latter was chosen because it would provide some indication of the numbers of patients with false-negative results on diagnostic 64-slice CT angiography who as a consequence were deemed not to require invasive CA but who then went on to suffer a cardiac event.

Participants

The participants were adults undergoing CT angiography using 64-slice or higher machines for the detection of CAD. Analysis was planned on the following patient subgroups, if evidence was available:

- patients in whom there was diagnostic uncertainty, or who were unable to perform exercise testing
- patients with definite heart disease being assessed with a view to revascularisation
- patients with suspected ACS
- patients with previous PCI including stenting
- patients with previous CABG
- patients with diabetes
- women, in case CT was less useful in smaller arteries.

Outcomes

Diagnostic accuracy studies had to report the absolute numbers of true positives, false positives, false negatives and true negatives, or sensitivity and specificity for CT angiography.

Prognostic studies had to provide information on the likelihood of future cardiac events. Assessment studies had to illustrate the pattern of CAD and suitability for revascularisation. Post-revascularisation studies were examined to assess the accuracy of 64-slice or higher CT angiography for detecting stenosis in stents or grafts.

Data extraction strategy

One reviewer screened the titles (and abstracts if available) of all reports identified by the search strategy. Full-text copies of all studies deemed to be potentially relevant were obtained and two reviewers independently assessed them for inclusion. Any disagreements were resolved by consensus or arbitration by a third party.

A data extraction form was developed and piloted. Two reviewers independently extracted details from full-text studies of study design, participants, index, comparator and reference standard tests, and outcome data. Any disagreements were resolved by consensus or arbitration by a third party. Abstracts were not data extracted.

Quality assessment strategy

Quality assessment was performed using QUADAS, a quality assessment tool developed for use in systematic reviews of diagnostic studies.[29] QUADAS was developed through a formal consensus method and was based on empirical evidence. The original QUADAS checklist contained 14 questions. The QUADAS tool was adapted to make it more applicable to evaluating the methodological quality of studies reporting tests for diagnosing and assessing CAD (see Appendix 2 for an example of the modified checklist).

Questions 1, 3, 4, 5, 6, 7, 10, 11, 12, 13 and 14 of the original QUADAS tool were retained (questions 1–11 in the modified version). Three questions in the original QUADAS tool that related to the quality of reporting rather than methodological quality were omitted from the modified version (questions 2, 8 and 9). These questions related to the description of the selection criteria, the execution of the index test and the execution of the reference standard test. Three questions were added to the modified checklist on whether an established cut-off point was used (question 12), whether data on observer variation were reported and within an acceptable range (question 13) and whether data were presented for appropriate subgroups of patients (question 14).

Two reviewers (GM, XJ) independently assessed the quality of all included studies using the modified version of QUADAS. Each of 14 questions was checked as 'Yes', 'No' or 'Unclear'. Each item was worded so that a rating of 'Yes' was always optimal in terms of methodological quality. Any disagreements were resolved by consensus or arbitration by a third party. Abstracts were not quality assessed.

Data analysis

Study level

The results of the individual studies were tabulated and sensitivity, specificity, positive and negative predictive values calculated. If reported in a given study, a separate 2×2 table was derived for patient level, all segments, individual arteries, stents and bypass grafts. The confidence intervals for the sensitivity and specificity of individual studies were calculated using the F distribution method[30] in MetaDiSc software.[31]

Data synthesis

Summary receiver operating characteristic (SROC) curves were produced for each test where three or more studies reported sufficient data. A separate SROC curve was derived for patient-level analysis, all segments, left main, LAD overall, LAD proximal, LCX overall, RCA overall, stents and bypass grafts where possible. The primary meta-analysis method was the hierarchical summary receiver operating characteristic (HSROC) model,[32] which was fitted using WinBUGS 1.4 using non-informative priors.[33] Fitting the full (asymmetric) HSROC model was initially attempted, but owing to numerical non-convergence a symmetric SROC model was used. This model takes proper account of the diseased and non-diseased sample sizes in each study, and allows estimation of random effects for the threshold and accuracy effects. The SROC curves from the HSROC models were produced on the corresponding SROC plots. For each model, summary sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios (DORs) were reported as a median and 95% credible interval (CrI). Credible intervals are the Bayesian equivalent of confidence intervals.

If numerical difficulties were encountered with the HSROC symmetric model and there was no evidence of heterogeneity, sensitivity and specificity were pooled using the weighted average method.[34] Similarly, pooled likelihood ratios and DORs were calculated using the DerSimonian and Laird random-effects method.[35] Where a study had an empty cell, a correction of 0.5 was added to all four cells. These analyses were carried out using MetaDiSc software;[31] corresponding 95% confidence intervals (CIs) (rather than CrIs) were reported. Heterogeneity of sensitivity and specificity was assessed separately using the I^2 statistic in MetaDiSc software.[31] This measure describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered to represent substantial heterogeneity.[36] Results reported were for the HSROC model unless otherwise stated.

Results

Number of studies identified

The results of the searches are summarised in *Table 1*. The numbers retrieved from the searches

TABLE 1 *Search results*

Database	No. retrieved
MEDLINE/EMBASE/MEDLINE In-Process multifile search (after deduplication in Ovid)	580
SCI	257
BIOSIS	197
CENTRAL	0
HMIC	23
CDSR	0
DARE	3
HTA Database	13
NRR	7
CCTR	1
Clinical Trials	1
ISI Proceedings	59
Conference Papers Index	24
Selected from screening conference abstracts	46
Total retrieved	**1211**

NRR, National Research Register.

in SCI, BIOSIS and CENTRAL include only the additional reports found after excluding those identified from the MEDLINE/EMBASE multifile search.

A total of 1211 reports was identified from the various searches, of which 275 reports (135 full-text papers; 140 abstracts) were selected for full assessment. *Table 2* details the numbers of these that were included and excluded. *Figure 6* shows a flow diagram outlining the screening process, with reasons for exclusion of full-text papers.

Number and type of included studies

Appendix 3 lists the 45 studies, published in 74 reports, that were included in the review of effectiveness. Forty-one studies, published in 68 reports,[37–104] met the inclusion criteria for studies of diagnostic accuracy. The primary reports were published in full-text papers for 21 and only as abstracts for 20. All used 64-slice CT angiography apart from the study by Motoyama and colleagues,[68] reported as an abstract, in which a prototype 256-slice CT machine was used. Five studies, published in seven reports,[55,105–110] provided information on the prognostic usefulness of 64-slice CT. The study by Hoffmann and colleagues[55] provided information on both diagnostic accuracy and prognostic usefulness of 64-slice CT. Of the five studies reporting prognostic usefulness, the primary reference was a full-text report for one and abstracts for the remaining four.

Number and type of excluded studies

A list of potentially relevant studies identified by the search strategy, for which full-text papers were obtained, but which subsequently failed to meet the inclusion criteria, is given in Appendix 4. These studies were excluded because they failed to meet one or more of the inclusion criteria in terms of types of studies, participants, test, reference standard or outcomes (see also *Figure 6*).

Characteristics of the included studies

Appendix 5 shows the characteristics of the included studies. Only full-text studies were formally data extracted. *Table 3* shows summary information for the full-text diagnostic accuracy studies.

TABLE 2 *Papers selected for full assessment*

	Full-text papers	Abstracts
Included in the report	22	52
Retained for background information	13	0
Excluded – did not meet inclusion criteria	96	88
Unobtainable papers	4	
Total	**135**	**140**

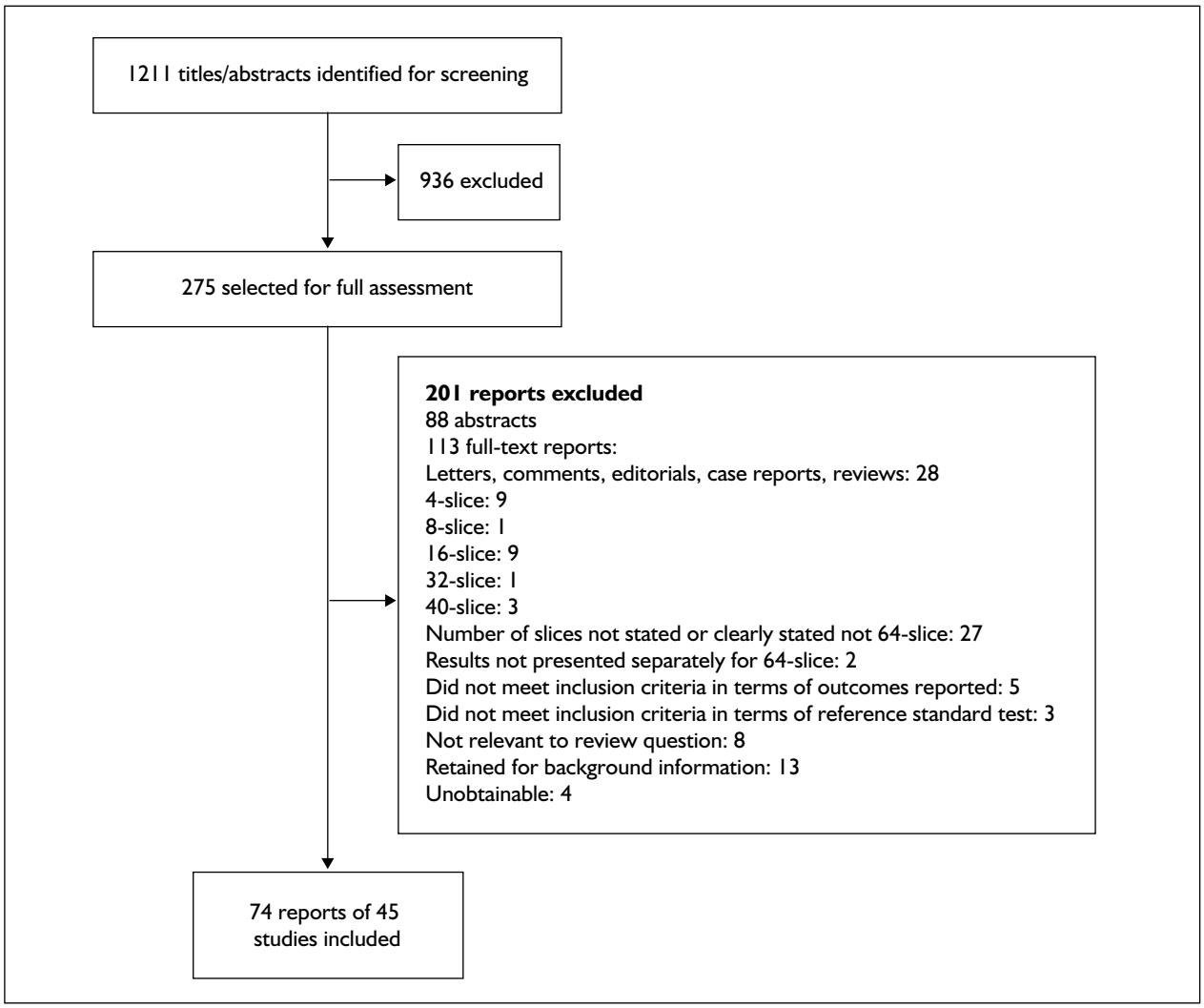


FIGURE 6 *Flow diagram outlining the screening process*

The 21 full-text studies reporting diagnostic accuracy enrolled 1333 participants, with 1176 included in the analysis. Fourteen studies gave no details of when they took place. The remaining eight studies[46,52,55,56,58,59,85,101] took place during the period from July 2004[56,58] to February 2006.[85] Eight studies took place in Germany,[56,58,71,77,86,89,93,94] four in the USA,[49,55,85,101] three in The Netherlands,[65,66,100] two in Switzerland,[59,79] and one each in France,[52] Japan[46] and Malaysia,[75] while one study involved centres in Italy and The Netherlands.[83] All but one of the full-text studies used Siemens Sensation 64 CT equipment. Schuijf and colleagues,[100] in a study set in The Netherlands, used a Toshiba Multi-Slice Aquilion 64 system.

Two studies gave no details of participant gender.[58,93] In the remaining 19 studies, of 1168 people included in the analysis, 822 (70%) were men and 346 (30%) were women. Across studies the median age of the participants was 61 years (range of means 54 to 69 years).

The 20 diagnostic accuracy studies reported as abstracts enrolled and analysed at least 1158 participants. In three studies reporting when they took place this was during the period from November 2004 to July 2005.[60,61,76] Five studies took place in Germany,[37,39,53,99,102] four in the USA,[48,60,61,97] three each in Japan[45,68,76] and The Netherlands,[62,82,84] two in Israel,[95,96] and one each in Brazil,[78] China[103] and Turkey.[72] Eight studies,[37,39,45,48,62,72,76,103] set in Germany (two), Japan (two), the USA, The Netherlands, Turkey and China (one each), used Siemens Sensation 64 machines. Two studies,[60,61] set in the USA, used GE Healthcare Light-Speed VCT machines,

TABLE 3 *Patient details, indication for CT and technique used (full-text diagnostic accuracy studies, n = 21)*

Patients	
Enrolled	1333
Analysed	1176
Gender	
Male	822 (70%)
Female	346 (30%)
NR	146
Age	
Median (range of means) across 21 studies	61 (54 to 69) years
Indication for CT angiography	
Suspected CAD	499 (49%)
Known history of CAD	219 (21%)
Preoperative scanning prior to valve surgery or CABG	120 (12%)
To assess implanted stents	89 (9%)
Other	95 (9%)
NR	292
Use of β-blocker to reduce heart rate	
Already on β-blocker treatment	140 (32%)
β-Blocker treatment given	184 (42%)
β-Blocker treatment not given	113 (26%)
NR	877
64-Slice CT angiography	
Heart rate during scan: mean of means (range of means) across 16 studies	63 (58–72) beats per minute
Total 64-slice CT scan time: range of mean scan times (seconds)	11.2–21.4 seconds
Radiation dose: range of means across 12 studies	Men and women: 6–14 mSv Men: 7.45–15.2 mSv Women: 10.2–21.4 mSv

Information was reported by some studies for those enrolled and by others for those analysed.
NR, not reported.

two,[95,96] set in Israel, used Philips Brilliance 64 machines and the study by Motoyama and colleagues,[68] set in Japan, used a Toshiba prototype 256-slice machine. Seven studies[53,78,82,84,97,99,102] gave no details of the CT equipment manufacturer.

In six studies giving details of gender,[37,39,45,95,96,102] of 592 people included in the analysis, 362 (61%) were men and 230 (39%) were women. The median age of the participants across six studies giving details of age was 60 years (range of means 58 to 68 years).[37,39,45,95,96,102]

The five studies reporting the prognostic usefulness of 64-slice CT enrolled at least 1785 participants, with 1778 included in the analysis. In two studies reporting when they took place, this was during the calendar year 2005[105] and from May to July 2005.[55] Four studies took place in the USA[55,105–107] and one in Israel.[110] In three studies giving details of gender,[55,106,110] of 629 people included in the analysis, 370 (59%) were men and 259 (41%) were women. The median age of the participants across three studies giving details of age was 56 years (range 54 to 62 years).[55,106,110]

Fryback and Thornbury[111] suggested a useful hierarchy for describing studies of diagnostic technologies (*Table 4*). All of the studies reporting diagnostic accuracy, including those reported as abstracts, were classed as level 2 (diagnostic accuracy) on the Fryback and Thornbury scale.[111] The study by Hoffmann and colleagues[55] reported both diagnostic accuracy and prognostic usefulness, and was classed as level 2 for the former and level 3 (diagnostic thinking) for the latter. The remaining four studies[105–107,110] reporting prognostic usefulness were classed as level 4 (therapeutic).

The Australian Medical Services Advisory Committee[112] provides a useful diagram that

TABLE 4 *Hierarchy of diagnostic efficacy*

	Level	Data products
1	Technical	Technical imaging quality
2	Diagnostic accuracy	Sensitivity, specificity, PPV, NPV
3	Diagnostic thinking	Likelihood ratio
4	Therapeutic	Changes in treatment of patients
5	Patient outcome	Improvement in morbidity and/or mortality
6	Societal	Cost–benefit analysis

illustrates the pathway linking the use of a diagnostic test to health outcomes (*Figure 7*), with the effectiveness of a test depending on whether the overall accuracy of testing is improved by including the index test (as a replacement or additional test), its impact on therapeutic decisions and the effectiveness of the therapies selected.[112] Four[55,106,107,110] of the five studies reporting prognostic usefulness provided information on patient outcomes.

Quality of the included studies

Figure 8 summarises the quality assessment for the full-text diagnostic studies, while the quality assessment results for each individual study are shown in Appendix 6.

The overall quality of the included full-text studies was reasonably good. In all studies the reference standard (either invasive CA or long-term follow-up) was considered likely to classify CAD correctly, partial verification bias was avoided in that all patients who received 64-slice CT angiography also received a reference standard test, differential verification bias was avoided in that patients received the same reference standard regardless of the index test result, incorporation bias was avoided in that the index test did not form part of the reference standard, and an explanation of study withdrawals was provided. The question on partial verification bias was checked 'Yes' for two studies,[55,56] in which only some patients received both index and reference standard tests, as it was only the results for the patients who received both tests that were included in the review.

In 95% of studies an established cut-off point was used to define a positive test result (e.g. stenosis > 50%). In 86% of studies uninterpretable test results were reported. In 85% of studies the period between 64-slice CT and the reference standard test was less than 6 months, a period considered short enough to be reasonably sure that the target condition had not changed between the two tests. In 85% of studies test review bias was avoided in that those interpreting 64-slice CT data were blinded to the results of the reference standard test. In 71% of studies diagnostic review bias was avoided in that those interpreting the reference standard test were blinded to the results of 64-slice CT.

In 48% of studies the participants belonged to specific groups (e.g. studies in which all patients had LBBB,[52] were being referred for cardiac valve surgery,[65] or had previously undergone PCI[86,89] or CABG.[77,94]

In 67% of studies participant subgroup analysis was reported or the whole participant group was

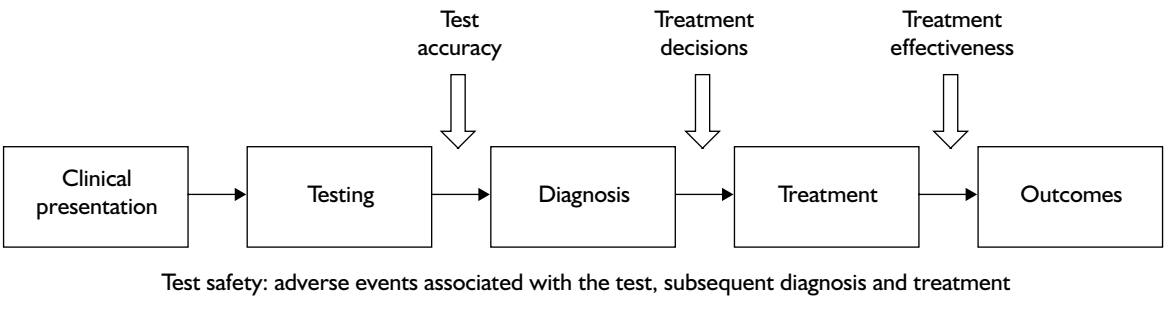


FIGURE 7 *Causal pathway and determinants of the clinical effectiveness of a diagnostic test. From* Guidelines for the assessment of diagnostic technologies.[112] *Copyright Commonwealth of Australia reproduced by permission.*

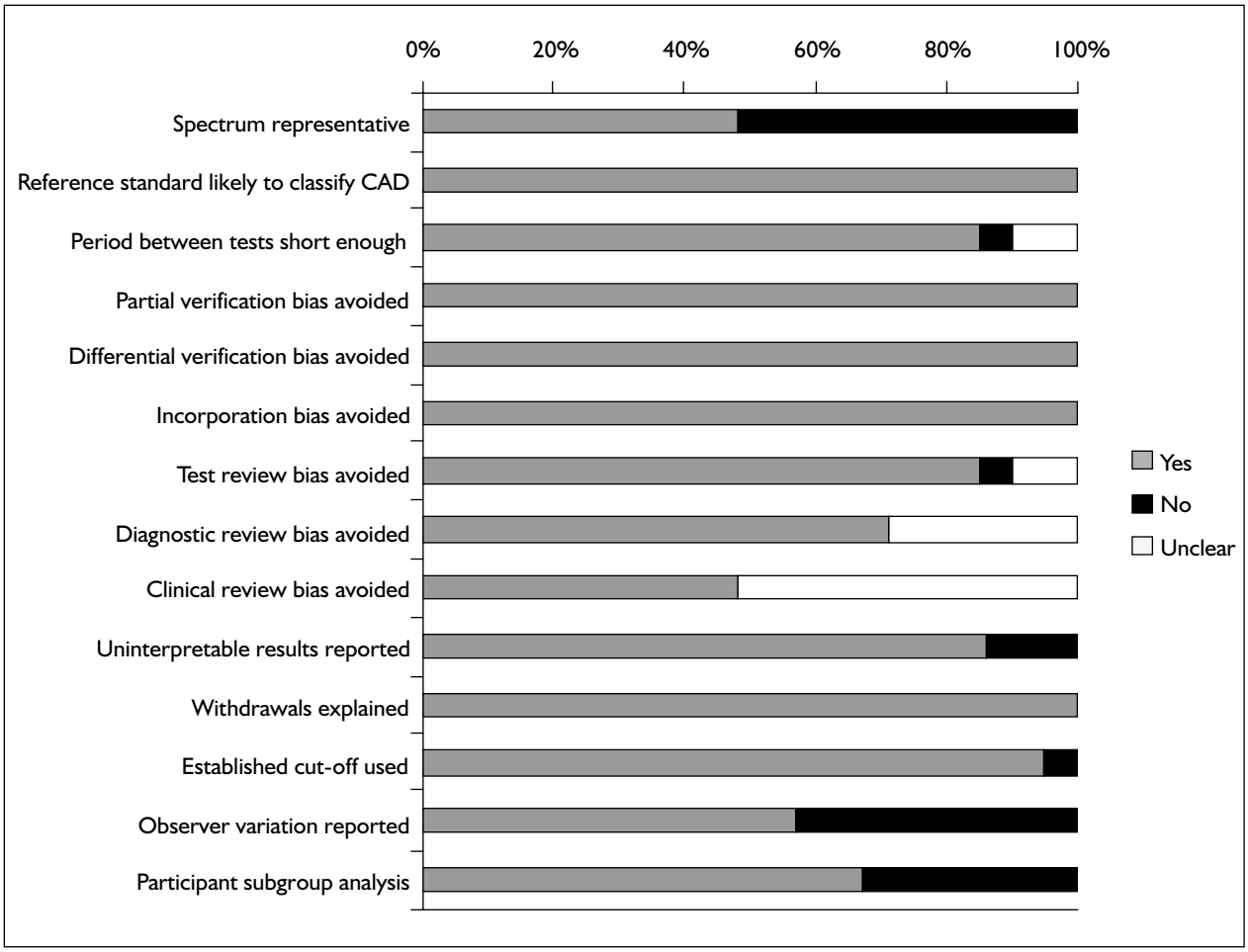


FIGURE 8 *Summary of quality assessment of diagnostic accuracy studies*

in effect considered to be a subgroup (e.g. the study by Ghostine and colleagues[52] in which all participants had LBBB), while 57% gave details of observer variation in interpreting study results, and in 48% of studies clinical review bias was avoided in that those interpreting 64-slice CT data were blinded to the patients' clinical history.

Studies reporting the diagnostic accuracy of 64-slice CT angiography

Overview

This section reports the diagnostic accuracy of 64-slice CT angiography on the following levels of analysis: patient, segment, left main artery, LAD artery, proximal LAD artery, LCX artery, RCA, stents/stented segments and CABG. For each of these levels of analysis figures are included showing, for 64-slice CT angiography compared with invasive CA as the reference standard, sensitivity and specificity of the individual studies, SROC curves and pooled estimates for sensitivity, specificity, positive and negative likelihood ratios and DOR. In all of the studies included in the pooled estimates the cut-off for a positive result was greater than 50% or at least 50% stenosis. Only full-text studies reported diagnostic accuracy at artery level. Appendix 7 shows the studies that reported data that allowed their inclusion in the pooled estimates for different levels of analysis. Individual study results are given in Appendix 8.

Patient-level analysis for the detection of CAD

Although segmental analysis is useful to validate the accuracy of the test, patient-level data are more useful in determining management. Eighteen studies (13 full text[46,52,55,65,66,71,77,79,83,85,93,94,100] and five studies reported as abstracts[39,62,95–97]) enrolling at least 1313 people, with 1286 included in the analysis, provided sufficient information to allow their inclusion in the pooled estimates for patient-level analysis. Across studies, the median prevalence of CAD at this cut-off was 58% (range 23 to 96%).

Figure 9 shows the sensitivity and specificity, with 95% CIs, for the 18 studies. Sensitivity ranged

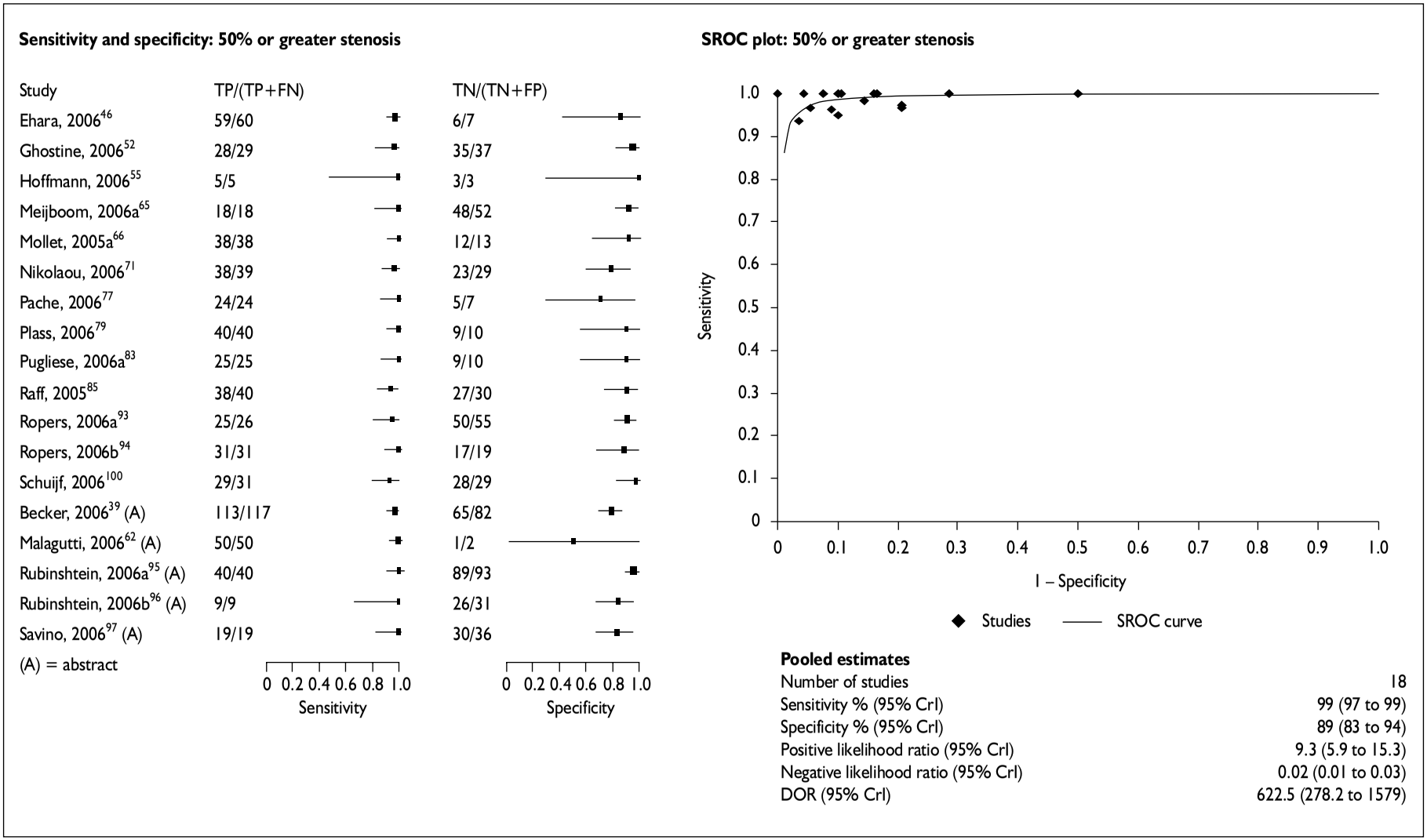


FIGURE 9 *Patient-level analysis: sensitivity, specificity, SROC curve and pooled estimates. FN, false negative; FP, false positive; TN, true negative; TP, true positive.*

from 94%[100] to 100%,[55,62,65,66,77,79,83,94–97] with a pooled sensitivity of 99% (95% CrI 97 to 99%). Specificity ranged from 50%[62] to 100%,[55] with a pooled specificity of 89% (95% CrI 83 to 94%). Across studies the median PPV was 93% (range 64 to 100%), while the median NPV was 100% (range 86 to 100%).

The study reported as an abstract by Malagutti and colleagues[62] demonstrated noticeable heterogeneity in terms of specificity. In this study all patients (n = 52) had previously undergone CABG surgery. The low specificity was due to the fact that, of two patients classed as having no significant (>50% luminal narrowing) CAD on invasive CA, one received a positive test result on 64-slice CT (false positive). The false-positive result may be due to the fact that, as reported by the study authors, overestimation of stenosis severity occurred more often in calcified segments. However, overall there was no evidence of substantial statistical heterogeneity in terms of sensitivity (I^2 = 0.1%) or specificity (I^2 = 31.7%).

In the 13 full-text studies included in the pooled estimates,[46,52,55,65,66,71,77,79,83,85,93,94,100] 11 (2%) of 718 patients could not be assessed because of unevaluable CT scans (median across studies 0%, range 0 to 6%).

Patient subgroups

Suspected and known CAD

Most studies contained a mixture of patients with suspected and known CAD and did not report the results of 64-slice CT angiography for these groups separately. However, four studies (three full text[71,85,93] and one abstract[97]) reported patient-level analysis (n = 245) and six studies (two full text[85,93] and four abstracts[37,82,97,99]) reported segment-level analysis (n > 5085) for those with suspected CAD (*Table 5*). Two full-text studies[71,83] reported patient-level analysis (n = 64) and three full-text studies[58,75,83] reported segment-level analysis (n = 2623) for those with known CAD (*Table 5*).

In terms of patient-level analysis, better sensitivity, PPV and NPV, but worse specificity, were reported for those with known CAD. The lowest NPV (93%) was reported by Nikolaou and colleagues[71] in a subgroup analysis of 39 patients with suspected CAD, but no explanation of the reasons for the false-negative results in this group was provided. For segment-level analysis, better sensitivity was reported for those with suspected CAD and better PPV for those with known CAD, while specificity and NPV were similar for both groups.

The study by Nikolaou and colleagues[71] reported patients with suspected and known CAD in subgroup analysis but only provided information on unevaluable scans for the whole patient population, while the studies by Beck and colleagues,[37] Pugliese and colleagues[82] and Savino and colleagues[97] did not report whether any of the scans were unevaluable. In the remaining studies, 64-slice CT scans for three (1%) of 209 patients and 240 (9%) of 2779 segments were unevaluable for those with suspected CAD, compared with four (4%) of 94 patients and 217 (8%) of 2853 segments for those with known CAD.

In conclusion, 64-slice CT is highly sensitive for detecting significant CAD in cases of diagnostic uncertainty, and the high NPV suggests that if 64-slice CT is negative, then patients may not need to be referred for further investigation by invasive CA.

Acute chest pain

Three studies (one full text[55] and two abstracts[39,84]) reported patient-level analysis

TABLE 5 *Studies reporting data separately for those with suspected and known CAD*

	No. of studies	Median % (range) sensitivity	Median % (range) specificity	Median % (range) PPV	Median % (range) NPV
Suspected CAD					
Patients (n = 245)	4	96 (95–100)	87 (82–91)	86 (76–93)	96 (93–100)
Segments (n > 5085)	6	92 (82–100)	97 (95–99)	68 (55–95)	99 (98–100)
Known CAD					
Patients (n = 64)	2	100 (both)	83 (75–90)	91 (85–96)	100 (both)
Segments (n = 2623)	3	85 (79–99)	96 (96–97)	78 (72–80)	98 (97–100)

The study by Pugliese and colleagues[82] reported sensitivity, specificity, PPV and NPV values for segment-level analysis for people with suspected CAD, but did not report the number of segments analysed.

(n = 232) for 64-slice CT angiography for patients admitted to hospital with acute chest pain. 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 for detecting 50% or greater stenosis. In the studies by Hoffmann and colleagues[55] and Pugliese and colleagues[84] the values for sensitivity, specificity, PPV and NPV were all 100%. None of the studies gave information on whether any of the scans were unevaluable.

Details of three prognostic studies,[55,95,107] including that by Hoffmann and colleagues, that went beyond the Fryback stage 2 classification (diagnostic accuracy, sensitivity and specificity of the images) are given in the section on prognostic usefulness of 64-slice CT angiography later in this chapter.

In conclusion, 64-slice CT angiography, if it were available 24 hours per day, might have a role to play in the assessment of acute chest pain and might allow some patients to be reassured and discharged, leading to a reduction in hospital admissions with associated cost savings.

PCI and CABGs
Details of studies reporting patient-level analysis on patients who have previously undergone PCI or CABG are included in the sections on stents and CABGs later in this chapter.

Diabetes
One study, reported as an abstract,[48] provided information on the accuracy of 64-slice CT angiography for detecting greater than 70% stenosis in three groups of high-risk patients, one of which was patients with diabetes (number not stated), reporting 87% sensitivity, 94% specificity, 87% PPV and 94% NPV.

Women
No study reported the diagnostic accuracy of 64-slice CT angiography separately for women.

Other
In the study by Ghostine and colleagues[52] all of the study participants (n = 66) had LBBB (limiting the diagnostic yield from an exercise ECG). In patient-level (n = 66) and segment-level (n = 990) analysis, respectively, Ghostine and colleagues[52] reported 97 and 72% sensitivity, 95 and 99% specificity, 93 and 91% PPV, and 97% NPV (both) for 64-slice CT angiography for detecting greater than 50% stenosis. In this study all scans at both patient and segment level were evaluated.

In the study by Meijboom and colleagues[65] all of the study participants had been referred for cardiac valve surgery. In this setting, exclusion of significant CAD may obviate the need for invasive investigation. Likewise, in some cases, knowledge of the severity of CAD may influence the decision on whether or not to operate. In patient-level (n = 70) and segment-level (n = 1003) analysis, respectively, Meijboom and colleagues[65] reported 100 and 94% sensitivity, 92 and 98% specificity, 82 and 65% PPV, and 100% NPV, (both) for 64-slice CT angiography for detecting 50% or greater stenosis. In this study all scans at both patient and segment level were evaluated.

Segment-level analysis
Seventeen studies (14 full text[46,52,58,59,65,66,71,75,79,83,85,93,94,100] and three abstracts[76,97,99]) enrolling at least 1102 people, with 1078 included in the analysis, provided sufficient information to allow their inclusion in the pooled estimates for segment-level analysis (n = 14,199). *Figure 10* shows the sensitivity and specificity, with 95% CIs, for the 17 studies. Sensitivity ranged from 72%[52] to 100%,[99] with a pooled sensitivity of 90% (95% CrI 85 to 94%). Specificity ranged from 76%[94] to 99%,[52,76] with a pooled specificity of 97% (95% CrI 95 to 98%). Across studies the median PPV was 76% (range 44 to 93%), while the median NPV was 99% (range 95 to 100%).

There was evidence of substantial statistical heterogeneity across the studies in terms of both sensitivity (I^2 = 80.1%) and specificity (I^2 = 95.1%). The study by Ropers and colleagues[94] was most noticeable in contributing to the heterogeneity in terms of specificity. In this study all of the participants (n = 50) had previously undergone CABG surgery. One reason suggested by the authors for the low specificity was that the prevalence of severe calcifications led to an overestimation of stenosis severity and consequently a high level of false-positive results.[94]

Thirteen full-text studies[46,52,58,59,65,66,71,75,83,85,93,94,100] reported that 997 (8%) of 12,476 segment scans could not be evaluated (median across studies 9%, range 0 to 18%). In the study by Ehara and colleagues[46] 82 (8%) of 966 segments were not evaluated owing to poor image quality, caused by irregular heart rhythm (29), sinus tachycardia above 90 beats per minute (bpm) (15), calcification (24), vessel motion

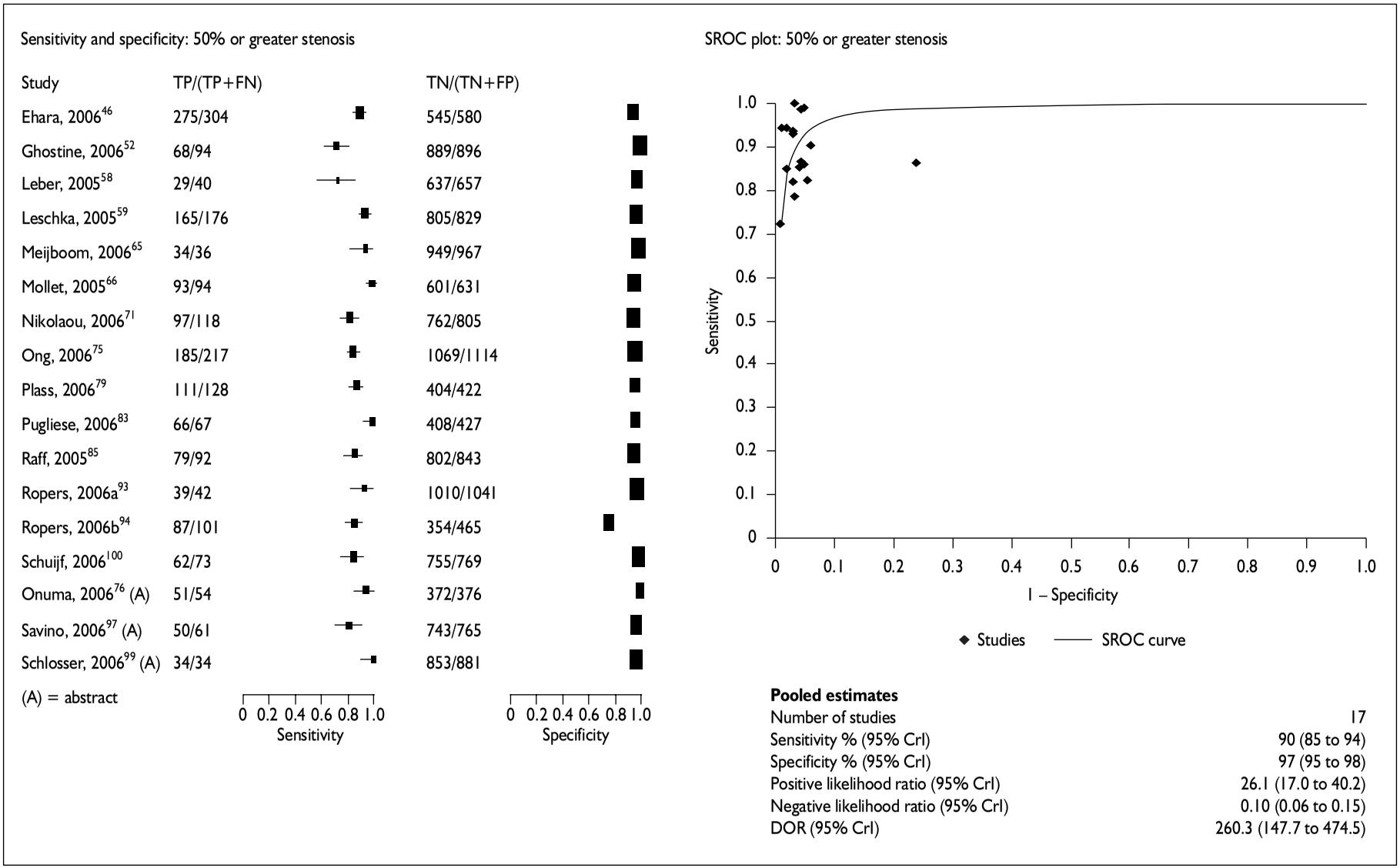


FIGURE 10 *Segment-level analysis: sensitivity, specificity, SROC curve and pooled estimates*

(five), inadequate breath-hold (three), low contrast opacification (five) and anomaly (one).

Proximal, mid and distal segments

Five studies[46,52,59,75,83] reported the sensitivity and specificity of 64-slice CT angiography for detecting 50% or greater stenosis in proximal, mid and distal segments of the RCA and LAD, and proximal and distal segments of the LCX (*Table 6*; see also Appendix 8). Sensitivity tended to be higher for proximal segments compared with distal segments, while in terms of specificity the results were more variable.

Coronary artery calcification

Three full-text studies[65,75,85] reported the accuracy of 64-slice CT angiography for detecting 50% or greater stenosis in segments affected by different degrees of calcification (n = 3269 segments). The results of these studies are summarised in *Table 7* (see also Appendix 8 for individual study results).

In the study by Meijboom and colleagues[65] all of the study participants (n = 70) had been referred for cardiac valve surgery. The presence of coronary calcium appeared to be associated with overestimation of the severity of stenoses, with no false positives in the 338 segments with an Agatston score (AS) 0–10, but seven (2%) false positives in the 465 segments with an AS 11–400, five (3%) false positives in the 146 segments with an AS 401–1000 and six (11%) false positives in the 54 segments with an AS above 1000 (see Appendix 8 for details of true and false positives and negatives).

All participants (n = 134) in the study by Ong and colleagues[75] had ischaemic heart disease and were classed as having either minimal to mild calcification (AS < 142) or moderate to heavy calcification (AS ⩾ 142). Again the presence of coronary calcium appeared to be associated with overestimation of stenosis severity, with 12 (2%) false positives in the 700 segments with an AS below 142 and 33 (5%) false positives in the 631 segments with an AS of 142 or above (see Appendix 8 for details of true and false positives and negatives).

In the study by Raff and colleagues[85] all of the study participants (n = 70) had suspected CAD. Patients were ranked by total AS, with segment calcium rated as: 0 = not calcified (none); 1 = calcium present, no image impairment (mild); 2 = calcium covering less than 50% of lumen (moderate); and 3 = calcium covering more than 50% of lumen in all planes including in cross-section (severe). There were 14 (2%) false positives in 709 segments with a calcium rating of none, five (6%) false positives in 89 segments rated as mild, six (13%) false positives in 48 segments rated as moderate and 16 (18%) false positives in 88 segments rated as severe (see Appendix 8), with the presence of severe coronary calcium associated with overestimation of stenosis severity. Raff and colleagues[85] reported that 64-slice CT angiography was highly accurate in the presence

TABLE 6 *Sensitivity and specificity for proximal, mid and distal segments*

Study	RCA artery			LAD artery			LCX artery	
	Proximal	Mid	Distal	Proximal	Mid	Distal	Proximal	Distal
Sensitivity (%)								
Ehara, 2006[46]	96	93	82	95	100	67	95	84
Ghostine, 2006[52]	50	70	67	94	84	–[a]	100	60
Leschka, 2005[59]	100	95	67	100	93	50	100	88
Ong, 2006[75]	97	60	83	91	97	100	80	60
Pugliese, 2006[83]	100	100	100	100	90	100	100	100
Specificity (%)								
Ehara, 2006[46]	92	92	95	90	93	100	90	75
Ghostine, 2006[52]	98	95	100	100	100	100	95	100
Leschka, 2005[59]	100	91	97	100	88	97	90	94
Ong, 2006[75]	97	93	98	91	92	99	93	95
Pugliese, 2006[83]	96	96	92	96	91	100	100	100

[a] In the study by Ghostine and colleagues,[52] for the analysis of the distal segment of the LAD artery, sensitivity [True positive/(True positive + False negative)] could not be calculated as there were no true positives and no false negatives.

TABLE 7 *64-Slice CT stenosis detection in segments affected by calcification*

Study and type of classification	Score	No.	Sens. %	Spec. %	PPV %	NPV %
Segments						
Meijboom, 2006[65]	0–10	338		100		100
AS	11–400	465	100	98	68	100
	401–1000	146	94	96	76	99
	>1000	54	75	88	33	98
Ong, 2006[75]						
AS	<142 AS	700	93	98	84	99
	⩾142 AS	631	82	93	79	94
Raff, 2005[85]						
Calcium rating						
	None	709	77	98	66	99
	Mild	89	87	93	72	97
	Moderate	48	92	83	65	97
	Severe	88	93	72	64	95
Patients						
Raff, 2005[85]						
AS	0–100	35	94	95	94	95
	101–400	17	100	88	90	100
	401–1804	18	93	67	93	67

AS, Agatston score; Sens., sensitivity; Spec., specificity.

of moderate calcification, but that extreme calcification reduced specificity and NPV.

In these studies in terms of segment-level analysis, sensitivity, specificity and PPV varied according to the degree of calcification, with lower values associated with increased coronary calcification, while the NPV values all remained high (range 94 to 100%).

Raff and colleagues[85] also reported patient-level analysis (n = 70). Study participants were classed as those having AS 0–100 (n = 35), AS 101–400 (n = 17) and AS 401–1804 (n = 18). There was one false positive in each of the three groups (see Appendix 8). Sensitivity and PPV values remained high at over 90% for all three categories, while specificity declined as the severity of calcification increased and NPV markedly declined in the group with the most severe coronary calcification.

In the study by Meijboom and colleagues[65] all 1003 segments were evaluated. Ong and colleagues[75] reported that 48 (6%) of 748 segments with AS below 142 were not evaluable, compared with 95 (13%) of 726 segments with AS of 142 or above. In the study by Raff and colleagues[85] 130 (12%) of 965 segments were not evaluated, but a breakdown was not provided by calcium rating, and none of the 70 participants was excluded from patient-level analysis owing to unevaluable CT scans.

Other studies reporting segment-level analysis cited coronary calcification as a cause of unevaluable CT scans.[45,46,93,94,99,100,102] Although in the study by Ghostine and colleagues[52] no segment was excluded from analysis owing to calcification, the authors stated that heavily calcified segments accounted for nine missed lesions and 12 underestimated lesions (35% and 46%, respectively, of 26 false negatives), as well as four overestimated lesions (57% of seven false positives).

The only study included in the review not to use 64-slice CT technology was that of Motoyama and colleagues.[68] In this study ten patients underwent CT angiography using a Toshiba prototype 256-slice machine, with segments of 2 mm or less in diameter excluded from analysis. Of the 101 segments greater than 2 mm in diameter remaining, none was subsequently excluded owing to motion artefact. In segment-based detection of significant (> 50% stenosis) CAD, when segments with severe calcification (number not stated) were excluded from analysis, sensitivity, specificity, PPV and NPV were 100%, 96%, 73% and 100%, respectively, compared with 100%, 90%, 61% and 100% when segments with severe calcification were assumed as having significant stenosis.[68]

Hence, the presence of coronary artery calcification reduces the accuracy of CT

angiography. This limitation is of most relevance for those with advanced CAD and so least relevant at the diagnostic end of the pathway.

Left main artery analysis

Five full-text studies[46,52,59,71,75] enrolling 408 people, with 406 included in the analysis, reported analysis of the left main coronary artery (n = 393). *Figure 11* shows the sensitivity and specificity, with 95% CIs, for the five studies. Sensitivity ranged from 90%[46] to 100%,[52,59,71,75] with a pooled sensitivity of 95% (95% CI 84 to 99%). All five studies reported a specificity of 100%, with a pooled specificity of 100% (95% CI 99 to 100%). Across studies the median PPV was 100% (range 90 to 100%), while all five studies reported a NPV of 100%.

There was no evidence of statistical heterogeneity for either sensitivity (I^2 = 0.0%) or specificity (I^2 = 0.0%).

In the studies by Ghostine and colleagues,[52] Leschka and colleagues[59] and Nikolaou and colleagues[71] all left main artery scans were evaluated (n = 201). Ehara and colleagues[46] reported that five (7%) of 69 left main artery CT scans were not evaluated owing to poor image quality, caused by irregular heart rhythm (two), calcification (two) and vessel motion (one). Ong and colleagues[75] reported that six (4%) of 134 left main scans were not evaluated, without providing further details.

LAD artery analysis

Seven full-text studies[46,52,59,65,71,75,83] enrolling 513 people, with 511 included in the analysis, reported analysis of the LAD artery (n = 1685). *Figure 12* shows the sensitivity and specificity, with 95% CIs, for the seven studies. Sensitivity ranged from 78%[71] to 100%.[65] The pooled sensitivity was 92% (95% CrI 83 to 97%). Specificity ranged from 90%[65] to 100%.[52] The pooled specificity was 96% (95% CrI 91 to 98%). Across studies the median PPV was 86% (range 63 to 100%), while the median NPV was 98% (range 95 to 100%).

There was evidence of substantial statistical heterogeneity for both sensitivity (I^2 = 55.8%), most obviously due to the relatively low sensitivity (78%) reported by Nikolaou and colleagues,[71] and specificity (I^2 = 83.0%), due to the very high specificity (100%) and extremely narrow confidence intervals (95% CI 99 to 100%) reported by Ghostine and colleagues.[52] The reason for the relatively low sensitivity reported by Nikolaou and colleagues[71] compared with other studies was unclear. In the study by Ghostine and colleagues[52] all 288 arteries classified as not having a stenosis greater than 50% on invasive CA were likewise classified by 64-slice CT (no false positives).

In the studies by Ghostine and colleagues,[52] Leschka and colleagues,[59] Meijboom and colleagues[65] and Pugliese and colleagues[83] all scans were evaluated (n = 702). Ehara and colleagues[46] reported that 32 (9%) of 345 CT LAD scans were not evaluated owing to poor image quality, caused by irregular heart rhythm (13), sinus tachycardia above 90 bpm (five), calcification (12) and vessel motion (two). Nikolaou and colleagues[71] reported that 29 (9%) of 340 CT LAD scans were unevaluable, with reasons mostly cardiac motion artefacts or small vessel calibre in distal segments. Ong and colleagues[75] reported that 43 (11%) of 402 LAD scans were not evaluated, without providing further details.

Proximal LAD artery analysis

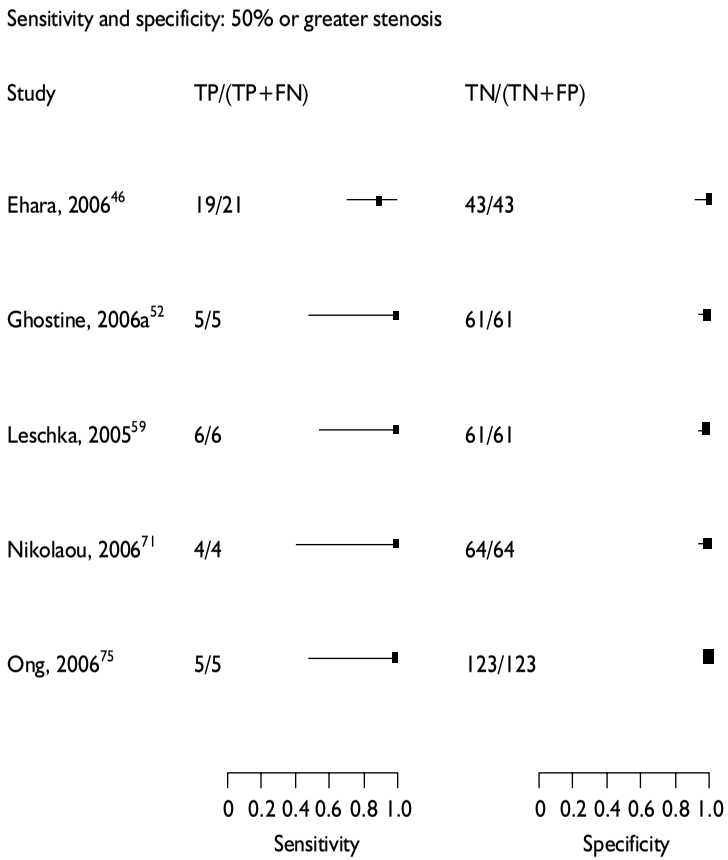
Five full-text studies[46,52,59,75,83] enrolling 371 people, with 369 included in the analysis, reported analysis of the proximal segment of the LAD artery (n = 358). *Figure 13* shows the sensitivity and specificity, with 95% CIs, for the five studies. Sensitivity ranged from 91%[75] to 100%,[59,83] with a pooled sensitivity of 97% (95% CrI 87 to 99%). Specificity ranged from 91%[75] to 100%,[52,59] with a pooled specificity of 97% (95% CrI 90 to 99%). Across studies the median PPV was 95% (range 85 to 100%), while the median NPV was 98% (range 90 to 100%).

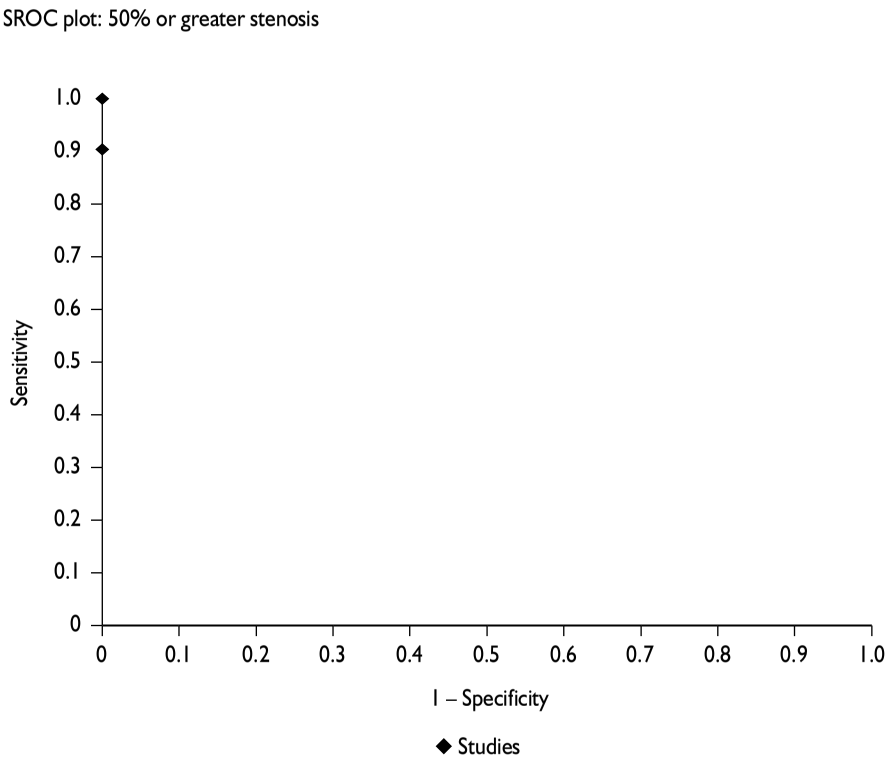
There was evidence of substantial statistical heterogeneity in terms of specificity (I^2 = 65.7%), but not sensitivity (I^2 = 21.8%).

In the studies by Ghostine and colleagues,[52] Leschka and colleagues[59] and Pugliese and colleagues[83] all scans were evaluated (n = 168). Ong and colleagues[75] reported that nine (7%) of 134 scans were not evaluated, without providing further details. Ehara and colleagues[46] did not report the number of LAD proximal scans that were unevaluable.

LCX artery analysis

Seven full-text studies[46,52,59,65,71,75,83] enrolling 513 people, with 511 included in the analysis, reported analysis of the LCX artery (n = 1351). *Figure 14* shows the sensitivity and specificity, with 95% CIs, for the seven studies. Sensitivity ranged from 59%[52] to 100%,[65] with a pooled sensitivity of 85%





Pooled estimates

Number of studies	5
Sensitivity % (95% CI)	95 (84 to 99)[a]
Specificity % (95% CI)	100 (99 to 100)[a]
Positive likelihood ratio (95% CI)	122.0 (35.3 to 421.1)[b]
Negative likelihood ratio (95% CI)	0.10 (0.04 to 0.24)[b]
DOR (95% CI)	1249 (232.2 to 6719)[b]

[a] Weighted average method; [b] DerSimonian and Laird random-effects method

FIGURE 11 *Left main artery analysis: sensitivity, specificity, SROC curve and pooled estimates*

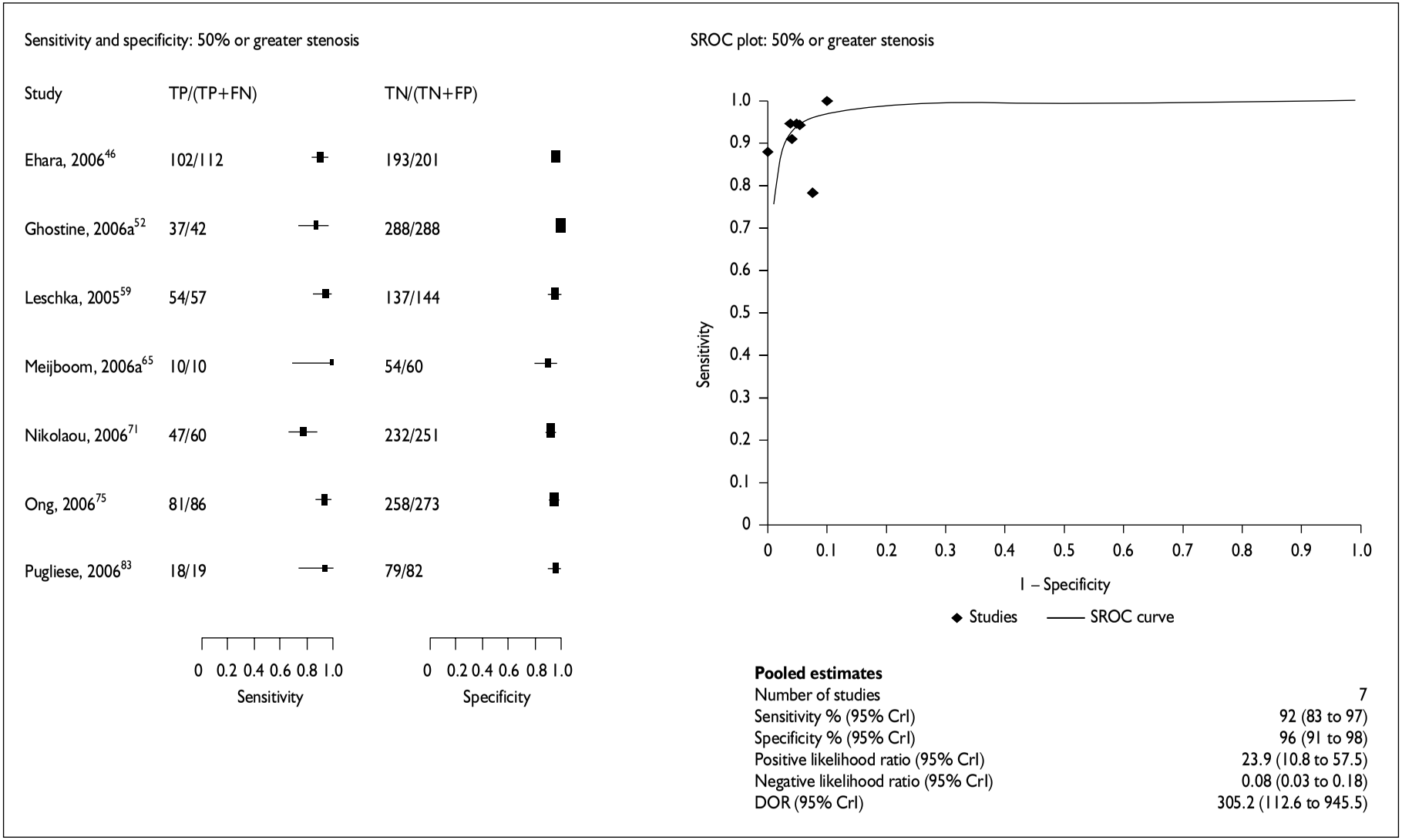


FIGURE 12 *LAD artery analysis: sensitivity, specificity, SROC curve and pooled estimates*

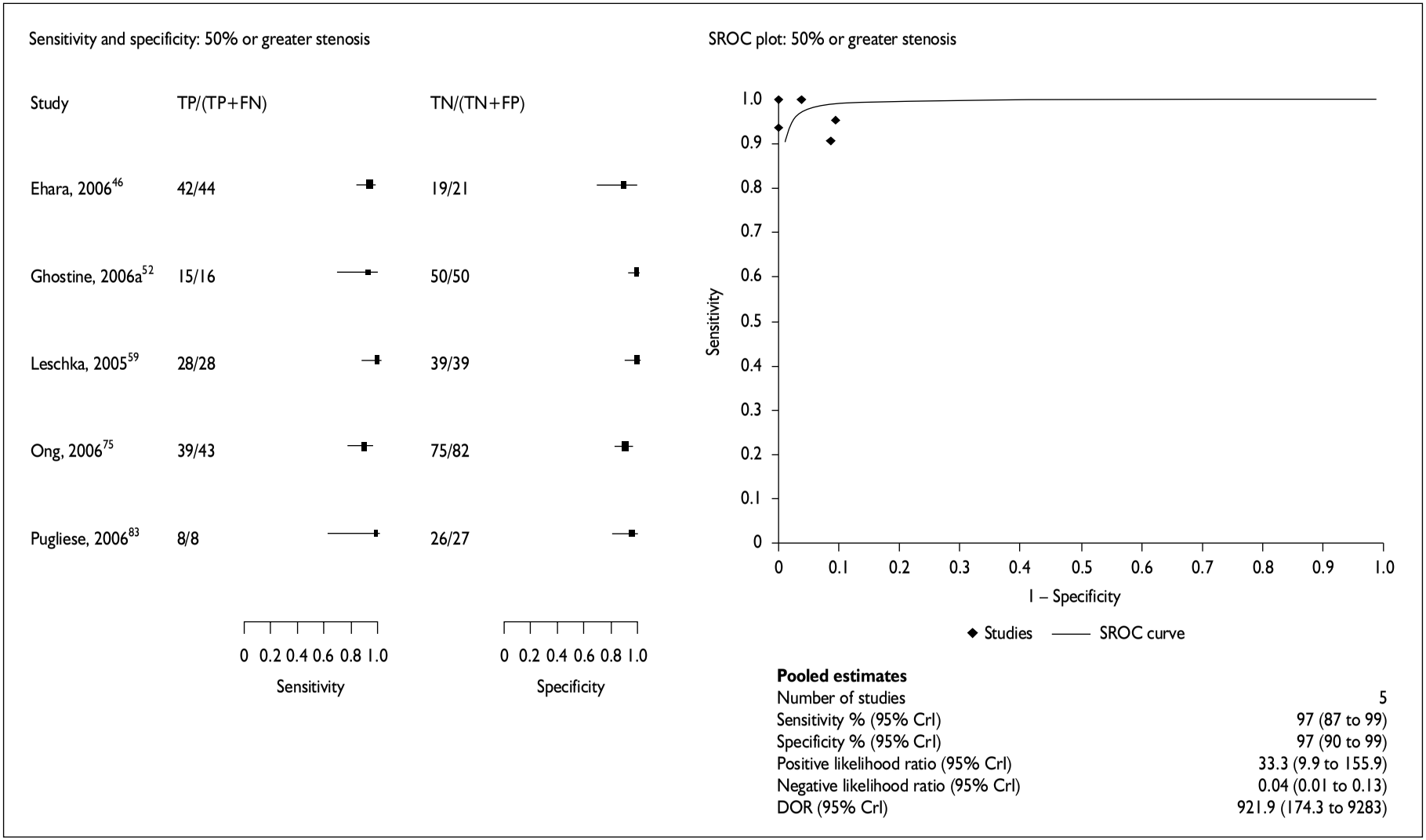


FIGURE 13 *Proximal LAD artery analysis: sensitivity, specificity, SROC curve and pooled estimates*

(95% CrI 69 to 94%). Specificity ranged from 92%[59] to 100%,[65] with a pooled specificity of 96% (95% CrI 92 to 99%). Across studies the median PPV was 81% (range 56 to 100%), while the median NPV was 98% (range 93 to 100%).

There was evidence of substantial statistical heterogeneity in terms of both sensitivity (I^2 = 67.5) and specificity (I^2 = 71.4). The study by Ghostine and colleagues[52] was most noticeable in contributing to the heterogeneity in terms of sensitivity. In this study all participants had LBBB and the authors reported that heavily calcified segments had contributed to 21 out of a total of 26 false positive results for all segments. However, the effect of calcification on sensitivity at individual artery level was not reported.

In the studies by Ghostine and colleagues,[52] Leschka and colleagues,[59] Meijboom and colleagues[65] and Pugliese and colleagues[83] all scans were evaluated (n = 560). Ehara and colleagues[46] reported that 34 (12%) of 276 CT LCX scans were not evaluated owing to poor image quality, caused by irregular heart rhythm (nine), sinus tachycardia above 90 bpm (eight), calcification (eight), vessel motion (two), inadequate breath-hold (two), low-contrast opacification (four) and anomaly (one). Nikolaou and colleagues[71] reported that 47 (14%) of 340 CT LCX scans were unevaluable, with reasons mostly cardiac motion artefacts or small vessel calibre in distal segments. Ong and colleagues[75] reported that 12 (4%) of 268 scans were not evaluated, without providing further details.

RCA analysis

Seven full-text studies[46,52,59,65,71,75,83] enrolling 513 people, with 511 included in the analysis, reported analysis of the RCA (n = 1567). *Figure 15* shows the sensitivity and specificity, with 95% CIs, for the seven studies. Sensitivity ranged from 52%[52] to 100%,[65] with a pooled sensitivity of 87% (95% CrI 77 to 95%). Specificity ranged from 95%[46,83] to 99%,[52] with a pooled specificity of 97% (95% CrI 92 to 98%). Across studies the median PPV was 82% (range 74 to 91%), while the median NPV was 98% (range 94 to 100%).

There was evidence of substantial statistical heterogeneity in terms of sensitivity (I^2 = 78.7%), but not specificity (I^2 = 29.1%). The study by Ghostine and colleagues[52] was most noticeable in contributing to the heterogeneity and, as for the LCX artery, underestimation of heavily calcified segments may have contributed to the relatively lower sensitivity reported.

In the studies by Ghostine and colleagues,[52] Leschka and colleagues,[59] Meijboom and colleagues[65] and Pugliese and colleagues[83] all scans were evaluated (n = 691). Ehara and colleagues[46] reported that 11 (4%) of 276 CT RCA scans were not evaluated owing to poor image quality, caused by irregular heart rhythm (five), sinus tachycardia above 90 bpm (two), calcification (two), inadequate breath-hold (one) and low-contrast opacification (one). Nikolaou and colleagues[71] reported that 21 (8%) of 272 CT RCA scans were unevaluable, with reasons mostly cardiac motion artefacts or small vessel calibre in distal segments. Ong and colleagues[75] reported that 42 (10%) of 402 scans were not evaluated, without providing further details.

Stents or stented segment analysis

Six studies (four full text[58,86,89,100] and two abstracts[45,72]) reported the accuracy of 64-slice CT angiography for detecting ⩾50% stenosis in patients who had undergone PCI.

Figure 16 shows the sensitivity and specificity, with 95% CIs, for the six studies reporting the analysis of stents or stented segments (n = 317). Sensitivity ranged from 50%[58] to 100%,[100] with a pooled sensitivity of 89% (95% CrI 68 to 97%). Specificity ranged from 56%[58] to 100%,[100] with a pooled specificity of 94% (95% CrI 83 to 98%). Across studies the median PPV was 77% (range 33 to 100%), while the median NPV was 96% (range 71 to 100%).

There was no evidence of substantial statistical heterogeneity in terms of sensitivity (I^2 = 30.1%), but there was in terms of specificity (I^2 = 74.5%). The study by Leber and colleagues[58] was most noticeable in contributing to the heterogeneity. The data from this study were based on the analysis of a small number of stented segments (n = 13), in which four of nine stents without any restenosis on invasive CA were diagnosed as having greater than 50% restenosis on 64-slice CT. The authors stated that the misclassification was due to artefacts caused by the dense stent material.[58]

Two studies (one full text[89] and one abstract[45]) involving 113 participants reported patient-level data. Across these two studies the median (range) values were 86% (83 to 89%) for sensitivity, 67% (46 to 87%) for specificity, 41% (10 to 71%) for PPV and 96% (both) for NPV.

Three studies (two full text[86,89] and one abstract[45]) reported that 59 (21%) of 276 scans of stents or

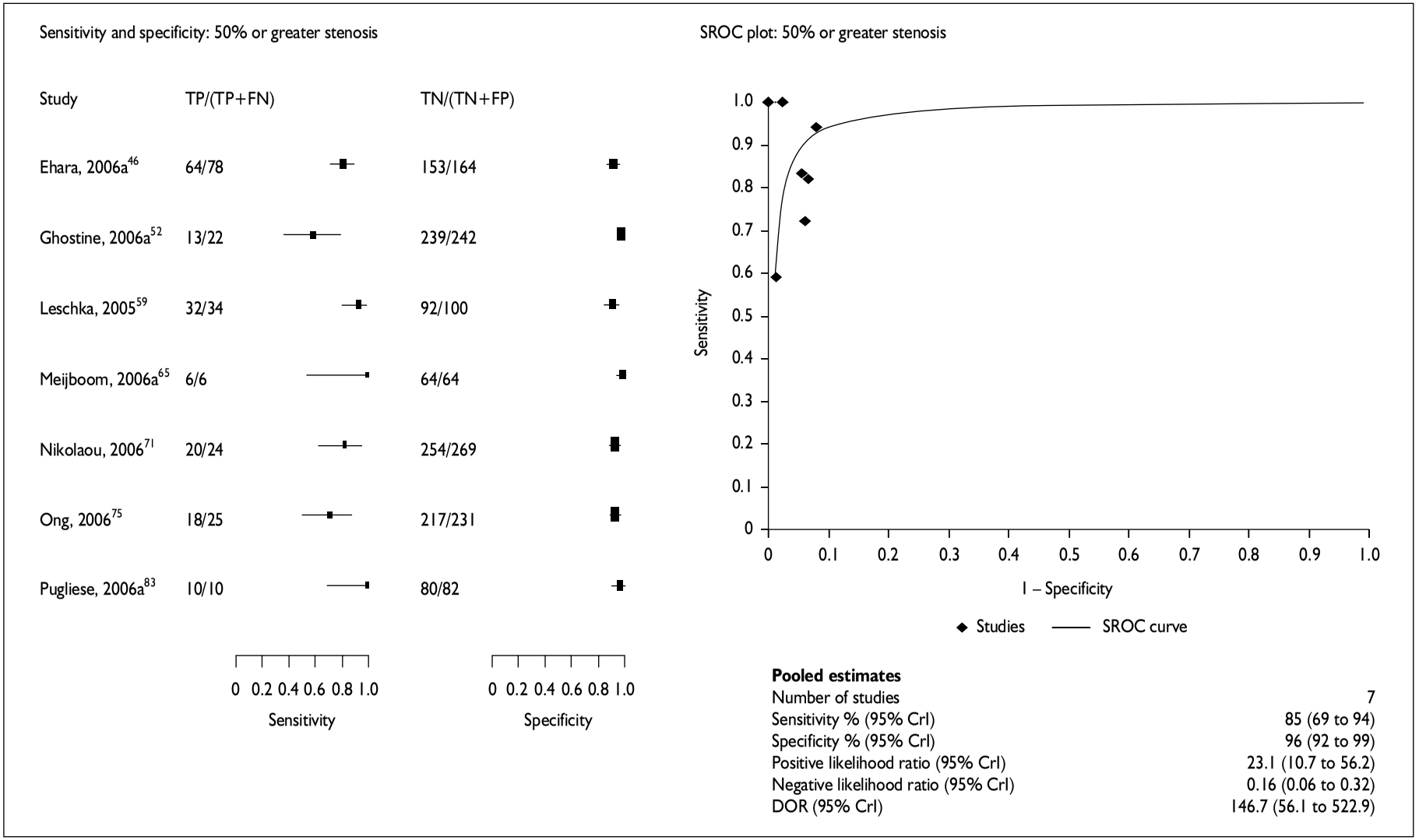


FIGURE 14 *LCX analysis: sensitivity, specificity, SROC curve and pooled estimates*

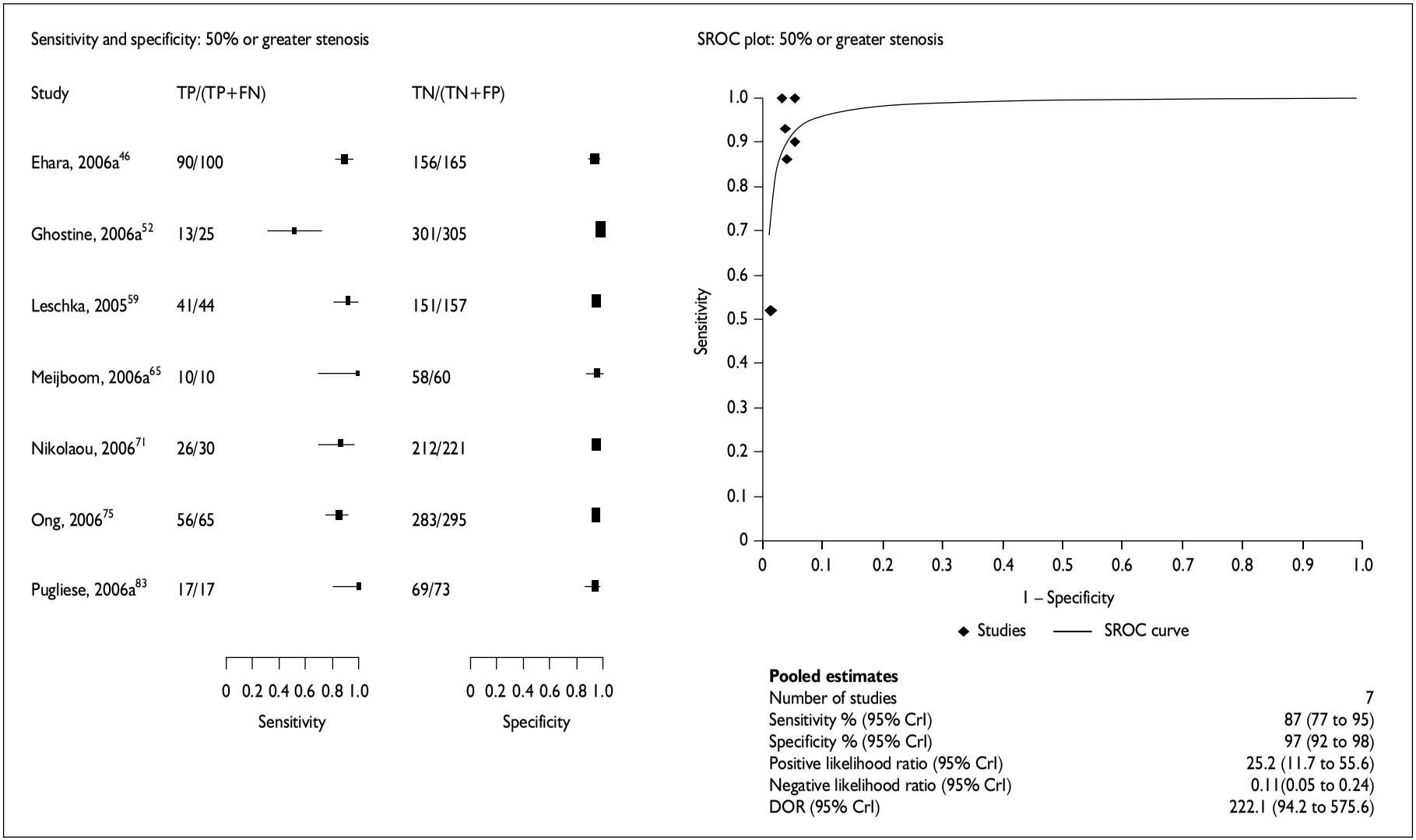


FIGURE 15 *RCA analysis: sensitivity, specificity, SROC curve and pooled estimates*

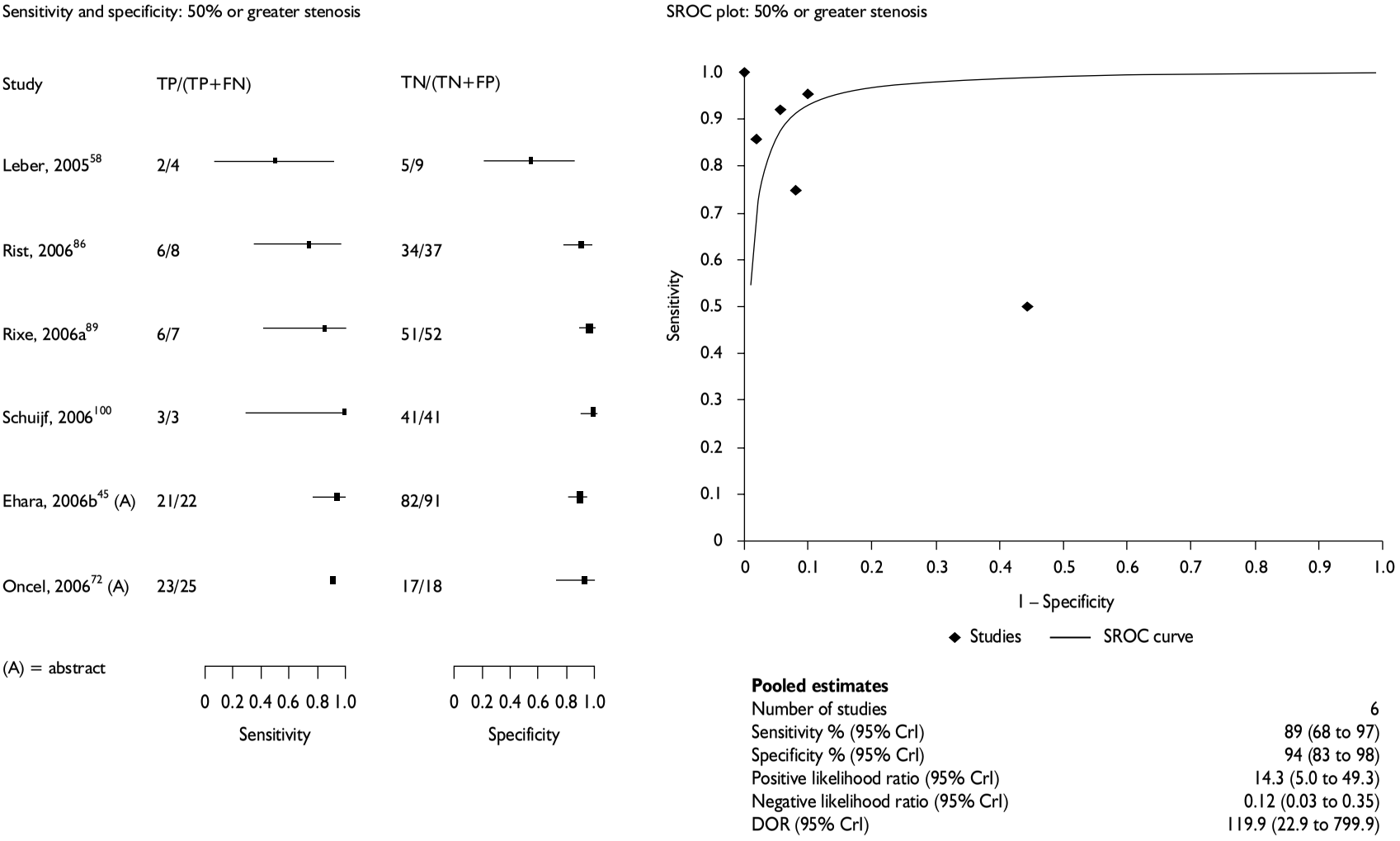


FIGURE 16 *Stents or stented segments analysis: sensitivity, specificity, SROC curve and pooled estimates*

stented segments could not be evaluated (median across studies 12%, range 2 to 42%), while no studies gave information on unevaluable scans at patient level. Rixe and colleagues[89] noted that stent type had an influence on evaluability, reporting that of the 31 stents with a diameter of 3.0 mm or larger that were classified as unevaluable, 30 were of the BxSonic (n = 20) or Cypher type (n = 10), both of which share the same strut system with a strut thickness of 0.14 mm. In comparison, only one of nine Taxus stents, which have a strut thickness of 0.13 mm, was classified as unevaluable.[89] In addition, Rixe and colleagues[89] noted that stent diameter was a significant influence on evaluability, stating that 3.5 mm was a threshold below which the rate of evaluable stents was very low. Rist and colleagues[86] also reported that the single case of poor image quality concerned a small (2.5-mm diameter) stent, which was uninterpretable owing to extensive metallic streak artefacts. They noted that the cases in which image quality was considered poor or moderate typically involved patients fitted with small-diameter stents in distal segments of the coronary arteries.[86]

In conclusion, although the 64-slice CT performance for identifying in-stent restenosis was reasonably good, it may vary according to the type, diameter and location of the stent.

CABG analysis

Four studies (two full text[77,94] and two abstracts[53,62]) reported the accuracy of 64-slice CT angiography to detect 50% or greater stenosis in people who had previously undergone CABG surgery.

Figure 17 shows the sensitivity and specificity, with 95% CIs, for the analysis of CABGs (n = 543). Sensitivity ranged from 97%[53] to 100%,[94] with a pooled sensitivity of 99% (95% CrI 95 to 100%). Specificity ranged from 89%[77] to 98%,[53] with a pooled specificity of 96% (95% CrI 86 to 99%). Across studies the median PPV was 93% (range 90 to 95%), while the median NPV was 99% (range 98 to 100%).

There was no evidence of substantial statistical heterogeneity in terms of either sensitivity (I^2 = 0.0%) or specificity (I^2 = 41.4%).

Three studies (two full text[77,94] and one abstract[62]) involving 133 participants reported patient-level data. Across these studies the median (range) values were 100% (all three studies) for sensitivity, 71% (50 to 89%) for specificity, 94% (92 to 98%) for PPV and 100% (all three studies) for NPV.

Only the studies by Pache and colleagues[77] and Ropers and colleagues[94] provided information on unevaluable scans, reporting that all bypass grafts (n = 231) were evaluable. The study by Pache and colleagues[77] reported that none of the 50 participants had to be excluded from patient-level analysis owing to unevaluable CT scans.

In conclusion, the performance of 64-slice CT angiography was very good for assessing graft patency.

Diagnostic accuracy of SPECT

Some patients in whom there is diagnostic uncertainty may be referred for a myocardial perfusion scan. Depending on their relative diagnostic performance, a potential use of 64-slice CT angiography may be to replace some perfusion scanning. In this review, primary studies of perfusion imaging were not formally searched for. Rather, the following information on the diagnostic accuracy of SPECT MPS was derived from two systematic reviews by Mowatt and colleagues[113] and Fleischmann and colleagues[114] and a critique of the Fleischmann review by Kymes and colleagues[115] (*Table 8*) identified from a search of the literature for review articles on perfusion imaging.

The review by Mowatt and colleagues[113] included studies comparing SPECT with stress ECG for the detection of CAD and in which invasive CA was the reference standard test. In 14 studies involving 3032 patients, ten studies used a cut-off of 50% or greater stenosis for a positive result, one used a cut-off of 60% or greater stenosis and one a cut-off of 70% or greater stenosis. Results were not pooled owing to heterogeneity among studies. Across studies the median sensitivity and specificity for SPECT was 81% (range 63 to 93%) and 65% (range 10 to 90%), respectively.[113]

Fleischmann and colleagues[114] compared the diagnostic accuracy of exercise SPECT versus exercise echocardiography, with invasive CA as the reference standard test. Studies performed exclusively in patients after MI, after PCI or CABG, or with unstable coronary syndromes were excluded. A positive SPECT result was as defined by the individual study authors (e.g. a fixed or reversible perfusion defect or a perfusion defect at rest or after exercise), with a cut-off for significant CAD also as defined by the individual study authors (e.g. ⩾50% or ⩾70% stenosis). In pooled data for SPECT weighted by sample size from 27 studies involving 3237 patients, sensitivity was 87%

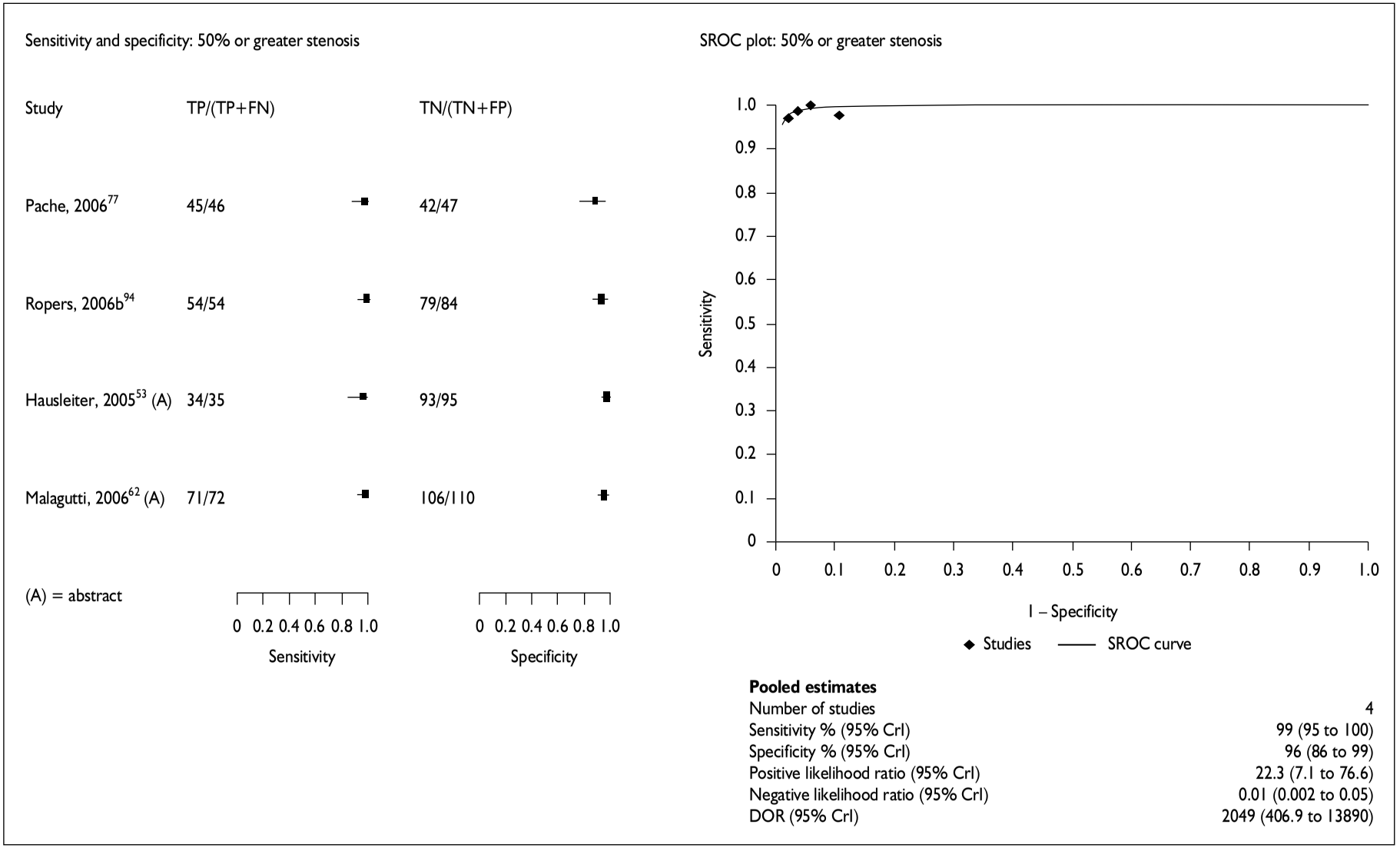


FIGURE 17 *CABG analysis: sensitivity, specificity, SROC curve and pooled estimates*

(95% CI 86 to 88%) and specificity 64% (95% CI 60 to 68%).[114]

Kymes and colleagues[115] critiqued the Fleischmann review, noting that the included studies were significantly heterogeneous ($p < 0.001$). Kymes and colleagues[115] reanalysed the same 27 studies and reported (using a fixed-effect model) a pooled sensitivity of 88% (95% CI 86 to 89%) and pooled specificity of 64% (95% CI 60% to 67%). Kymes and colleagues[115] also reported (using a random-effects model) a pooled sensitivity of 87% (95% CI 83 to 90%) and pooled specificity of 69% (95% CI 60 to 77%). Within each meta-analysis they also presented pooled data for studies stratified for sources of heterogeneity.

When these results are compared with the 99% (95% CrI 97 to 99%) sensitivity and 89% (95% CrI 83 to 94%) specificity in the pooled estimates for 64-slice CT angiography for patient-based detection of significant CAD, this indicates that there could potentially be a role for 64-slice CT to replace some perfusion imaging.

Studies reporting the prognostic usefulness of 64-slice CT angiography

Five studies (one full text[55] and four abstracts[95,105–107]) provided information on the prognostic usefulness of 64-slice CT angiography.

Acute chest pain

The study by Hoffmann and colleagues[55] involved 103 patients admitted to the hospital emergency department between May and July 2005 for chest pain and who had negative initial cardiac biomarkers and a non-diagnostic ECG on presentation. The aims of the study included an examination of whether 64-slice CT angiographic patterns of CAD – any coronary atherosclerotic plaque and significant stenosis – were associated with risk of ACS and whether they provided incremental value to standard cardiovascular risk factors and standard clinical risk assessment. Sixty-four-slice CT data were not used to define ACS.

Of the 103 patients, 14 were diagnosed with ACS (five with an acute MI and nine with unstable angina pectoris). Hoffmann and colleagues[55] reported that in multivariate logistic regression analyses both initial models containing either traditional risk factors or the categorised clinical estimates of probability of ACS did not predict ACS [likelihood ratio (LR) 8.41, $p = 0.13$, and LR 1.94, $p = 0.38$]. Adding the extent of coronary atherosclerotic plaque on 64-slice CT as a continuous variable provided incremental information and improved both the model with traditional risk factors (LR, 23.27, $p = 0.0007$) and the model with the categorised clinical estimates of probability of ACS (LR, 19.1, $p = 0.0003$).[55]

In 81 of 89 patients who were diagnosed as not having an ACS during hospitalisation, telephone follow-up was conducted at a mean of 5.2 months (SD 0.3) after hospital discharge, with no patient having suffered a major cardiovascular event.[55] Hoffmann and colleagues[55] concluded that the absence of coronary artery plaque or significant stenosis on 64-slice CT had an excellent NPV for the subsequent diagnosis of ACS, potentially identifying a group of patients who could be sent home safely on the basis of CT findings.

Gallagher and colleagues,[107] in a prospective study set in the USA, compared the accuracy of 64-slice CT with that of stress myocardial perfusion imaging (MPI) in low-risk chest pain patients admitted to the emergency department, with all patients receiving rest/stress MPI and 64-slice CT. Patients with a positive MPI scan (inducible ischaemia or submaximal heart rate response) and/or a positive CT scan (calcium score >400, stenosis >50%, or uninterpretable images due to severe calcification or motion artefacts) were considered for invasive CA, while patients with negative results were discharged. Telephone follow-up at 30 days and chart review aimed to identify major adverse cardiac events. They reported that 64-slice CT and MPI were both negative in 52 of 93 patients, who were

TABLE 8 *Sensitivity and specificity of SPECT for detecting significant CAD*

Study	No. of studies	No. of patients	Measure	Sensitivity %	Specificity %
Mowatt, 2004[113]	14	3032	Median (range)	81 (63 to 93)	65 (10 to 90)
Fleischmann, 1998[114]	27	3237	Pooled, fixed effect (95% CI)	87 (86 to 88)	64 (60 to 68)
Kymes, 2000[115]	27	3237	Pooled, fixed effect (95% CI)	88 (86 to 89)	64 (60 to 67)
			Pooled, random effects (95% CI)	87 (83 to 90)	69 (60 to 77)

subsequently discharged without undergoing invasive CA. During the 30-day follow-up period 13 patients with positive scans on 64-slice CT and/or MPI underwent invasive CA. Of seven patients with coronary stenoses greater than 50% on invasive CA, six required revascularisation.[107] There were no additional 30-day adverse cardiac events. Gallagher and colleagues[107] concluded that the accuracy of 64-slice CT for the detection or exclusion of ACS or significant coronary stenosis in low-risk emergency department chest pain patients was comparable with that of stress MPI.

Rubinshtein and colleagues,[95] in a study set in Israel, aimed to examine the role of 64-slice CT in assessing 40 patients presenting to the emergency department with chest pain of uncertain cause. Diagnosis, decision to hospitalise and intended management (intensive therapy/early intervention versus medical management) were made and recorded. Following 64-slice CT, change in diagnosis, need for early intervention and/or hospitalisation were noted.

Following 64-slice CT the diagnosis of ACS was revised in 14 (50%) of 28 patients, hospitalisation cancelled in 15 (44%) of 34 patients and early invasive CA postponed in 16 (67%) of 24, but advanced in one (6%) of 16 patients.[95] At 30-day follow-up there were no adverse cardiac events in the 15 patients discharged on the basis of negative or low-risk CT findings. Rubinshtein and colleagues[95] stated that 64-slice CT had resulted in the primary diagnosis, decision to hospitalise and decision concerning early intervention being altered in nearly half of the patients, and that the decision to discharge patients from the emergency department based on 64-slice CT results had proved to be efficient and safe.

In conclusion, the evidence from the few studies reporting prognostic usefulness of 64-slice CT angiography suggests that it can affect the way in which people presenting with ACS are managed and reduce the need for some hospital admissions and invasive CAs. However, this is based on only three studies involving 236 low-risk patients, two of which were reported as abstracts and had a follow-up of only 30 days.

Elective investigation of CAD

The aim of the study by Auseon and colleagues[105] was to determine, in a university hospital in the USA, the impact of the first year (2005) of use of 64-slice CT on invasive coronary angiographic procedures in diagnosing and treating atherosclerotic heart disease. The findings from 1056 64-slice CT examinations were recorded along with subsequent invasive CAs and cardiac surgeries. The annual throughput of patients in the cardiac catheterisation laboratories was tabulated and assessed for change after the introduction of 64-slice CT.[105]

Auseon and colleagues[105] reported that from 2000 to 2004 there was an average yearly increase of 8.7% in diagnostic cardiac catheterisation volume and 15.2% in percutaneous interventions. Following the introduction of 64-slice CT in 2005, diagnostic catheterisation volume increased by 7% and percutaneous interventions by 15%. The authors concluded that in its first year of use 64-slice CT had a significant impact on the diagnosis and treatment of atherosclerotic heart disease, stating that after the introduction of 64-slice CT only 94 (9%) of 1056 patients went on to receive invasive CA, 24 of whom required a cardiovascular operative procedure. However, the annual rates of increase in diagnostic catheterisation volume and percutaneous interventions were not significantly affected.[105]

The aim of the study by Danciu and colleagues[106] was to review the initial experience with 64-slice CT in a single 20-physician cardiology group in the USA. All records of studies performed during the first 6 months of 64-slice CT usage were reviewed. Charts were abstracted for demographic data, referral patterns and indications, prior cardiac testing, results of 64-slice CT and clinical decisions based on these. Short-term follow-up was obtained in all patients. Records of 486 patients were included, of whom 58% were men, 56% had hypertension, 67% dyslipidaemia, 15% diabetes mellitus and 29% prior CAD. The indications for 64-slice CT were abnormal stress test (47%), unexplained symptoms after stress test (35%), high risk for CAD (10%), cardiomyopathy (3%) and other (5%), including congenital heart disease and post-transplant.[106]

Danciu and colleagues[106] reported that CT ruled out CAD in 30% of patients without prior known disease. Invasive CA was recommended in 88 patients (18%) and avoided in 398 patients (82%). Sixty-four-slice CT missed six moderate, but not severe, stenoses and overestimated six lesions. During 300 patient-years of follow-up, two hospitalisations for minor CAD-related issues were noted in the medically treated patients.[106] The authors concluded that the use of 64-slice CT angiography could potentially avoid an invasive procedure in up to 80% of cases in a patient

population similar to that included in their study.[106]

64-Slice CT angiography image quality

Twenty-five studies (17 full-text[46,49,52,56,58,59,66,71,75,79,83,86,89,93,94,100,101] and eight abstracts[39,45,68,72,76,82,97,99,102]) reported information on 64-slice CT image quality. *Table 9* shows, for different levels of analysis, the median rate (range) across studies providing information on image quality for those scans classed as poor quality. This was 6% (0 to 8%) for patient-level analysis, 3% (0 to 13%) for segment analysis, 7% (0 to 42%) for stent analysis and 0% for bypass graft analysis. In some studies images classed as poor quality were still included in the analysis. Factors affecting image quality included the presence of motion artefacts, poor contrast-to-noise ratio, luminal calcification, small vessel diameter and stents.

64-Slice CT angiography interobserver variation

According to Altman,[116] kappa values less than 0.20 indicate poor agreement, those between 0.21 and 0.40 fair agreement, between 0.41 and 0.60 moderate agreement, between 0.61 and 0.80 good agreement, and between 0.81 and 1.00 very good agreement. Ten full-text studies[46,55,56,59,65,66,71,79,83,86] reported the results of kappa analysis for interobserver variation in assessing 64-slice CT scans (*Table 10*). The median kappa score across these studies was 0.74 (range 0.53 to 0.95). None of the studies reported as abstracts provided information on interobserver variation. In conclusion, there appeared to be good overall interobserver agreement for 64-slice CT, with the exception of analysis of stents. However, as none of the studies reported the degree of uncertainty around these values the true level of agreement is somewhat unclear.

TABLE 9 *Studies reporting poor-quality 64-slice CT images*

Unit of analysis	No. of studies	Poor-quality scans, median (range) % across studies
Patients		
Full-text studies	4	6 (6 to 7)
Abstracts	3	2 (0 to 8)
Total	7	6 (0 to 8)
Segments		
Full-text studies	9	4 (0 to 13)
Abstracts	5	3 (0 to 11)
Total	14	3 (0 to 13)
Stents		
Full-text studies	2	22 (2 to 42)
Abstracts	2	6 (0 to 12)
Total	4	7 (0 to 42)
Bypass grafts		
Full-text studies	1	0

TABLE 10 *64-Slice CT interobserver variation in detecting significant stenosis*

Study	Unit of analysis	Kappa
Ehara, 2006a[46]	Segment	0.95
Hoffmann, 2006[55]	Patient	0.82
Johnson, 2007[56]	Patient	0.81
Leschka, 2005[59]	Unclear whether patient or segment	0.95
Meijboom, 2006[65]	Segment	0.71
Mollet, 2005[66]	Unclear whether patient or segment	0.73
Nikolaou, 2006[71]	Patient	0.81
Plass, 2006[78]	Unclear whether patient or segment	0.93
Pugliese, 2006a[83]	Unclear whether patient or segment	0.73
Rist, 2006[86]	Stent	0.53

Summary

Twenty-one diagnostic accuracy studies reported as full-text papers and 20 reported as abstracts, along with one full-text study reporting prognostic usefulness and four studies reported as abstracts, met the inclusion criteria for the review. The diagnostic accuracy and prognostic studies enrolled over 2500 and 1700 people, respectively. As measured by the modified QUADAS checklist, the overall quality of the full-text diagnostic accuracy studies was reasonably good. In all studies the reference standard was considered likely to classify CAD correctly and all patients who received 64-slice CT angiography also received the same reference standard regardless of the 64-slice CT result. In 85% of studies those interpreting 64-slice CT data were blinded to the results of the reference standard test and 71% of studies vice versa. In 48% of studies the participants belonged to specific groups, for example those with LBBB, or who had undergone previous PCI or CABG, or who had been referred for cardiac valve surgery.

Table 11 summarises, across different levels of analysis, the results of those diagnostic accuracy studies meeting the inclusion criteria for the review that reported true and false positives and negatives or provided information enabling these data to be calculated, thereby allowing them to be included in the pooled estimates. These studies used 64-slice CT angiography with the aim of detecting 50% or greater stenosis in people with suspected or known CAD, with invasive CA used as the reference standard. The median prevalence of CAD across these studies at this cut-off was 58% (range 23 to 96%). The pooled sensitivity (95% CrI) for the different levels of analysis ranged from 85% (69 to 94%) for the LCX artery to 99% (97 to 99%) for both patient-level analysis and CABG analysis (95 to 100%), with left main artery analysis and proximal LAD analysis also showing values of 95% or higher. Pooled specificity ranged from 89% (95% CrI 83 to 94%) for patient-level analysis to 100% (95% CI 99 to 100%) for left main artery analysis, with all of the other levels of analysis apart from stents showing values of 95% or higher. The median PPV (range) at 76% (44 to 93%) was lowest for segment-level analysis and at 100% (90 to 100%) highest for left main artery analysis, with proximal LAD analysis also showing a high value at 95% (85 to 100%). Median NPVs for all levels of analysis (apart from stents, 96%, range 71 to 100%) showed values of 98% or higher.

The studies were heterogeneous in terms of their participants. In some studies the participants were all suspected CAD, in others they were all known CAD, or a mixture of suspected/known CAD, or with previous CABG or had LBBB. The prevalence of significant CAD (≥50% stenosis) in the studies included in the pooled estimates ranged from 23 to 96%. However, as assessed by the I^2 statistic, there was no evidence of substantial statistical heterogeneity in terms of sensitivity or specificity across studies reporting patient-level analysis, left main artery analysis or bypass graft analysis, no evidence of substantial statistical heterogeneity in terms of sensitivity across studies reporting proximal LAD artery or stents/stented segments analysis, or in terms of specificity across studies reporting RCA analysis.

TABLE 11 *Summary of diagnostic accuracy results for different levels of analysis*

Level of analysis	No. of studies	No. analysed	Pooled sensitivity % (95% CrI)	Pooled specificity % (95% CrI)	PPV median % (range)	NPV median % (range)
Patient	18	1,286	99 (97 to 99)	89 (83 to 94)	93 (64 to 100)	100 (86 to 100)
Segment	17	14,199	90 (85 to 94)	97 (95 to 98)	76 (44 to 93)	99 (95 to 100)
Left main artery[a]	5	393	95 (84 to 99)	100 (99 to 100)	100 (90 to 100)	100[b]
LAD overall	7	1,685	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	1,351	85 (69 to 94)	96 (92 to 99)	81 (56 to 100)	98 (93 to 100)
RCA overall	7	1,567	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)

[a] For left main artery analysis the 95% intervals around the pooled sensitivity and specificity estimates are confidence intervals (CIs) rather than credible intervals (CrIs).
[b] All five studies reporting left main artery analysis had an NPV of 100%.

A comparison of 11 studies separately reporting suspected and known CAD found that, in terms of patient-level analysis (n = 309), 64-slice CT had higher sensitivity, PPV and NPV, but lower specificity, for known compared with suspected CAD. In segment-level analysis (n > 7708), 64-slice CT reported higher sensitivity for suspected CAD and lower PPV for known CAD, while specificity and NPV were similar for both groups.

Three studies[65,75,85] involving 274 people (3269 segments) reported the accuracy of 64-slice CT angiography for detecting 50% or greater stenosis in segments affected by different degrees of calcification. In two studies[65,75] sensitivity, specificity, PPV and NPV decreased as the severity of calcification increased, while in the third study[85] sensitivity increased, specificity decreased, and PPV and NPV remained broadly similar.

Seven studies[49,59,75,79,93,94,102] stated that segments smaller than 1.5 mm in diameter were excluded from the analysis, while one study[68] excluded segments 2 mm in diameter or smaller. In the 13 full-text studies included in the pooled estimates for patient-based detection of CAD, 11 (2%) of 718 patients could not be assessed owing to unevaluable CT scans (median across studies 0%, range 0 to 6%). In segment-level analysis, 13 studies reported that 997 (8%) of 12,476 CT segment scans could not be evaluated (median across studies 9%, range 0 to 18%). Non-evaluability was due to poor image quality, for reasons such as irregular heart rhythm and coronary calcification. Ten studies[46,55,56,59,65,66,71,79,83,86] reported interobserver variation in assessing 64-slice CT scans, with a median kappa score across studies of 0.74 (range 0.53 to 0.95).

Some patients in whom there is diagnostic uncertainty may be referred for a perfusion scan, and a possible use for 64-slice CT angiography, depending on relative diagnostic performance, may be to replace some perfusion scanning. Two systematic reviews[113,114] and one paper[115] that reanalysed data from one of the reviews provided information on the sensitivity and specificity of SPECT. Depending on the type of analysis undertaken, SPECT sensitivity was reported as 81%, 87% or 88%, while specificity was 64%, 65% or 69%.

Five studies (one full text[55] and four studies reported as abstracts[95,105–107]) provided information on the prognostic usefulness of 64-slice CT angiography. In three studies the patient populations were those with suspected ACS. Hoffmann and colleagues,[55] in a study involving 103 patients with acute chest pain with a mean follow-up of 5.2 months, reported that 81 patients diagnosed as not having ACS had experienced no major cardiovascular events at follow-up, and concluded that 64-slice CT angiography had very good NPV for the subsequent diagnosis of ACS in the short term. Gallagher and colleagues,[107] in a study of low-risk patients admitted to the hospital emergency department with chest pain, reported that those with negative 64-slice CT and MPI scans (n = 52) who were discharged experienced no adverse cardiac events during the 30-day follow-up. Rubinshtein and colleagues[95] examined the role of 64-slice CT angiography in patients (n = 40) presenting to the hospital emergency department with chest pain of uncertain cause. The authors reported that taking account of 64-slice CT angiography had led to the diagnosis being revised in 14 (50%) of 28 patients, hospitalisation cancelled in 15 (44%) of 34 patients and early invasive CA postponed in 16 (67%) of 24, but brought forward in one (6%) of 16 patients. At 30-day follow-up there were no adverse cardiac events in the 15 patients discharged on the basis of negative or low-risk 64-slice CT findings.

Of the other two studies, Auseon and colleagues[105] reported that, in the year following the introduction of 64-slice CT compared with the previous 4 years, the yearly rates of increase in diagnostic catheterisation volume (7% versus 8.7%) and percutaneous interventions (15% versus 15.2%) had not been significantly affected. Danciu and colleagues[106] reported that in the first 6 months following the introduction of 64-slice CT, of 486 patients CT results had led to invasive CA being recommended in 88 (18%) patients and avoided in 398 (82%), of whom there were subsequently two hospitalisations for minor CAD-related issues.

In conclusion, at a cut-off of 50% or greater stenosis, the high NPVs reported across various levels of analysis by the diagnostic accuracy studies appear to be borne out by the few prognostic studies included in the review that followed up patients subsequently discharged from hospital on the basis of negative/low-risk 64-slice CT angiography scans, who were then found not to have experienced any adverse cardiac events, although these results were based on short-term (mostly 30-day) follow-up.

The implications for invasive CA workload are as follows.

If 64-slice CT angiography is available for the investigation of suspected ACS, some low-risk patients may potentially be reassured and discharged based on CT findings. However, troponin-positive patients (i.e. those with MI) would still need invasive testing with a view to possible revascularisation. Troponin-negative patients often have atypical symptoms and would tend to be clinically assessed and possibly undergo exercise testing rather than receiving an invasive CA test. In three diagnostic studies[39,55,84] included in this review the populations were patients suspected of having ACS (n = 232). In these studies, for patient-based detection of significant CAD, 69 (95%) of 73 patients testing negative on 64-slice CT were true negatives by invasive CA, suggesting that, based on these results, around 30% (69/232) of invasive CA tests may potentially be avoided for this patient group. Across the studies the median NPV was 100% (range 94 to 100%). (In the study reporting a 94% NPV,[39] three of four patients whose scans could not be evaluated were classed as false negatives, which had the effect of lowering the NPV value.)

In the elective investigation of suspected CAD, CT has sufficiently high NPV to rule out significant CAD in many cases, thereby reducing demands on invasive CA. In four studies[71,85,93,97,102] included in this review, those with suspected CAD comprised the entire patient population or a subgroup that was reported separately (n = 245). One of the four studies[71,102] involving 39 patients did not report true and false positives and negatives. In the remaining three studies, for patient-based detection of significant CAD, 107 (97%) of 110 patients testing negative on 64-slice CT were true negatives by invasive CA, suggesting that, based on these results, around 52% (107/206) of invasive CA tests may potentially be avoided for this patient group. Across these three studies the median NPV was 98% (range 93 to 100%).

Sixty-four-slice CT angiography may also replace some perfusion scanning tests. In two systematic reviews[113,114] of SPECT MPS, sensitivity was reported as a median of 81% across studies (range 63 to 93%)[113] or pooled estimate of 87% (fixed-effect model, 95% CI 86 to 88%),[114] while specificity was reported as a median of 65% across studies (range 10 to 90%)[113] or pooled estimate of 64% (fixed-effect model, 95% CI 60 to 68%).[114] This compares with the pooled estimates for 64-slice CT angiography patient-based detection of significant CAD of 99% (95% CrI 97 to 99%) sensitivity and 89% (95% CrI 83 to 94%) specificity.

In assessment of prognosis, 64-slice CT can identify patterns of CAD which carry the greatest risk of mortality, and in whom revascularisation is indicated on prognostic grounds. However, 64-slice CT does not at present seem sufficient to replace invasive CA in assessment of patients referred for CABG.

After revascularisation, 64-slice CT angiography is more accurate for identifying significant stenosis in bypass grafts (pooled estimates, sensitivity 99%, 95% CrI 95 to 100%; specificity 96%, 95%, CrI 86 to 99%; median PPV 93%, range 90 to 95%; NPV 99%, range 98 to 100%) than it is for identifying significant stenosis in stents (pooled estimates, sensitivity 89%, 95% CrI 68 to 97%; specificity 94%, 95% CrI 83 to 98%; median PPV 77%, range 33 to 100%; NPV 96%, range 71 to 100%).

In patients referred for cardiac valve surgery, 64-slice CT angiography may have a role to play in obviating the need for invasive investigation in patients whose CT test results reveal no significant CAD.

In conclusion, if in patient-based detection of significant (≥50% stenosis) CAD, and taking other factors into account such as pretest probability of CAD, a negative 64-slice CT angiography test allowed an invasive CA test to be avoided, then, depending on the patient groups involved, this could potentially result in some reduction in invasive CA workload.

Chapter 3

Assessment of cost-effectiveness

Methods

Search strategy

Studies that reported both costs and outcomes of MSCT screening were sought for the systematic review of the literature. Searches were restricted to reports published in English and to publications from 1996 onwards.

Databases searched were MEDLINE (1996 to November week 3 2006), EMBASE (1996 to week 49 2006), Medline In-Process (14 December 2006), NHS EED (December 2006), HTA Database (December 2006) and HMIC (2000 to May 2006). In addition, recent conference proceedings and reference lists of all included studies were scanned to identify additional potentially relevant studies. Full details of the search strategies used are documented in Appendix 1.

Results

Number of studies identified

A total of 144 reports was identified from the searches, of which 47 papers were selected for full-text assessment. No studies of the cost-effectiveness of multidetector computed tomography (MDCT) for CAD were identified. One study identifying the necessary cost and accuracy of MDCT for it to be cost-effective relative to gadolinium-enhanced MRI was identified.[117] As a consequence, the studies briefly reviewed below have been used to inform the modelling of the cost-effectiveness of MDCT in terms of the structures of both a short-term model and a more speculative long-term model, and also to inform the characteristics of the other tests involved in the diagnosis of CAD within this modelling: exercise ECG, myocardial perfusion scanning and CA.

Economic literature review

Several original articles relating to other testing strategies were identified, the more informative of which are briefly reviewed below to inform possible model structure and model inputs for this review.[117–122] *Table 12* summarises these studies. Some systematic reviews and HTAs of MDCT for CAD were identified, but again these involved no cost-effectiveness analyses. They did outline a number of cost-effectiveness issues likely to arise with using MDCT for CAD, the 2005 review of the Medical Advisory Secretariat of the Ontario Ministry of Health[22] being the most informative of these.

Visser and colleagues[117] project the required cost and accuracy of MDCT for it to be cost-effective, on the basis of a WTP of $100,000 per QALY. Unfortunately, the comparator test for their study is gadolinium-enhanced MRI, which is of limited practical relevance to the UK setting. Given this, that the accuracy of MDCT has to be defined over several dimensions, and the US setting in terms of costs, the projected required accuracy for MDCT is of little relevance to the current review.

Garber and Solomon[118] evaluate the cost-effectiveness of five non-invasive diagnostic tests against angiography: exercise testing, planar thallium imaging, stress echocardiogram, SPECT and PET. The costs of these are estimated as $110, $221, $265, $475 and $1500, respectively, these being taken from Medicare with the exception of PET which, since Medicare does not reimburse for PET myocardial imaging, is based on an unspecified insurer. A short-term diagnostic model with patients receiving their continued medication with ongoing observation, intensified medical management or revascularisation is coupled with a longer term model of the effectiveness of these treatments in terms of avoiding angina, infarctions and death. Intervention costs are also taken from Medicare, these being $1180 for CA coupled with catheterisation, $11,685 for PCI as the Medicare average of one- and two-vessel procedures, and $32,824 for CABG. The paper estimates an infarction resulting in a single admission to cost $7415.

In terms of the model structure, a negative non-invasive test at the diagnostic stage leads to discharge and continued medical management, with ongoing observation. A positive non-invasive test result is assumed to result in angiography, with its associated very low risks of complication, such as infarction and death. The non-invasive tests were viewed not as potential replacements for angiography in assessing CAD, but only as means

TABLE 12 *Summary of studies relating to other testing strategies*

Study	Country	Perspective	Comparators	Main results
Cost-effectiveness modelling of diagnostic tests for CAD				
Visser, 2003[117]	USA	Societal	MDCT enhanced MRI	Given a WTP of $100,000 per QALY MDCT cost-effective if test cost $300 and sensitivity 85%
Garber, 1999[118]	USA	Societal	Stress ECG Exercise Echo Planar thallium imaging MPS PET	Thallium imaging similar effectiveness to Echo but more expensive PET more expensive and inferior to sending all to angiography
Kuntz, 1999[119]	USA	Societal	Exercise ECG Exercise Echo MPS	Among typical angina patients: • $41,900 per QALY for move from exercise ECG to exercise Echo • $54,800 per QALY for move from exercise ECG to SPECT • $36,400 per QALY for move from exercise echo to routine angiography For non-specific chest pain: • $57,700 per QALY for move from no testing to exercise ECG
Underwood, 1999[120]	UK	Healthcare system	Exercise ECG Exercise Echo MPS	Strategies involving MPS as an interim prior to angiography are cheaper and equally effective both at diagnosis and for outcome over 2 years
Review article of cost-effectiveness consideration of MDCT diagnosis of CAD				
Ontario MoH, 2005[22]	Canada	Healthcare system	MDCT	MDCT faster turnaround times may reduce waiting lists for CT, provided that complementary inputs (e.g. portering) are available However, as applications for MDCT expand, the number of CT tests requested may similarly expand
Cost-effectiveness modelling of MPS diagnosis of CAD, as nearest likely comparator to MDCT				
Patterson, 1995[123]	USA	Healthcare system	Exercise ECG MPS PET	CAD patients not correctly diagnosed and treated lose an average of 3 QALYs • If prevalence of CAD is <70% PET has the lowest cost per QALY • If prevalence of CAD is >70% angiography has the lowest cost per QALY
Mowatt, 2004[113]	UK	Healthcare system	Exercise ECG MPS	If prevalence of CAD is 10.5%, for MPS–angiography as compared to ECG–MPS-angiography, cost-effectiveness would be £14,123 per QALY As the prevalence of CAD rises the cost effectiveness of this move improves

Echo, echocardiography; PET, positron emission tomography; QALY, quality-adjusted life-year; WTP, willingness to pay.

of reducing the number of angiographies required through hopefully being able to rule out significant CAD. If the angiography results in no significant CAD, patients are discharged and managed as for a negative non-invasive test. All positive CAD states may be managed medically. One-vessel, two-vessel and three-vessel or left main disease are treated differently for prognostic reasons. Three-vessel or left main disease is taken to require CABG.

Sensitivities were estimated from 68% for exercise ECG, through 76% and 79% for echocardiography and thallium imaging, respectively, to 88% for

SPECT and 91% for PET, with specificities being 77%, 88%, 73%, 77% and 82%, respectively. These were not differentiated by degree of disease with the exception of sensitivity to left main or three-vessel disease, where exercise ECG again performed least well at 86%, followed by 94% and 93% for echocardiography and thallium imaging, respectively, and 98% for SPECT.

While the clinical inputs and model structure are of more interest to the current review, the cost-effectiveness estimates of Garber and Soloman,[118] in a population with a 50% prevalence of CAD, suggest that thallium imaging has a very similar but possibly slightly inferior effectiveness compared to echocardiography, but is around $120–150 more expensive overall per patient. Similarly, PET is slightly more expensive than sending all immediately to angiography, and performs more poorly. Sensitivity analyses tended to confirm these results, with echocardiography having similar effectiveness but reduced costs compared with thallium imaging, and angiography typically dominating PET.

Kuntz and colleagues[119] mirror the above, but examine exercise ECG, exercise echocardiography and exercise SPECT in the US context. Sensitivities are reported as 68%, 85% and 87%, respectively, the gap in sensitivities between exercise echocardiography and exercise SPECT being somewhat less than in Garber and Solomon's[118] report between echocardiography and SPECT. Specificities are reported as 77%, 77% and 64%, again with exercise echocardiography being anticipated to perform relatively better than the corollary in Garber. The unit costs of the two papers are similar. Kuntz also assumed that some tests would be indeterminate, with an indeterminacy rate for exercise ECG of 30%, for exercise echocardiography of 10% and for exercise SPECT of 2%, although the source of these estimates is unclear. The prevalence of CAD was estimated as 95%, 71% and 18% in men with typical, atypical and non-specific chest pain, the prevalences for women being 68%, 30% and 6%, respectively. For typical angina, angiography appears cost-effective relative to all the other tests, with cost-effectiveness ratios of around $30,000 per QALY. Within atypical angina, angiography has more marginal cost-effectiveness relative to the other tests, its cost-effectiveness ratio rising to around $70,000 per QALY relative to exercise echocardiography and exercise SPECT. For atypical angina, only the move from exercise echocardiography to exercise SPECT is unlikely to be cost-effective, involving an anticipated cost per QALY of around $110,000.

As with other papers reviewed in this section, the relevance of the results of Kuntz to the current review is limited, other than to highlight the importance of the underlying CAD prevalence. The model structure and clinical inputs are of greater interest. A lifetime cost–utility analysis is undertaken within a decision-tree model structure, the immediate short-term model of diagnosis having the three possibilities of no diagnostic testing, non-invasive testing with a positive result leading to CA, and all patients going straight to angiography. CA was assumed to have perfect sensitivity and specificity, but also a small mortality risk. CA was also able to split patients with one- and two-vessel disease, who within the modelling should receive percutaneous transluminal coronary angioplasty (PTCA), from those with three-vessel or left main disease who should receive CABG. Both PTCA and CABG had their own small procedural mortality risk, but among survivors conferred a reduction in the mortality risk associated with CAD and MI. Both true and false negatives were deemed at low risk and so only received medication. While the overall model structure appears reasonable, a major weakness may be in the treatment of false negatives. They appear to be assumed only to receive medication, but in practice it may be that as medication proves insufficient in managing their symptoms or as their disease progresses they will present again and so undergo further testing. If this occurs it will mitigate a poorer specificity of any particular testing strategy, with a proportion of the false negatives who have not had an event in the intervening period re-presenting for further testing each year.

Underwood and colleagues[120] undertake a similar analysis to those reported above, examining diagnostic strategies involving exercise ECG, MPI and CA from a UK perspective. For the current review their results are mainly of interest owing to the unit costs reported, with an exercise ECG costing £70, a rest echocardiogram £100, MPI £220, angiography £1100, angioplasty £3700 and CABG £6900, based on costs from the Royal Brompton Hospital, London. Four diagnostic strategies were examined which variously sequenced exercise ECG, MPI and CA. The text of the paper is not explicit, but it appears likely that if an earlier test in the sequence was negative no further tests were performed, but an indeterminate result or a positive result would result in the next test in the strategy. Strategies

were defined as exercise ECG followed by angiography, exercise ECG followed by MPI followed by angiography, MPI followed by angiography, and angiography alone. A further slight complication to the diagnostic pathway within the paper was that any false negative experiencing an event during a largely unspecified follow-up period would have their diagnosis altered to become a true positive.

The second strategy of perfusion imaging in the interim between exercise ECG and angiography was found to have a diagnostic cost of £269 as against £335 for all ECG-positive patients being sent straight to angiography. The third strategy of no exercise ECG before perfusion imaging is of similar average diagnostic cost to the first strategy of ECG then angiography, but has higher downstream patient management costs among non-CAD patients. However, the results of Underwood are confused by it being reported that the proportion of true positives among final positive results is less than 100% for all testing strategies other than coronary angiography. Given that each testing strategy has CA as the final test, it not clear how these results were arrived at.

Two papers were available only as abstracts. Raff and colleagues[122] report a study among 200 patients with low-risk acute chest pain randomised either to immediate 64-slice CT or to a largely unspecified usual care algorithm that included enzyme testing and stress nuclear scanning. Those undergoing 64-slice CT had a median time to diagnosis of 3.3 hours compared with 12.0 hours for usual care. This lowered the median cost of care to $1595 compared with $1784 for usual care, in spite of 64-slice CT leading to more patients going on to invasive angiography: 11% as against 3% for usual care. It is not entirely clear whether the costs of angiography were included within these estimates, but the abstract concludes that 64-slice CT can rapidly rule out CAD in chest pain without increasing risk. How this conclusion was arrived at is also unclear, given that there does not appear to have been any gold-standard investigation or long-term follow-up for those discharged without angiography. The only outcomes appear to be cost, time to diagnosis and time to discharge.

Cole and colleagues[121] report the results of a study of 206 patients with mildly abnormal or equivocal nuclear perfusion imaging who underwent immediate 64-slice CT rather than immediate catheterisation for the diagnosis of CAD at the discretion of the cardiologist. A cost analysis found these patients to cost on average $1809 as against $4075 for the immediate catheterisation, so realising an average cost saving of $2266 per patient. The abstract did not report any measurement of patient outcomes or cost-effectiveness.

The economic literature search also identified four review articles,[10,17,22,124] although none identified any economic studies of 64-slice CT for CAD. They did, however, note a number of economic considerations that would affect the likely cost-effectiveness of 64-slice CT in CAD. As already mentioned, the 2005 review of the Medical Advisory Secretariat of the Ontario Ministry of Health[22] is the most informative of these from an economic viewpoint. This notes a major investment in Ontario in MDCT scanners, and that proponents of MDCT scanning suggest that the fast turnaround time will reduce waiting times for CT scans.

The review is at pains to point out that any such reduction in waiting times would depend on a number of other factors within the system, down to aspects as simple as having sufficient portering staff to transfer patients. Another aspect that may affect waiting times is the increase in demand for CT scans as more indications are found to take advantage of the new MDCT's greater accuracy. The review also questions the extent to which cardiologists will be prepared to rely solely on the MDCT scan result. At least in the interim some mistrust may arise, given the assumed gold-standard nature of angiography. It is also possible that professional differences of opinion may arise, given that radiologists perform MDCT scans while cardiologists perform angiographies, which may in the short to medium term see cardiologists continue to perform angiographies despite MDCT results being available.

On a more prosaic level, if after a positive MDCT an angiography is required, the additional diagnostic MDCT test may actually increase waiting times, simply as a result of more tests being sequenced. This is not to say that costs will necessarily increase if a negative MDCT could confidently be used to rule out CAD. The review also fails to consider the effect this may have on waiting times for angiography. The review is wrong to state that the waiting time for angiography and other cardiac procedures will increase if both MDCT and angiography are performed on the same patient. This will only necessarily occur if both MDCT and angiography

are performed on all patients regardless of MDCT results. The review estimates a scan time for MDCT of 15–40 minutes, compared with 60 minutes for traditional angiography.

In common with all the identified studies, the review does not consider the possibility of combining diagnostic angiography with angioplasty during the same catheterisation laboratory appointment if angioplasty is found to be indicated. Depending on timings and the percentage of patients in whom angioplasty is indicated, the possibility of combining angioplasty with angiography at the same catheterisation laboratory appointment could have a significant impact on the likely cost-effectiveness of MDCT within the diagnostic pathway.

Modelling the cost-effectiveness of MPS

Given the lack of studies addressing the cost-effectiveness of MDCT scanning, an obvious alternative to inform modelling approaches and structure is to examine studies of the non-invasive comparator to MDCT: MPS, as briefly outlined in the summary of Kuntz and colleagues[119] above. SPECT MPS for the diagnosis of CAD has recently been the subject of a systematic review by Mowatt and colleagues.[113] The economic literature review of Mowatt and colleagues highlighted the importance of the modelling approach adopted by Patterson and colleagues,[123] this being adopted by a further three studies of the literature review, the modelling section of Mowatt and colleagues[113] also drawing a number of key parameter estimates from Patterson and colleagues. Both Patterson and colleagues[123] and Mowatt and colleagues[113] adopt a similar modelling strategy of a short-term decision-tree model for the diagnostic element, coupled with longer term modelling of the downstream impact of the resultant distribution of patient diagnoses.

Patterson and colleagues[123] compare a range of diagnostic strategies involving ECG, MPS, PET and coronary angiography:

- ECG followed by CA where ECG positive or indeterminate
- MPS followed by CA where MPS positive or indeterminate
- PET followed by CA where PET positive or indeterminate
- CA alone.

Non-invasive tests were taken to have a death rate of 5 per 100,000 and a complication rate of 5 per 10,000. CA was taken to have a death rate of 150 per 100,000 and a complication rate of 200 per 10,000. Complications were taken to be a non-fatal MI requiring a week's stay in hospital. CA was taken as the gold standard, resulting in all test strategies resulting in no false positives. Coupling the above strategies and assumptions with the sensitivity, specificity, indeterminacy and cost of the tests enabled estimates of each testing strategy's number of true positives, false negatives, true negatives, deaths and cost within the short-term diagnostic model. Indeterminacy rates of 18% for ECG and 9% for MPS were somewhat closer to each other than the 30% for ECG and 2% for MPS of Kuntz.[119]

These were then coupled with a longer term model of the downstream impact of the treatment of true positives and the lack of treatment of false negatives. This was based on an assumption that correct treatment would see 30% receive medical treatment, 30% PTCA and 40% CABG surgery. For each of these groups, and for whether they were treated or not treated, the average QALYs achieved were estimated, based on

- the proportion likely to be alive at the 10-year point
- the proportion likely to die before the 10-year point
- the likely longevity of those dying before the 10-year point
- their associated quality of life.

This was done for both true positives and false negatives. This resulted in a 10-year estimate of 7.09 undiscounted QALYs for those correctly treated, and 4.09 undiscounted QALYs for those incorrectly not treated: a net effect of a missed diagnosis of 3 QALYs. While this method for the longer term modelling has the benefits of simplicity, it may fail to take into account false-negative patients re-presenting with symptoms at a later time and subsequently being correctly diagnosed.

Mowatt and colleagues[113] adopted a similar approach to that of Patterson and colleagues[123] for the short-term modelling of different diagnostic strategies in their assessment of the cost-effectiveness of MPS for the diagnosis of CAD:

- ECG followed by CA where ECG positive or indeterminate
- ECG followed by MPS where ECG positive or indeterminate, followed by CA where MPS positive or indeterminate

- MPS followed by CA where MPS positive or indeterminate
- CA alone.

The complications from testing were dropped in their model. Sensitivities and specificities were estimated by the review, with the indeterminacy rates and mortality risks of the tests being drawn from Patterson and colleagues.[123] CA was again taken to be the gold standard, implying that there were no false positives from any of the diagnostic strategies. There is an additional qualification of those with CAD being either high risk or medium risk, the balance between these being 59:41. It appears that the sensitivity, specificity and indeterminacy of tests are taken to be the same for high risk and medium risk and the distinction between patients has no impact on the short-term diagnostic modelling base case.

Within the short-term diagnostic modelling, the distinction between high risk and medium risk appears only to impact within a sensitivity analysis where SPECT is assumed to be able to identify a proportion of medium-risk patients, these not requiring CA. Regardless of the background prevalence, the strategy of ECG followed by MPS followed by CA was found to always be the cheapest, then ECG followed by CA, then MPS followed by CA. The strategy of referring all to CA was found to be the most expensive, given the high cost of CA and the avoidance of it among some patients with the other diagnostic strategies. The ordering of strategies by the percentage of those with CAD correctly diagnosed was the same as the cost ordering, the incremental cost per correct true diagnosis falling as the background prevalence rose.

In contrast to Patterson,[123] the short-term modelling of the diagnostic pathways was augmented by a relatively sophisticated longer term Markov cost–utility model. Subsequent to the short-term diagnostic model, patients could be low-risk true negatives, medium-risk false negatives, high-risk false negatives, medium-risk true positives or high-risk true positives. As all strategies had CA as a final test for those not deemed negative by previous tests, there were no false positives. Within each Markov cycle patient-specific mortality rates were applied, with there also being a patient-specific possibility of MI, also with its associated death rate. Survivors of MI automatically transferred to be high-risk true positives. Thereafter, true positives could progress to revascularisation through either PTCA or CABG, with there also being a small probability of low-risk true-negative patients also progressing to revascularisation. Within the longer term modelling, there was also a probability of false negatives being rediagnosed before any event such as an MI, which served to lessen the differences between the long-term outcomes of the four diagnostic strategies.

Coupling the short-term diagnostic model with the longer term model yielded estimates of cost and average QALYs. What is immediately striking within the combined results are the limited differences that arise from the long-term modelling over the 25-year time-horizon. The incremental costs of moving between strategies of the short-term modelling are affected by less than 10% when long-term costs are added, while the difference in QALYs between the ECG–MPS–CA testing strategy and the gold standard of CA alone is less than a quarter of one per cent. This will in part have been due to later diagnosis of false negatives being permitted, which lessens the distinctions between the testing strategies in comparison to Patterson and colleagues.[123] But the assumptions as to later diagnosis rates also raise questions as to the practical impact of what could be viewed as illustrative long-term modelling within this area. A key uncertainty remains the rate at which false negatives remain undiagnosed and untreated, and at risk of an event such as a fatal MI.

Clinical effectiveness of 64-slice CT against MPS and CA for CAD diagnosis: implications for modelling

The clinical effectiveness section outlines, for patient-based detection of significant CAD, a pooled estimate for the sensitivity of 64-slice CT of 99% (95% CI 97 to 99%) and a specificity of 89% (95% CI 83 to 94%), with an average of 2% of scans not being read within the studies contained in the pooled estimates.

The economic model of Mowatt and colleagues[113] took a sensitivity for MPS of 83% (95% CI 63 to 93%) and a specificity of 59% (95% CI 44 to 90%) by pooling the results of the studies identified within the clinical effectiveness section, although the clinical effectiveness section did not itself pool results owing to heterogeneity of studies. These estimates were coupled with an indeterminacy rate of 9% taken from Patterson and colleagues.[123] Similarly, the sensitivity and specificity of ECG were estimated from the pooled clinical data of the review and estimated as being 66% (95% CI 42 to 92%) and 60% (95% CI 43 to 83%), respectively,

together with an indeterminacy rate of 18% from Patterson and colleagues.[123]

Two other reviews of the accuracy of MPS for the diagnosis of CAD are also available, by Fleischmann and colleagues[114] and Kymes and colleagues.[115] The Fleischmann review[114] reported pooled data for SPECT from 27 studies, to arrive at estimates of sensitivity of 87% (95% CI 86 to 88%) and of specificity of 64% (95% CI 60 to 68%), although this has been criticised for pooling heterogeneous studies. Kymes and colleagues[115] reanalysed the same 27 studies using a random-effects model. This slightly improved the central estimates for sensitivity and specificity, 86.9% and 69.0% respectively, also increasing the uncertainty around these estimates to give confidence intervals of 83.3 to 89.8% for the sensitivity and 60.0 to 77.0% for the specificity of MPS.

Given these values for sensitivity and specificity, coupled with failure rates and unreadable scans, it seems clear that a diagnostic strategy using 64-slice CT as a non-invasive test is unlikely to be inferior in clinical effectiveness terms to a similar strategy using MPS as a non-invasive test. The costs of 64-slice CT also appear to be less than those of MPS, and as a consequence short-term diagnostic modelling will demonstrate that 64-slice CT is superior to MPS. In these circumstances there is little need to consider the downstream impact and longer term modelling as outlined by Patterson and colleagues[123] and by Mowatt and colleagues.[113]

The picture remains more complicated for a comparison of 64-slice CT and CA, given the gold-standard nature of CA. Despite the extremely high sensitivity of 64-slice CT and the associated ability virtually to rule out significant CAD in those testing negative, this still falls slightly short of the gold standard of CA. The somewhat poorer specificity also makes it unlikely in at least the short term that a positive result will be taken as confirmation of significant CAD being present. Confirmation of CAD through CA is likely to remain necessary for patients with a 64-slice CT positive result. Given this, a strategy involving 64-slice CT and CA is unlikely to outperform in every dimension one where only CA is used. While short-term modelling has been undertaken and will prove to be sufficient to form the main basis of conclusions, for completeness and to illustrate where future research needs might apply, a long-term model along the lines of Mowatt and colleagues[113] has also been undertaken. However, given the data uncertainties associated with this longer term modelling as outlined below, it should be viewed as illustrative rather than definitive.

Cost-effectiveness of 64-slice CT against MPS and CA: short-term diagnostic model

The test accuracies of the previous section can be summarised as in *Table 13*. All of the tests in *Table 13* take CA as the gold standard with 100% sensitivity and specificity, but also as having a small risk of death of around 150 per 100,000 tested. There is a considerable range of test accuracy values for both MPS and ECG, and there is no obvious reason to prefer one set of estimates to another. Simple averaging of these suggests the data shown in *Table 14*.

TABLE 13 *Test accuracies*

Source	Test	Sensitivity	Specificity	Indeterminate
Evaluation report	64-Slice CT	99%	89%	2%
Kymes, 2000[115]	MPS	87%	69%	–
Mowatt, 2004[113]	MPS	83%	59%	9%
	Exercise ECG (ETT)	66%	60%	18%
Kuntz 1999[119]	MPS	87%	64%	2%
	Exercise ECG (ETT)	68%	77%	30%

TABLE 14 *Scenarios in terms of test accuracies*

	Test	Sensitivity	Specificity	Indeterminate
Base case	64-Slice CT	99%	89%	2%
	CA	100%	100%	0%
	MPS	86%	64%	6%
	Exercise ECG	67%	69%	24%

A relatively simple short-term diagnostic decision-tree model similar to the literature in the preceding two sections was adopted for the assessment of the short-term performance of different diagnostic strategies, similar to those outlined above (see the sections 'Economic Literature review', p. 41 and 'Modelling the cost-effectiveness of MPS', p. 45).

Tests other than CA may be determinate or indeterminate. Where, for example, an image cannot be read or interpreted clearly these patients are referred to the next test in the sequence. If the test is determinate, a positive test result leads to referral to the next test in the sequence. If the test is determinate, a negative test result can be either a true negative or a false negative. CA, being an invasive procedure, is also associated with a small death rate.

A patient might undergo up to three tests within the diagnostic strategies: exercise ECG, followed by MDCT, MPS or CA, with MDCT or MPS in turn being followed by CA. For example, the test strategy of exercise ECG followed by MDCT followed by CA would be as shown in *Figure 18*.

Note that within this diagnostic strategy, given the assumed gold standard of CA there would be no false positives.

Current expert opinion suggests that all diagnostic test strategies would require CA as a final confirmation of diagnosis. However, this may in part be reflective of tests other than MDCT having a somewhat poorer sensitivity than CA. It may be envisaged, given the high sensitivity of MDCT, that this alone could be used as final confirmation of a diagnosis (although not enough for assessment for revascularisation) of CAD. As a consequence, in addition to the strategies where positive results are always finally confirmed by CA, two strategies where MDCT is the final test in the diagnostic pathway will be considered.

Strategies 4, 5 and 6 in *Table 15* mirror the first three strategies, only with there being no prior ECG, with strategy 8 similarly mirroring strategy 7. It should be noted that in some patients exercise ECG is not possible, for example those with arthritis or LBBB (*Table 15*). These are included not as accurate representations of current or possible service structure, but rather to present more clearly the cost-effectiveness of the main tests of interest in the absence of uncertainty as to the prevalence of CAD among those coming through from ECG. However, major uncertainties within the modelling remain as to the CAD prevalence in the population presenting for diagnosis and in the CAD prevalence among those being referred on from ECG for further diagnostic tests. One might expect that the proportion with CAD would increase after each positive test.

Strategies 7 and 8 represent a departure from the modelling of the literature, in that there will be some false positives within the diagnostic pathway. Note that within these it has been assumed that any indeterminate test results still go on to CA. The more speculative modelling suggests that among those deemed to be medium risk there is an annual 50% likelihood of undergoing revascularisation. However, these figures relate to previous diagnostic pathways within which there were no false positives. If the CAD prevalence in

TABLE 15 *Strategies involving comparators to 64-slice CT*

Test order	1st	2nd	3rd
Strategy 1	ECG	MPS	CA
Strategy 2	ECG	CT	CA
Strategy 3	ECG	CA	Nil
Strategy 4	MPS	CA	Nil
Strategy 5	CT	CA	Nil
Strategy 6	CA	Nil	Nil
Strategy 7	ECG	CT	Nil
Strategy 8	CT	Nil	Nil

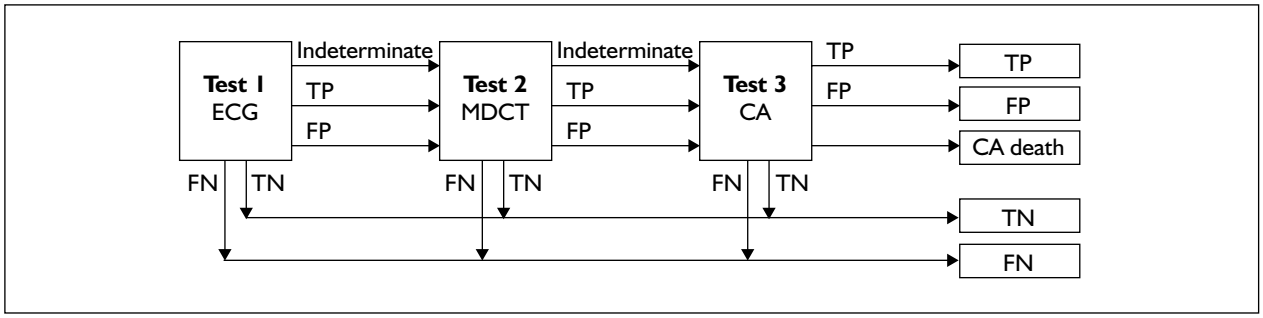


FIGURE 18 *Test strategy of exercise ECG followed by MDCT followed by CA*

the presenting group were relatively low, these false positives could make up a relatively large proportion of those given a positive diagnosis.

As noted above, a key clinical uncertainty relates to the prevalence of CAD in the relevant patient population. Shaw and colleagues,[125] in a study of 11,372 stable angina patients referred to MPS or CA for diagnosis, found in the CA group a prevalence of 57%, with those having CAD being split 41% medium risk and 59% high risk. However, this population seems likely to have already been tested with exercise ECG. If so, given the accuracy and indeterminacy rates for ECG as reported above, this would suggest a prevalence of around 50% in the population being referred to ECG. It is unclear what previous testing these patients may have had before being eligible for inclusion in the study,[125] which is also US based. The papers in the literature review have used a range of values, with Mowatt and colleagues[113] reflecting this and taking a base case of 10.5% CAD prevalence from the British Heart Foundation statistics for 50-year-old men, but varying this all the way up to 90% to reflect the underlying uncertainty as to the likely prevalence of CAD in those referred for diagnosis.

Within the short-term diagnostic model it is desirable that those with CAD are assessed as positive, and within the modelling strategies considered this would always lead to eventual CA. This is despite the very small death rate associated with CA. What is clearly undesirable from both a cost and clinical viewpoint is sending those without CAD for angiography. As a consequence, the death rates from these undesirable CAs are also reported in the results below. All results relate to a hypothetical cohort of 100 patients.

Costs of MPS, MDCT and CA were provided by Aberdeen Royal Infirmary, based on a bottom–up costing approach. Although capital costs for MPS and MDCT were similar between the two, with the £800,000 capital cost for 64-slice CT being in line with the range of £600,000 to £1.2 million reported by the Horizon Scanning Technology Briefing,[126] fewer MPS investigations could be performed per session. As a consequence, despite similar staff costs per session, the cost per MPS investigation was estimated at around £293 while the cost per 64-slice CT investigation was estimated at around £206.

CA was estimated as costing on average £320. Expert opinion indicated that around five CAs would be performed during each clinical session, the same as had been indicated for CT scans. The greater cost of CA largely arose from the increased staffing levels required. However, it may be possible that more CT scans could be performed within a session compared with CA.

The £293 per MPS investigation corresponds closely to the detailed bottom–up costing undertaken by Underwood and colleagues,[120] which when uprated to current prices using the Hospital and Community Health Services (HCHS) pay and prices index would correspond to £311. Underwood and colleagues derived 1996 costs from the average from a number of hospitals through a very detailed bottom–up costing where all resource use was itemised and costed (G. Mowatt, University of Aberdeen, 2007). Underwood and colleagues[120] also undertook a similar exercise for CA, which in current prices equates to £1556. Note that this is considerably higher than the current NHS reference costs for angiography within healthcare resource group (HRG) E02op, which are around £370, although it is not immediately clear whether these reference costs might also encompass coronary investigation techniques other than just invasive CA. Given this uncertainty, sensitivity analyses will be presented for the cost of CA.

NHS reference costs give a cost of £66 per exercise test which will be adopted for the modelling. This cost has little impact on the modelling, being common to strategies 1, 2, 3 and 7. Similarly, while strategies 4, 5, 6 and 8 do not involve this cost, the intention of modelling these strategies is not to permit a read across between them and strategies 1, 2, 3 and 7, but rather to illustrate more clearly the cost-effectiveness of 64-slice CT if the prevalence of CAD in those being referred on from ECG was known with greater certainty than it is at present.

The base case will assume the costs per test shown in *Table 16*, although given the uncertainty around the relative cost of CT and CA, a sensitivity analysis using higher costs of CA also will be performed.

TABLE 16 *Base-case costs per test*

Test	Cost	Source
Exercise ECG	£66	NHS reference costs
64-Slice CT	£206	Aberdeen Royal Infirmary
MPS	£293	Aberdeen Royal Infirmary
CA	£320	Aberdeen Royal Infirmary

Short-term diagnostic modelling: base-case results

The cost-effectiveness of the different diagnostic strategies is presented in *Table 17*. For the base case, as was anticipated given costs and clinical effectiveness results, the strategies involving 64-slice CT in place of MPS are superior in all dimensions. While 64-slice CT is cost-saving relative to MPS, this cost saving is gradually eroded as the prevalence of CAD increases in the presenting population. The considerably better specificity of 64-slice CT than MPS is of gradually less importance as the prevalence of CAD in the presenting population rises, since this increase implies that the number of false positives being wrongly sent for costly CA falls. However, as would be anticipated given costs and clinical effectiveness, a strategy with 64-slice CT is better in all dimensions than a strategy with MPS at the same point within the strategy.

Sending patients directly to CA without a 64-slice CT is more expensive for lower prevalences of CAD. When the prevalence of CAD is low, the CT scan with its high specificity manages to rule out CAD in a high percentage of patients, with the additional benefit of avoiding the admittedly small mortality risk associated with CA among these patients. However, as the prevalence of CAD rises, a greater proportion of patients are referred on to CA, with 64-slice CT ruling out CAD and the need for CA in fewer and fewer cases. Since 64-slice CT is not that much less expensive than CA in the base case, the prevalence of CAD does not have to be particularly high for 64-slice CT followed by CA to become more expensive than having all patients go straight to CA.

With regard to diagnostic accuracy, strategies with immediate CA also perform considerably better than their counterpart involving an interim MPS investigation, in large part because of the poor specificity of MPS. The same is not true with regard to the comparison with strategies involving 64-slice CT investigations. Sixty-four-slice CT results in extremely few false negatives, and as a consequence the number of true positives detected by strategies involving 64-slice CT is only marginally worse than those where patients are sent immediately to CA without an interim 64-slice CT investigation. Indeed, given the assumed death rate of 150 per 100,000 from invasive CA, it appears likely that the avoidance of deaths from CA among those without CAD given the reasonable specificity of 64-slice CT may be sufficient to outweigh the very marginally fewer number of true positives detected by strategies involving 64-slice CT.

The strategies where CT scanning is taken to be sufficient to form a diagnosis without the need for

TABLE 17 *Cost-effectiveness of the different diagnostic strategies*

Base case	Strategy							
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**
10% CAD prevalence								
TPs	6.50	7.41	7.48	8.67	9.89	9.99	7.42	9.90
FPs	0.00	0.00	0.00	0.00	0.00	0.00	4.61	9.70
CAD-negative deaths	0.03	0.01	0.06	0.05	0.02	0.14	0.00	0.00
Cost	£28,876	£21,085	£22,695	£43,553	£27,449	£32,000	£17,283	£21,240
30% CAD prevalence								
TPs	19.49	22.22	22.44	26.01	29.66	29.96	22.26	29.71
FPs	0.00	0.00	0.00	0.00	0.00	0.00	3.59	7.55
CAD-negative deaths	0.02	0.01	0.05	0.04	0.01	0.11	0.00	0.00
Cost	£33,430	£26,572	£24,446	£46,561	£32,969	£32,000	£18,445	£21,240
50% CAD prevalence								
TPs	32.48	37.04	37.40	43.35	49.44	49.93	37.09	49.51
FPs	0.00	0.00	0.00	0.00	0.00	0.00	2.56	5.39
CAD-negative deaths	0.01	0.00	0.04	0.03	0.01	0.08	0.00	0.00
Cost	£37,985	£32,058	£26,197	£49,569	£38,488	£32,000	£19,607	£21,240
70% CAD prevalence								
TPs	45.47	51.85	52.37	60.70	69.21	69.90	51.93	69.31
FPs	0.00	0.00	0.00	0.00	0.00	0.00	1.54	3.23
CAD-negative deaths	0.01	0.00	0.02	0.02	0.01	0.05	0.00	0.00
Cost	£42,539	£37,544	£27,948	£52,577	£44,007	£32,000	£20,770	£21,240

CA are around one-quarter to one-third less expensive than if those scanned as CT positive require CA. However, this is at the expense of considerable numbers of false positives at low CAD prevalences, and even at higher CAD prevalences the proportion of false positives is not insignificant. For the strategies where 64-slice CT replaces CA at the lower CAD prevalences of 10% and 30%, the additional treatment cost associated with a false positive would be £1100 and £1600, respectively, for the diagnostic cost advantage of 64-slice CT to be overturned by greater downstream costs from the treatment of false positives. For the higher CAD prevalence of 50%, this additional treatment cost associated with a false positive would have to rise to between £2000 and £2500 for the diagnostic cost advantage of 64-slice CT to be overturned by greater downstream costs from the treatment of false positives, while for a CAD prevalence of 70% the additional downstream cost of false positives would have to rise to over £4500.

In terms of the clinical impact, replacing CA with 64-slice CT has only a minor impact on the number of true positives detected. If the deaths associated with CA are factored in, 64-slice CT looks increasingly attractive. However, this applies only with regard to the diagnostic pathway, not the assessment one.

Sensitivity analysis: cost of CA

The cost of CA is one of the key inputs. Underwood and colleagues[120] suggest a considerably greater cost of £1556 as compared with the £320 of the base case. Taking a rough midpoint of these gives a cost per CA of £900, which results in the revised diagnostic strategy costs shown in *Table 18*. Although the performances of strategies with 64-slice CT before CA relative to those without are not particularly affected by this, there is an obvious major impact on the relative performance of 64-slice CT replacing CA. To render 64-slice CT strategies more expensive than CA, for a CAD prevalence of 10%, the additional cost of a false positive would have to be around £7000. For a CAD prevalence of 50% the corresponding range is £9000–10,000, while for CAD prevalences of 50% and 70% the ranges increase to £12,000–16,000 and £20,000–30,000.

Sensitivity analysis: poorer 64-slice CT test performance

Applying the lower confidence limit values for 64-slice CT for both its sensitivity (97%) and its specificity (83%) results in the costs as shown in *Table 19*. While this does not affect the superiority of 64-slice CT over MPS, it naturally causes 64-slice CT to perform slightly worse when set against those strategies in which no interim non-invasive test, MPS or 64-slice CT, is performed with patients going straight to CA. However, the differences remain relatively slight in terms of the number of true positives being diagnosed, particularly for lower CAD prevalences. The main impact is on the greater number of false positives that result from strategies in which 64-slice CT replaces CA.

Illustrative longer term modelling

The above short term diagnostic modelling suggests that given the high sensitivity of 64-slice CT, diagnostic strategies involving 64-slice CT are likely to be cost-effective for low CAD-prevalent populations as a negative test result means that unnecessary invasive CAs can be reliably avoided. Sixty-four-slice CT is anticipated to dominate strategies where it replaces MPS.

Illustrative longer term modelling can be undertaken to explore the possible effects of diagnosis and misdiagnosis for CAD for the diagnostic strategies with the greatest uncertainty around their relative cost-effectiveness: strategies 2, 3 and 7. This modelling follows the format of that presented in Mowatt and colleagues,[113] the model structure being presented in Appendix 9. Long-term model inputs are likewise mainly drawn from Mowatt and colleagues[113] as

TABLE 18 *Sensitivity analysis*

£900 per CA	Strategy							
	S1	S2	S3	S4	S5	S6	S7	S8
10% CAD prevalence	£42,540	£28,561	£51,866	£69,386	£39,864	£90,000	£17,866	£22,400
30% CAD prevalence	£52,444	£41,948	£56,791	£77,846	£55,387	£90,000	£19,092	£22,400
50% CAD prevalence	£62,347	£55,334	£61,716	£86,306	£70,910	£90,000	£20,318	£22,400
70% CAD prevalence	£72,251	£68,721	£66,641	£94,766	£86,433	£90,000	£21,543	£22,400

TABLE 19 *Sensitivity analysis: poorer 64-slice CT test performance*

Lower effectiveness	Strategy							
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**
10% CAD prevalence								
TPs	6.50	7.26	7.48	8.67	9.69	9.99	7.27	9.71
FPs	0.00	0.00	0.00	0.00	0.00	0.00	7.13	14.99
CAD-negative deaths	0.03	0.01	0.06	0.05	0.03	0.14	0.00	0.00
Cost	£28,876	£21,844	£22,695	£43,553	£29,080	£32,000	£17,283	£21,240
30% CAD prevalence								
TPs	19.49	21.78	22.44	26.01	29.07	29.96	21.82	29.12
FPs	0.00	0.00	0.00	0.00	0.00	0.00	5.55	11.66
CAD-negative deaths	0.02	0.01	0.05	0.04	0.02	0.11	0.00	0.00
Cost	£33,430	£27,057	£24,446	£46,561	£34,098	£32,000	£18,445	£21,240
50% CAD prevalence								
TPs	32.48	36.30	37.40	43.35	48.46	49.93	36.36	48.53
FPs	0.00	0.00	0.00	0.00	0.00	0.00	3.96	8.33
CAD-negative deaths	0.01	0.01	0.04	0.03	0.01	0.08	0.00	0.00
Cost	£37,985	£32,270	£26,197	£49,569	£39,115	£32,000	£19,607	£21,240
70% CAD prevalence								
TPs	45.47	50.83	52.37	60.70	67.84	69.90	50.90	67.94
FPs	0.00	0.00	0.00	0.00	0.00	0.00	2.38	5.00
CAD-negative deaths	0.01	0.00	0.02	0.02	0.01	0.05	0.00	0.00
Cost	£42,539	£37,483	£27,948	£52,577	£44,133	£32,000	£20,770	£21,240

summarised in Appendix 10, although the costs of MI, PTCA and CABG are taken from NHS reference costs.

The short-term diagnostic model results in patients being true negatives who are deemed to be at low risk, true positives, false negatives or false positives. Note that in strategies with CA, there are no false positives since all positive test results will, if they remain positive from interim tests, eventually face CA, which will identify false positives and correctly classify them as true negatives. Those with CAD, whether true positives or false negatives, are roughly equally split between being high risk and being medium risk, based on the results of Shaw and colleagues,[125] that around 41% of those with CAD had single-vessel disease and 59% had multiple-vessel disease or left main disease. Note that a key underlying assumption of the longer term modelling is that the sensitivities and specificities of tests do not vary across disease severity. While a simplifying assumption, this may to some extent underestimate the cost-effectiveness of strategy 2 to the extent that 64-slice CT is more likely to detect high-risk disease and result in the immediate treatment of those at most risk.

In common with the short-term modelling, the effect of a higher CA cost and of the lower CI effectiveness bound of 64-slice CT can be explored. Note also that the base case assumes that correct diagnosis of false negatives only occurs after an event. This is partly unrealistic because some patients will present again with symptoms, given that they will not be receiving the ideal treatment. As a consequence, the effects of this can be explored by an arbitrary assumption of an annual 10% rediagnosis rate among false negatives.

Table 20 shows the longer term modelling results over a 25-year time-horizon. From the base case, in clinical effectiveness terms strategies 2 and 3 are effectively identical, strategy 3 being only marginally inferior owing to the slightly higher death rate from the initial CA diagnoses.

Higher costs for CA affect the analyses as would be anticipated, increasing the anticipated savings from strategy 7 to around £300 per patient at the low CAD prevalence, this increasing in line with the base case to around £400 per patient at the higher CAD prevalence. As with the short-term modelling, while the lower CI bound for the effectiveness of 64-slice CT leads to a lower aggregate QALY, given the tightness of the CIs the impact of this is limited. Similarly, if patients wrongly diagnosed as being of low risk return with symptoms, and are reclassified correctly as being of higher risk and treated accordingly, this tends

TABLE 20 *Longer term modelling: base case*

	Base case		Higher CA cost		Lower CT effect		Re-presentations	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	Cost	QALYs
10% CAD prevalence								
S2	£616,732	1060.5	£624,208	1060.5	£617,104	1060.4	£619,099	1061.3
S3	£618,196	1060.0	£647,367	1060.0	£618,196	1060.0	£620,496	1060.7
S7	£618,629	1056.9	£618,629	1056.9	£620,972	1055.0	£620,996	1057.6
30% CAD prevalence								
S2	£642,800	1005.2	£658,176	1005.2	£642,174	1004.8	£649,901	1007.4
S3	£640,966	1005.0	£673,311	1005.0	£640,966	1005.0	£647,865	1007.1
S7	£639,186	1002.6	£639,186	1002.6	£640,195	1000.8	£646,288	1004.8
50% CAD prevalence								
S2	£668,868	949.9	£692,144	949.9	£667,245	949.2	£680,704	953.6
S3	£663,736	949.9	£699,255	949.9	£663,736	949.9	£675,235	953.5
S7	£659,743	948.3	£659,743	948.3	£659,418	946.6	£671,579	952.0
70% CAD prevalence								
S2	£694,935	894.6	£726,112	894.6	£692,316	893.6	£711,506	899.7
S3	£686,506	894.9	£725,199	894.9	£686,506	894.9	£702,605	899.9
S7	£680,300	894.0	£680,300	894.0	£678,640	892.4	£696,871	899.1

to reduce any differences between the diagnostic strategies in terms of patient impact.

Economic considerations for chest pain admissions and diagnosis of ACS

Patients presenting with chest pain but with negative initial cardiac biomarkers and negative ECG results may be admitted for observation and repeat tests. The immediate availability of 64-slice CT within a 24-hour emergency department setting may reduce the likelihood of admission. Variable availability of CT through the day would reduce the scope for reducing admissions.

Among those admitted for observation for 24 hours, with twice negative troponin tests, 64-slice CT could be used to rule out the need for CA, possibly in place of or subsequent to an exercise test. The European Society of Cardiology recommends that among low-risk patients with twice negative troponin tests, only those showing significant ischaemia during an exercise test should be considered for CA. While formal estimates of the sensitivity and specificity of 64-slice CT are not available for such circumstances, it appears likely that the performance of 64-slice CT may be superior to that of exercise testing. Paralleling the conclusions as to the diagnosis of CAD, if exercise ECG has a poor specificity in this setting and if the prevalence of ACS is also low among those with twice negative troponin tests, as seems reasonable to conclude, the introduction of 64-slice CT before CA may reduce costs through the avoidance of unnecessary CA. Provided that its sensitivity is no worse than that of the exercise test in these circumstances, patients could also benefit from its introduction. However, MPS could perform a similar role, and it is not clear which if either would necessarily be superior in this setting.

Discussion

Sixty-four-slice CT appears to be superior to MPS for the diagnosis of CAD in all clinical dimensions and also in terms of cost. As a consequence, diagnostic strategies involving 64-slice CT in place of MPS appear to be cost-effective in the short term.

The high sensitivity and NPV of 64-slice CT suggest scope for avoiding unnecessary CAs in those referred for investigation but who do not have CAD. Given the invasive nature of CA and a possible, although small, associated death rate, avoiding these unnecessary CAs through the use of 64-slice CT may also confer a small immediate survival advantage. This in itself may be sufficient to outweigh the marginally inferior rates of detection of true positives by strategies involving 64-slice CT.

The avoidance of unnecessary CAs through the use of 64-slice CT may result in cost savings even if positive results still require confirmation by CA. However, as the prevalence of CAD in the presenting population increases, so the cost of CA relative to that of 64-slice CT has to rise for this to remain the case.

If 64-slice CT can displace CA in the diagnostic pathway, it is likely that the average diagnostic cost per patient can be reduced by around one-quarter to one-third. Given the sensitivity of 64-slice CT, there is only a very minor clinical difference in terms of the number of patients with CAD who are wrongly diagnosed as being of low risk. The principal difference in strategies where 64-slice CT scanning replaces CA is in the number of false positives. These would only matter if they were treated medically, since those referred for assessment for revascularisation would be correctly diagnosed at angiography. However, some apparently treated successfully by medical treatment alone would be receiving unnecessary treatment and incur unnecessary anxiety.

In conclusion, the main value of 64-slice CT may be to rule out significant CAD both in the elective investigation of suspected CAD and in those presenting with acute chest pain.

Chapter 4
Discussion

Statement of principal findings

The included diagnostic accuracy studies reported the sensitivity and specificity of multislice CT angiography using 64-slice or higher machines for detecting CAD compared with invasive CA as the reference standard. Studies that reported true and false positive and negative results or provided information that allowed these data to be calculated were included in the pooled estimates (meta-analyses). Almost all studies used a cut-off for significant CAD of greater than 50% or at least 50% stenosis, allowing a common cut-off to be used for studies included in the pooled estimates.

Meta-analyses were performed on a number of different levels:

- patient
- segment
- left main artery
- LAD artery
- proximal LAD artery
- LCX artery
- RCA
- stents or stented segments
- CABGs.

Although segmental analysis is useful to validate the accuracy of the test, patient-level data are more useful in determining management. In the pooled estimates, 64-slice CT angiography was highly sensitive (99%, 95% CrI 97 to 99%) for patient-based detection of significant CAD, while across studies the median NPV was very high (100%, range 86 to 100%). These results suggest that one of the potential benefits of 64-slice CT angiography may be to avoid the use of invasive CA in people with a low pretest probability of CAD who have negative/low-risk CT scans. In the 13 full-text studies included in the pooled estimates for patient-based detection of CAD, 11 (2%) of 718 patients could not be assessed owing to unevaluable CT scans (median 0%, range 0 to 6%). Two studies[65,85] reported that all vessels were analysed including those less than 1.5 mm in diameter, while three studies[79,93,94] reported that all vessels of less than 1.5 mm were excluded from analysis.

The studies included in the pooled estimates were heterogeneous with respect to the participants and prevalence of significant (≥50% stenosis) CAD. In some studies the whole patient population had suspected CAD, in others known CAD or a mixture of suspected and known CAD, in others acute chest pain, had previously undergone PCI or CABG, had LBBB or had all been referred for cardiac valve surgery. The median prevalence of significant CAD across these studies was 58% (range 23 to 96%). Nevertheless, there was no substantial statistical heterogeneity across the studies as assessed by the I^2 statistic (I^2 for sensitivity = 0.1%; I^2 for specificity = 31.7%), where a value above 50% is considered to represent substantial statistical heterogeneity.

The overall quality of the full-text diagnostic accuracy studies was reasonably good. This was partly due to the review's strict inclusion criteria. Only studies in which results were reported for participants who received both 64-slice or higher CT angiography (index test) and a reference standard of either invasive CA or long-term follow-up were included. In some studies only some of the participants received both the index test and reference standard and it was these participants whose results were included, rather than the whole patient population. In all studies the reference standard was considered likely to classify CAD correctly. In 85% of studies those interpreting 64-slice CT data were blinded to the results of the reference standard test and in 71% of studies vice versa. In 48% of studies the participants belonged to specific groups, for example those with LBBB, or who had undergone previous PCI or CABG, or who had been referred for cardiac valve surgery. While this would cause a problem with spectrum bias if the results of these studies were applied to all who may receive CT angiography, their data are nevertheless useful when considering the specific groups studied, for example in excluding the presence of significant CAD in patients before scheduled aortic valve replacement.

In segment-level analysis compared with patient-based detection, sensitivity was lower (90%, 95% CrI 85 to 94%, versus 99%, 95% CrI 97 to 99%) and specificity higher (97%, 95% CrI 95 to 98%,

versus 89%, 95% CrI 83 to 94%), while across studies the median NPV was similar (99%, range 95 to 100%, versus 100%, range 86 to 100%). At individual coronary artery level diagnostic accuracy was highest for the left main artery and lowest for the LCX artery. Sensitivity ranged from 85% (95% CrI 69 to 94%) for LCX to 95% (95% CI 84 to 99%) for the left main artery, specificity ranged from 96% for both LAD (95% CrI 91 to 98%) and LCX (95% CrI 92 to 99%) to 100% (95% CI 99 to 100%) for the left main artery, while across studies the PPV ranged from 81% (range 56 to 100%) for the LCX to 100% (range 90 to 100%) for the left main artery and NPV was very high, ranging from 98% for the LAD (range 95 to 100%), LCX (range 93 to 100%) and RCA (range 94 to 100%) to 100% (all five studies) for the left main artery. For the proximal LAD artery analysis sensitivity was 97% (95% CrI 87 to 99%) and specificity was 97% (95% CrI 90 to 99%), while across studies the median PPV and NPV were 95% (range 85 to 100%) and 98% (range 90 to 100%), respectively. Diagnostic accuracy was higher for analysis of CABGs, with 99% (95% CrI 95 to 100%) sensitivity and 96% (95% CrI 86 to 99%) specificity, while across studies the median PPV and NPV were 93% (range 90 to 95%) and 99% (range 98 to 100%), respectively. Given that data are reported and analysed at levels in addition to the patient level and that a number of studies contributed data to more than one level of analysis, some degree of correlation may exist between the results for the different levels of analysis.

Although there are suggestions that imaging of stents is improving with greater experience and better machines, in the included studies assessment of stents caused some problems for 64-slice CT. In the pooled estimates sensitivity was 89% (95% CrI 68 to 97%) and specificity 94% (95% CrI 83 to 98%), while across studies the median values for PPV and NPV were 77% (range 33 to 100%) and 96% (range 71 to 100%), respectively. In the study by Leber and colleagues[58] four of nine stents without any restenosis on invasive CA were diagnosed as having greater than 50% restenosis on 64-slice CT, owing to artefacts caused by the dense stent material. In the study by Rixe and colleagues,[89] 30 of 31 stents with a diameter of at least 3.0 mm that were classified as unevaluable were of a type with a strut thickness of 0.14 mm, while only one with a strut thickness of 0.13 mm was classified as unevaluable. Rist and colleagues[86] noted that the cases in which image quality was considered poor or moderate typically involved patients fitted with small-diameter stents in distal segments of the coronary arteries, and that 3.5 mm was a threshold below which the rate of evaluable stents was very low. Therefore, although the performance of 64-slice CT for identifying in-stent restenosis was reasonably good, it may vary according to the type, diameter and location of the stent.

Coronary artery calcification caused some 64-slice CT scans to be either unevaluable or misclassified. Ong and colleagues[75] reported that 48 (6%) of 748 segments with AS below 142 were not evaluable, compared with 95 (13%) of 726 segments with AS of 142 or above. Although in the study by Ghostine and colleagues[52] no segment was excluded from analysis owing to calcification, the authors reported that heavily calcified segments accounted for 21 (81%) of 26 false-negative results. Raff and colleagues[85] reported 14 (2%) false positives in 709 segments with a calcium rating of none, five (6%) false positives in 89 segments rated as mild, six (13%) false positives in 48 segments rated as moderate and 16 (18%) false positives in 88 segments rated as severe. Other studies cited coronary calcification as a cause of unevaluable CT scans.[45,46,93,94,99,100,102] Therefore, some patients with severe coronary artery calcification may be considered less suitable for 64-slice CT angiography.

Five studies (one full text[55] and four reported as abstracts[95,105–107]) provided information on the prognostic usefulness of 64-slice CT angiography, with three reporting patients with suspected ACS, although with only short-term (mostly 30-day) follow-up. Hoffmann and colleagues[55] concluded that 64-slice CT angiography had very good negative predictive value for the subsequent diagnosis of ACS in the short term. Gallagher and colleagues[107] reported that patients with chest pain, with negative 64-slice CT and MPI scans (n = 52) who were discharged, experienced no adverse cardiac events during a 30-day follow-up. Rubinshtein and colleagues[95] reported that taking account of 64-slice CT angiography had led to a revised diagnosis in 14 (50%) of 28 chest pain patients, hospitalisation cancelled in 15 (44%) of 34 and early invasive CA postponed in 16 (67%) of 24, but brought forward in one (6%) of 16 patients. At 30-day follow-up there were no adverse cardiac events in the 15 patients discharged on the basis of negative or low-risk 64-slice CT findings. Of the other two studies, Auseon and colleagues[105] reported that, in the year following the introduction of 64-slice CT compared with the previous 4 years, the yearly

rates of increase in diagnostic catheterisation volume and percutaneous interventions had not been significantly affected. Danciu and colleagues[106] reported that in the first 6 months following the introduction of 64-slice CT, invasive CA had been avoided in 398 (82%) of 486 patients.

Some invasive CA may also potentially be avoided in the prognostic assessment of patients with known CAD. Once CAD has been confirmed, medical management may or may not relieve symptoms. If it does not, patients are usually referred for potential revascularisation as in *Figure 4* (p. 9). If symptoms are relieved by medical management, revascularisation may still be of value on prognostic grounds, in those with proximal disease, such as left main, LAD or triple-vessel disease. At present prognosis is assessed by an ETT (those who can exercise using the Bruce protocol for over 6 minutes without symptoms or ECG changes being unlikely to have prognostically poor patterns of disease) or by invasive CA. Given the very good performance of 64-slice CT in detecting proximal disease, CT provides another option in this group of patients. In the absence of significant proximal CAD, patients with well-controlled symptoms could receive medical management rather than revascularisation.

Sixty-four-slice CT angiography may have the potential to replace some perfusion scanning tests. In two systematic reviews[113,114] of SPECT MPS, sensitivity was reported as a median of 81% across studies (range 63 to 93%)[113] or pooled estimate of 87% (fixed-effect model, 95% CI 86 to 88%),[114] while specificity was reported as a median of 65% across studies (range 10 to 90%)[113] or pooled estimate of 64% (fixed-effect model, 95% CI 60 to 68%).[114]

In conclusion, for patient-based detection of significant (≥50% stenosis) CAD, the high sensitivity in the pooled estimates and the high NPV across studies suggest that one of the major potential benefits of 64-slice CT could be that of avoiding invasive CA in people with negative/low-risk CT scans. The high NPV values in the diagnostic studies appear to be supported by the few prognostic studies that followed up patients discharged from hospital on the basis of negative/low-risk 64-slice CT scans, although these results need to be interpreted with caution as they were based on short-term (mostly 30-day) follow-up and from only five studies, four of which were reported as abstracts.

Cost-effectiveness

Sixty-four-slice CT angiography appears to be superior to MPS for the diagnosis of CAD in all clinical dimensions and also in terms of cost. As a consequence, diagnostic strategies involving 64-slice CT in place of MPS appear to be cost-effective in the short term. This short-term diagnostic cost-effectiveness will carry through to improved patient outcomes, and with the proviso that treatments for CAD are cost-effective diagnostic strategies involving 64-slice CT in place of MPS will also be more cost-effective in the longer term.

Given the high sensitivity of 64-slice CT, diagnostic strategies involving it have an almost identical PPV to those where there is no interim non-invasive test and patients are sent directly for invasive CA. The reasonably high specificity of 64-slice CT also avoids the costs of unnecessary invasive CAs in those referred for investigation but who do not have CAD. Given the invasive nature of CA and a possible, although small, associated death rate, avoiding these unnecessary CAs through the use of 64-slice CT may also confer a small immediate survival advantage on the presenting population. This in itself may be sufficient to outweigh the marginally inferior rates of detection of true positives by strategies involving 64-slice CT.

The avoidance of unnecessary invasive CAs through the use of 64-slice CT also appears likely to result in overall cost savings in the diagnostic pathway. Only if both the cost of invasive CA is relatively low and the prevalence of CAD in the presenting population is relatively high is it likely that the use of 64-slice CT in the diagnostic pathway will result in a higher overall diagnostic cost per patient.

Longer term illustrative modelling indicates that strategies involving 64-slice CT are likely to be cost-effective options, but considerable uncertainties surround this modelling, as outlined in the previous section.

Provided that within the population presenting to 64-slice CT the prevalence of CAD is not too high, owing to either a high general population prevalence or extremely accurate exercise testing, and that 64-slice CT is a reasonable amount cheaper than invasive CA, the short-term diagnostic model enables the conclusion that 64-slice CT is likely to be a cost-effective option in the diagnosis of CAD.

Strengths and limitations of the review

In terms of strengths, the reference standard – invasive CA – was the same for all of the included diagnostic studies, and only the results for people who received both tests were included in the meta-analyses, thereby avoiding partial and differential verification bias. Meta-analyses were undertaken on a number of different levels, including patient, segment and individual artery level, as well as for stents/stented segments and CABGs. In terms of limitations, non-English-language studies were excluded. Only five studies (four of which were abstracts) reported the prognostic usefulness of 64-slice CT angiography, with only short-term (mostly 30-day) follow-up.

The lack of outcome data makes modelling inevitably speculative. Ideally, we would have data on outcomes from all the arms of the diagrams in Chapter 1 (*Figures 1–5*). For example, the outcomes in patients who would be false negatives are not known. If their CAD progresses, they may present again and be correctly diagnosed, in which case little harm has been done. However, they may suffer a fatal heart attack and die, leading to life-years lost.

Uncertainties

When considering whether 64-slice CT may replace some invasive CA, one issue to bear in mind is that the technical factors that enhance image quality in 64-slice CT also result in a higher radiation dose compared with invasive CA. This has resulted in concerns being raised about repetitive use of 64-slice CT or use in younger individuals or women of childbearing age.[127]

For MSCT, radiation dose depends on X-ray tube voltage, current, scan time, speed of table movement and the number of overlapping adjacent scans.[128] Retrospective ECG gating is used to obtain images during the diastolic phase of the cardiac cycle, when motion is least. Using ECG-controlled dose modulation reduces the tube current during the less important systolic phase, when motion is greatest, resulting in a 30–50% reduction in the effective radiation dose.[7] However, dose modulation may not be appropriate for certain categories of patients, such as those with arrhythmias or fast heart rates, for whom it may be necessary to obtain images throughout the cardiac cycle without loss of image quality.[77] Effective dose is an estimate of the whole-body dose that would be required to produce the same risk as partial-body dose delivered by a localised radiological procedure.[128]

A systematic review by Stein and colleagues[9] quoted an effective radiation dose of 11–22 mSv for 64-slice CT angiography, which could be reduced to 7–11 mSv by using ECG-controlled dose modulation. A study by Hausleiter and colleagues[8] on multislice CT radiation dose estimates reported an effective radiation dose of 11.0 (SD 4.1) mSv for 64-slice CT. In a subgroup analysis, effective radiation dose was reduced from 14.8 (SD 1.8) mSv to 9.4 (SD 1.0) mSv by using ECG-controlled dose modulation.[8] Effective dose values quoted for invasive CA include less than 5 mSv by a British Cardiovascular Society Working Group,[12] 4–8 mSv by the TEC[10] and 5–10 mSv by the International Commission on Radiological Protection (ICRP).[129] The ICRP[129] also quotes typical effective doses of 13–16 mSv for sestamibi MPI and 35–40 mSv for thallium MPI. By comparison, the average yearly effective dose of background radiation is around 2.5 mSv.[9] The ICRP states that the maximal yearly effective dose of radiation should not exceed 50 mSv in radiation workers or 100 mSv over 5 years.[129]

In this review 12 full-text studies reported 64-slice CT radiation dose, with six studies[52,55,56,58,71,86] providing information for the patient group as a whole and six[65,66,83,85,93,94] reporting men and women separately. Across the studies reporting this information for the patient group as a whole, the CT radiation dose ranged from 6–11 mSv[55] to 10–14 mSv,[58] with all studies using ECG-controlled dose modulation. In studies reporting CT radiation dose separately for men and women, women tended to receive a higher dose. Across these studies the radiation dose ranged from 7.5 mSv[93] to 15.2 mSv[65,66] for men and from 10.2 mSv[94] to 21.4 mSv[65,66] for women. Only two of these studies[93,94] used ECG-controlled dose modulation, reporting an estimated radiation dose of 7.5 mSv[93] and 8.6 mSv[94] for men and 10.2 mSv[93] and 12.2 mSv[94] for women. Across the four studies not using dose modulation, the radiation dose ranged from 13 mSv[85] to 15.2 mSv[65,66] for men and from 18 mSv[85] to 21.4 mSv[65,66] for women. In total, 11 full-text studies[52,55,56,58,71,75,77,86,89,93,94] used ECG-dependent dose modulation, five[59,65,66,83,85] did not, and the remainder, and all studies reported as abstracts, did not report this information.

Motion artefact remains a problem with heart rates above 70 bpm, although β-blockers can be used to reduce the heart rate in an attempt to minimise this. Across 16 included studies reporting the average heart rate during the CT scan, this ranged from 58 to 72 bpm. In studies reporting whether or not β-blockers were given, 140 (32%) patients were already on β-blocker treatment, 184 (42%) were given β-blockers to reduce heart rate and 113 (26%) did not receive β-blockers.

Increased image noise associated with the thinner slices from 64-slice CT may adversely affect test accuracy in obese patients. However, only one of the included studies reported test performance according to patient weight. Raff and colleagues[85] reported patient-based detection of significant (> 50% stenosis) CAD for patients with a BMI of 30 or greater (obese) compared with those with BMI below 25 (normal). For the BMI 30 or greater group compared with the BMI below 25 group, sensitivity was 90 versus 100%, specificity was 86 versus 100%, PPV was 90 versus 100% and NPV was 86 versus 100%.[85] None of the included studies mentioned weight as an exclusion criterion and none, other than Raff and colleagues, raised the issue of weight in the discussion sections of their reports.

Calcification in the coronary arteries would often be a problem, and as one of this review's anonymous referees pointed out, those with high levels of calcification such as elderly people with diabetes are often not included in trials.

One issue to be considered is the cut-off used to describe significant CAD, usually 50% and occasionally 70% stenosis. These figures are based on the degrees of stenosis at which lesions are thought to be of potential functional significance and where revascularisation may be indicated. However, these figures are based on two outcomes: relief of anginal symptoms, and reduction in mortality in those with patterns of CAD associated with the poorest prognosis, such as left main stem disease.

Sixty-four-slice CT would also show lesser degrees of stenosis, and could therefore influence management other than revascularisation. For example, a patient with 30% stenosis may receive lifestyle advice, a statin, and perhaps intensified control of blood pressure or blood glucose. Several studies have reported regression of CAD after statin treatment, although usually modest.[126,127]

64-Slice CT angiography in the detection of non-calcified plaques

It is thought that MI usually follows the rupture of an atheromatous plaque, and that the plaques most likely to rupture are soft, lipid-rich non-calcified ones. Most patients with such plaques will have other evidence of arterial disease, but Hausleiter and colleagues[53] reported that in a small proportion, non-calcified plaques were the only sign of CAD. They carried out 64-slice CT angiography in 161 patients who were considered to be at moderate risk of significant CAD, based on having chest pain with negative stress tests, or positive stress tests without chest pain, or neither but with intermittent arrhythmias. Of these patients, 98 had coronary calcifications and 63 did not. Ten of the 63 (6.2% of the whole group) had non-calcified plaques. Such plaques were also seen in 38 of the 98 patients with calcifications. Only 23 of the group had invasive CA, but it was noteworthy that most of the non-calcified plaques caused less than 50% stenosis. There were 40 non-calcified plaques in these 23 patients and about half caused only minor wall irregularities, with less than 25% stenosis. Nine had stenosis between 25% and 50% and 11 had greater than 50% stenosis and were treated by PCI.

Chin and colleagues[130] also studied vulnerable plaques in a mixed group of patients who had stable angina, unstable angina or non-ST elevated MI, and ST-elevated MI. They hypothesised that the 'culprit' lesions might have lower density, because of lower calcification and overlying thrombus, and developed a measure of vessel density. They confirmed that culprit lesions had lower density. Chin and colleagues also noted that 25% of culprit lesions were associated with less than 50% stenosis. They suggested that further research was needed into how best to use CT to examine plaque morphology.

There are two implications from these studies. The first is that invasive CA is not quite a gold standard, and will miss some vulnerable plaques on which coronary thrombosis can occur. Secondly, advances in CT technology now allow the identification of vulnerable plaques. Neither paper gave details of time and other costs.

256-Slice machines

CT technology is advancing rapidly and the first 256-slice machines are now arriving. It is perhaps

too early to say whether 256-slice machines will carry a significant marginal benefit over 64-slice machines. Only one study[68] included in this review used a 256-slice machine (Toshiba prototype), involving ten patients. In segment-based detection of significant (>50% stenosis) CAD, when segments with severe calcification were excluded from analysis, sensitivity, specificity, PPV and NPV were 100%, 96%, 73% and 100%, respectively.[68] By comparison, in the pooled estimates for 64-slice CT segment-based detection of significant CAD, sensitivity and specificity were 90% (95% CrI 85 to 94%) and 97% (95% CrI 95 to 98%), respectively, while across studies the median PPV and NPV were 76% (range 44 to 93%) and 99% (range 95 to 100%), respectively.

Implementation issues

If 64-slice CT were to be used in people with acute chest pain, it would need to be readily available, ideally 24 hours a day. This would have implications for radiographer staffing and the expertise of on-call radiologists. It is unlikely that all on-call radiologists would have experience in cardiac CT, except in some very large hospitals with subspecialty interests. An on-call registrar would be unlikely to have the expertise. Overnight admissions with early-morning CT followed by discharge after a cardiologist ward round may be a more realistic scenario. That would reduce the savings, as would any increased on-call service.

It is likely that more centres will provide immediate angioplasty for MI in future,[131] which may mean that immediate angiography is more readily available than immediate CT.

The effect of replacing an invasive with a non-invasive test needs to be considered, since demand may increase. A recent example has been the introduction of CT pulmonary angiography; far larger numbers of CT pulmonary angiography studies are done than of the invasive conventional pulmonary angiography which preceded it (G. Walsh, Royal Berkshire Hospital: personal communication, 2007). Increased use may negate any cost savings from reducing angiography.

Acceptability to patients may be an issue for two reasons. One is the radiation dose. The other is claustrophobia; not all patients would be willing to enter the scanner.

Chapter 5
Conclusions

Implications for practice

The proportion of invasive CA that could be replaced by 64-slice CT is currently uncertain. Further information is needed on current CA workload. Reduction in CA would be mainly at the diagnostic end of the pathway, both in elective assessment of chest pain of possibly anginal origin, and in emergency assessment of suspected acute coronary syndromes in patients with normal or equivocal ECGs and negative troponin tests. In the emergency situation, some hospital admissions may be avoided; however, 64-slice CT would need to be readily available, ideally on a 24-hour basis, which is unlikely to be the case in most hospitals.

Some perfusion studies could be replaced by 64-slice CT angiography.

Assuming that the NHS does invest in more modern CT machines, one issue is whether to acquire 64-slice machines or wait until 256-slice machines become available. Evidence on 256-slice CT is currently sparse, but the review of publications in Chapter 1 showed that the pace of research is brisk, and it is likely that evidence on the next generation will be available within 18 months or so. It is very unlikely that performance would be less good, and if the cost difference between 64-slice and 256-slice machines was small, it could be argued that the NHS should bypass 64-slice machines in favour of 256-slice ones. However, the pace of change will create difficulties in decision-making on replacing old CT systems; no matter what a radiology department buys, there will be something better coming along in a year or two, although the marginal costs and benefits will be unknown. There must come a time when the extra data do not provide additional clinical benefit, but it is unclear when that point will be reached.

Recommendations for research

As previously noted, CT technology is advancing rapidly and the first 256-slice machines are arriving. Studies are required of their marginal advantages and costs over 64-slice CT. Because of its newness most information available on 256-slice CT is commercial in origin. One of the main potential advantages of 256-slice machines is that of obtaining all the necessary information on one cardiac cycle, resulting in faster scans, avoiding problems with ECG gating, and delivering a lower radiation dose (which may be particularly important if CT was to be used as a screening test in relatively low-risk populations).

More research is needed on the usefulness of 64-slice CT in people with suspected ACS, in terms of both diagnostic accuracy and prognostic value, with a follow-up of at least 1 year for prognostic studies. It would also be important to show the additional value, if any, of 64-slice CT in this setting over and above standard methods of risk stratification. This review identified only a few studies, mostly reported as abstracts, containing very small numbers of patients, most of whom were low risk and would be expected to have low event rates. In addition, the results of prognostic studies involving patients with suspected ACS were based on only short-term (mostly 30-day) follow-up.

There have been a few reports on the potential of 64-slice CT to examine plaque morphology, and more research is needed here, although whether that should be done using 64-slice machines or the emerging 256-slice ones is for debate.

The role of CT in identifying patients for CABG needs further research. CT can identify stenoses, but research is needed into its ability to identify distal insertion sites and adequacy of run-off. Such research may be done by carrying out CT in a large group of patients before CABG (with preceding invasive CA), with assessment of suitability for CABG by observers unaware of the invasive CA results and arterial findings at CABG.

In deciding patient selection criteria, research studies involving 64-slice or higher CT angiography should take account of concerns raised about repetitive use, or use in younger individuals or women of childbearing age.

Few of the studies so far have looked at effects on outcomes. Most have been at stage 2 in the Fryback and Thornbury classification.

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Contribution of authors

Graham Mowatt (Research Fellow) screened the search results, assessed full-text studies for inclusion, undertook data extraction and quality assessment, drafted the chapter on clinical effectiveness and coordinated the review. Ewen Cummins (Honorary Senior Research Fellow) drafted the chapter on the economic appraisal and economic literature review. Norman Waugh (Professor of Public Health) prepared the protocol, drafted the background chapter and commented on drafts of other chapters. Shonagh Walker (Specialist Registrar in Radiology) helped to draft part of the background chapter, provided expert advice and commented on drafts. Jonathan Cook (Statistician) drafted the data analysis section of the review, conducted the statistical analysis and commented on drafts. Xueli Jia undertook data extraction and quality assessment, helped to draft parts of the chapter on clinical effectiveness and commented on drafts. Graham Hillis (Senior Lecturer in Cardiology) provided expert advice and commented on drafts. Cynthia Fraser (Information Officer) developed and ran the search strategies, obtained papers and formatted the references. All authors assisted in preparing the manuscript, reading and commenting on drafts, and reading the final draft.

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129. International Commission on Radiological Protection. *Managing patient dose in multi-detector computed tomography (MDCT)*. Draft consultation document 2006-12-11 [document on the Internet]. International Commission on Radiological Protection; 2006. URL: http://www.icrp.org/docs/ICRP-MDCT-for_web_cons_32_219_06.pdf. Accessed March 2007.

130. Chin SP, Ong TK, Chan WL, Liew CK, Seyfarth MT, Alan FYY, *et al*. 64-Row multi-dector computed tomography coronary image from a center with early experience: first illustration of learning curve. *J Geriatr Cardiol* 2006;**3**:29–34.

131. Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica MR, *et al*. Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation. *Health Technol Assess* 2003;**7**(15).

Appendix 1

Search strategies

Clinical effectiveness

Search strategies used to identify reports of clinical effectiveness of MSCT for CAD.

MEDLINE (2002 to November week 3 2006), EMBASE (2002 to week 49 2006), Medline In-Process (14 December 2006)

Ovid Multifile Search URL:
http://gateway.ovid.com/athens

1 exp myocardial ischemia/ use medf
2 exp ischemic heart disease/ use emef
3 exp coronary artery disease/
4 exp myocardial infarction/
5 exp chest pain/
6 coronary artery blood flow/ use emef
7 (isch?emi$ adj3 (heart or coronary or myocardial)).tw.
8 ((myocardial or coronary or heart) adj3 (infarct$ or thrombosis or stenosis or restenosis or arteriosclerosis or arter$)).tw.
9 angina.tw.
10 (chest adj3 pain).tw.
11 or/1-10
12 tomography, x-ray computed/ use medf
13 tomography, spiral computed/ use medf
14 computer assisted tomography/ use emef
15 computed tomographic angiography/ use emef
16 electron beam tomography/ use emef
17 high resolution computer tomography/ use emef
18 spiral computer assisted tomography/ use emef
19 or/12-18
20 (detector? or slice? or slide? or row?).tw.
21 19 and 20
22 multidetector computed tomography/ use emef
23 (msct or mdct).tw.
24 (multi slice? or multislice?).tw.
25 (multi row? or multirow?).tw.
26 (multi slide? or multislide?).tw.
27 (multi detect$ or multidetect$).tw.
28 (tomograph$ adj5 (multi$ or slice? or row? or slide? or detector?)).tw.
29 or/21-28
30 11 and 29
31 exp coronary angiography/
32 ((coronary or myocardi$) adj3 (angiograph$ or angiogram$ or arteriograph$)).tw.
33 or/31-32
34 30 and 33
35 animal/ not human/ use medf
36 (animal/ or nonhuman/) not human/ use emef
37 34 not (35 or 36)
38 remove duplicates from 37
39 limit 38 to yr="2002 - 2006"
40 eng.la.
41 39 and 40

SCI (2002 to 9 December 2006), ISI Proceedings (7 December 2006), BIOSIS (2002 to 8 December 2006)

Web of Knowledge URL: http://wok.mimas.ac.uk/

#1 TS=(ischemi* SAME (heart OR coronary OR myocardial))
#2 TS=(ischaemi* SAME (heart OR coronary OR myocardial))
#3 TS=((myocardial OR coronary OR heart) SAME (infarct* OR thrombosis OR stenosis))
#4 TS=((myocardial OR coronary OR heart) SAME (restenosis OR arteriosclerosis OR arter*))
#5 TS=angina
#6 TS=(chest SAME pain)
#7 #6 OR #5 OR #4 OR #3 OR #2 OR #1
#8 TS=(msct OR mdct)
#9 TS=(multislice* OR multi slice*)
#10 TS=(multi row* OR multirow*)
#11 TS=(multislide* OR multi slide*)
#12 TS=(multidetector* OR multi detector*)
#13 TS=(tomograph* SAME (multi* OR slice* OR row* OR slide* OR detector*))
#14 #13 OR #12 OR #11 OR #10 OR #9 OR #8
#15 #14 AND #7
#16 TS=(angiograph* OR angiogram* OR arteriograph*)
#17 #16 AND #15

Cochrane Library (Issue 4, 2006)

URL: http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME

#1 MeSH descriptor Myocardial Ischemia explode all trees
#2 MeSH descriptor Coronary Disease explode all trees

#3 MeSH descriptor Myocardial Infarction explode all trees
#4 MeSH descriptor Chest Pain explode all trees
#5 (ischemi* or ischaemi*) NEAR/3 (heart OR coronary OR myocardial):ti,ab,kw
#6 (chest NEAR/3 pain):ti,ab,kw
#7 (myocardial OR coronary OR heart) NEAR/3 (infarct* or thrombosis OR stenosis):ti,ab,kw
#8 (myocardial or heart or coronary) NEAR/3 (restenosis or arteriosclerosis or arter*)
#9 (angina):ti,ab,kw
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 MeSH descriptor Tomography, X-Ray Computed, this term only
#12 MeSH descriptor Tomography, Spiral Computed, this term only
#13 (detector* or slice* or slide* or row*):ti,ab,kw
#14 ((#11 OR #12) AND #13)
#15 (msct or mdct):ti,ab,kw or (multislice* or multi slice*):ti,ab,kw or (multirow* or multi row*):ti,ab,kw or (multislide* or multi slide*):ti,ab,kw or (multidetector* or multi detector*):ti,ab,kw
#16 (tomograph* near/5 (multi* or slice* or slide* or row* or detector*)):ti,ab,kw
#17 (#14 OR #15 OR #16)
#18 (#10 AND #17)
#19 (#18), from 2002 to 2006

DARE (December 2006)
URL: http://www.crd.york.ac.uk/crdweb/

tomograph/All fields AND multi or detector or slide or slice or row/All fields AND coronary or heart or myocardial or angina or isch?emia or isch?emic/All fields

NRR (Issue 3, 2006)
URL: http://www.update-software.com/National/

#1. MYOCARDIAL ISCHEMIA explode all trees (MeSH)
#2. CORONARY DISEASE explode all trees (MeSH)
#3. MYOCARDIAL INFARCTION explode all trees (MeSH)
#4. CHEST PAIN explode all trees (MeSH)
#5. (heart or coronary or myocardial)
#6. angina
#7. (#1 or #2 or #3 or #4 or #5 or #6)
#8. TOMOGRAPHY X-RAY COMPUTED single term (MeSH)
#9. TOMOGRAPHY SPIRAL COMPUTED single term (MeSH)
#10. (#8 or #9)
#11. (detector* or slice* or slide* or multi* or row*)
#12. (#10 and #11)
#13. (msct or mdct) 1
#14. (multislice* or (multi next slice*))
#15. (multirow* or (multi next row*))
#16. (multislide* or (multi next slide*))
#17. (multidetector* or (multi next detector*))
#18. tomograph* 1
#19. (#11 and #18)
#20. (#12 or #13 or #14 or #15 or #16 or #17 or #19)
#21. (#7 and #20)

Clinical Trials (July 2006)
URL: http://clinicaltrials.gov/ct/gui/c/r

(heart or coronary or myocardial) and tomograph*

Current Controlled Trials (December 2006)
URL: http://www.controlled-trials.com/

tomograph% and (multi% or detector% or slide* or slice% or row%) and (heart or coronary or myocardial)

Conference Papers Index (2002 to 31 August 2006)
CSA URL: http://www.csa1.co.uk/

((MDCT or MSCT) or (((multi* or detector* or slice*) or row*) and (ct or tomography))) and ((coronary or cardiac or heart) or (myocardial or ischemi* or ischaemi*) or (stenosis or restenosis or Arteriosclerosis)

Cost-effectiveness and economic evaluations

Search strategies used to identify reports of cost-effectiveness and economic evaluations of MSCT for CAD.

MEDLINE (1996 to November week 3 2006), EMBASE (1996 to week 49 2006), Medline In-Process (14 December 2006)
Ovid Multifile Search URL: http://gateway.ovid.com/

1 exp "costs and cost analysis"/
2 economics/
3 exp economics,hospital/
4 exp economics,medical/
5 economics,pharmaceutical/

6 exp budgets/
7 exp models, economic/
8 exp decision theory/
9 ec.fs. use medf
10 monte carlo method/
11 markov chains/
12 exp quality of life/
13 "Value of Life"/
14 cost of illness/
15 exp health status indicators/
16 cost$.ti.
17 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
18 economics model$.tw.
19 (economics$ or pharmacoeconomic$ or pharmo-economic$).ti.
20 (price$ or pricing$).tw.
21 (financial or finance or finances or financed).tw.
22 (value adj2 (money or monetary)).tw.
23 quality adjusted life.tw.
24 disability adjusted life.tw.
25 (qaly? or qald? or qale? or qtime? or daly?).tw.
26 (euroqol or euro qol or eq5d or eq 5d).tw.
27 (hql or hqol or h qol or hrqol or hr qol).tw.
28 (hye or hyes).tw.
29 (health adj3 (indicator? or status or utilit?)).tw.
30 markov$.tw.
31 monte carlo.tw.
32 (decision$ adj2 (tree? or analy$ or model$)).tw.
33 or/1-32
34 exp myocardial ischemia/ use medf
35 exp ischemic heart disease/ use emef
36 exp coronary artery disease/
37 exp myocardial infarction/
38 exp chest pain/
39 coronary artery blood flow/ use emef
40 (isch?emi$ adj3 (heart or coronary or myocardial)).tw
41 ((myocardial or coronary or heart) adj3 (infarct$ or thrombosis or stenosis or restenosis or arteriosclerosis or arter$)).tw.
42 angina.tw.
43 (chest adj3 pain).tw.
44 or/34-43
45 tomography, x-ray computed/ use medf
46 tomography, spiral computed/ use medf
47 computer assisted tomography/ use emef
48 computed tomographic angiography/ use emef
49 electron beam tomography/ use emef
50 high resolution computer tomography/ use emef
51 spiral computer assisted tomography/ use emef
52 or/45-51
53 (detector? or slice? or slide? or row?).tw.
54 52 and 53
55 multidetector computed tomography/ use emef
56 (msct or mdct).tw.
57 (multi slice? or multislice?).tw.
58 (multi row? or multirow?).tw.
59 (multi slide? or multislide?).tw
60 (multi detect$ or multidetect$).tw.
61 (tomograph$ adj5 (multi$ or slice? or row? or slide? or detector?)).tw.
62 or/54-61
63 33 and 44 and 62
64 remove duplicates from 63

NHS EED (December 2006)

URL: http://nhscrd.york.ac.uk/welcome.htm

tomograph/All fields AND multi or detector or slide or slice or row/All fields AND coronary or heart or myocardial or angina or isch?emia or isch?emic/All fields

General searches

Search strategies used to identify reports of clinical effectiveness or cost-effectiveness of MSCT for CAD.

HMIC (2000 to May 2006)

URL: http://gateway.ovid.com/

1 computed tomography scanners/
2 (detector? or slice? or slide? or row?).tw.
3 1 and 2
4 (multi slice? or multislice?).tw.
5 (msct or mdct).tw.
6 (multi row? or multirow?).tw.
7 (multi slide? or multislide?).tw.
8 (multi detect$ or multidetect$).tw.
9 (tomograph$ adj5 (multi$ or slice? or row? or slide? or detector?)).tw
10 3 or 9

HTA Database (December 2006)

URL: http://nhscrd.york.ac.uk/welcome.htm

tomograph/All fields AND multi or detector or slide or slice or row/All fields AND coronary or heart or myocardial or angina or isch?emia or isch?emic/All fields

Conference proceedings

American College of Cardiology

53rd Annual Scientific Sessions, New Orleans, March 2004
54th Annual Scientific Sessions, Orlando, March 2005

55th Annual Scientific Sessions, Atlanta, March 2006

American Heart Association

Annual Scientific Sessions, Orlando, November 2003
Annual Scientific Sessions, New Orleans, November 2004
Annual Scientific Sessions, Dallas, November 2005

European Society of Radiology

European Congress on Radiology, Vienna, March 2003
European Congress on Radiology, Vienna, March 2004
European Congress on Radiology, Vienna, March 2005
European Congress on Radiology, Vienna, March 2006

European Society of Cardiology

Annual Congress, Munich, August 2004
Annual Congress, Stockholm, September 2005

North American Society of Cardiology Imaging

32nd Annual Meeting, Ameila Island, Florida, 2004
33rd Annual Meeting, Ameila Island, Florida, 2005

Radiological Society of North American

Annual Scientific Meeting, Chicago, December 2003
Annual Scientific Meeting, Chicago, December 2004
Annual Scientific Meeting, Chicago, December 2005

Society of Cardiovascular Tomography

1st Scientific Meeting, Washington DC, July 2006

World Congress of Cardiology 2006

Barcelona, September 2006

WEBSITES

Searched for other evidence-based reports and background information.

American College of Cardiology
URL: http://www.acc.org/ (accessed May 2006)

American College of Radiology
URL: http://www.acr.org/s_acr/index.asp (accessed May 2006)

American Heart Association
URL: http://my.americanheart.org/portal/professional (accessed May 2006)

British Society of Cardiac Radiology
URL: http://www.bscr.co.uk/ (accessed May 2006)

Cardiac Radiographers Advisory Group
URL: http://www.craguk.org/ (accessed May 2006)

European Society of Cardiac Radiology
URL: http://www.escr.org/society_ear.shtml (accessed May 2006)

European Society of Cardiology
URL: http://www.escardio.org/ (accessed May 2006)

Health Protection Agency
URL: http://www.hpa.org.uk/ (accessed May 2006)

ImPACT (Imaging Performance Assessment of CT scanners) Group
URL: http://www.impactscan.org/ (accessed May 2006)

Radiological Society of North America
URL: http://www.rsna.org/ (accessed May 2006)

TRIP database
URL: http://www.tripdatabase.com/ (accessed May 2006)

Systematic reviews comparing MSCT with SPECT for CAD

DARE (December 2006)
HTA Database (December 2006)
URL: http://www.crd.york.ac.uk/crdweb/

Medion Database (December 2006)
URL: http://www.mediondatabase.nl/

Exp Myocardial Ischemia/di

Appendix 2

Modified QUADAS quality assessment checklist

Quality assessment checklist (derived from QUADAS tool)[29]

Study ID: **Paper no.:**

Assessor initials: **Date assessed:**

Item	Yes	No	Unclear
Mandatory quality items			
1. Was the spectrum of patients representative of the patients who will receive the test in practice?			
2. Is the reference standard likely to correctly classify the target condition?			
3. Is the time period between the reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?[a]			
4. Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?			
5. Did patients receive the same reference standard regardless of the index test result?			
6. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?			
7. Were the index test results interpreted without knowledge of the results of the reference standard?			
8. Were the reference standard results interpreted without knowledge of the results of the index test?			
9. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?[b]			
10. Were uninterpretable/intermediate test results reported?			
11. Were withdrawals from the study explained?			
Additional items			
12. Has an established cut-off point been used?[c]			
13. Were data on observer variation reported and within an acceptable range?			
14. Were data presented for appropriate subgroups of patients?[d]			

[a] For Q3 to be checked Yes, the period should be less than 6 months.
[b] For Q9 to be checked Yes, the data should be for CT results only.
[c] For Q12, one example of an established cut-off point is >50% stenosis.
[d] For Q14, appropriate subgroups include people with suspected CAD, known CAD, diabetes, previous PCI or CABG, and women.

Appendix 3

List of included studies

Diagnostic studies (full text)

Ehara (2006a)[46]

Primary reference
Ehara M, Surmely J-F, Kawai M, Katoh O, Matsubara T, Terashima M, *et al*. Diagnostic accuracy of 64-slice computed tomography for detecting angiographically significant coronary artery stenosis in an unselected consecutive patient population: comparison with conventional invasive angiography. *Circ J* 2006; **70**:564–71.

Secondary references
Ehara M, Kato O, Matsubara T, Terashima M, Tsuchikane E, Suzuki T, *et al*. Accuracy of non-invasive angiography with 64-slice computed tomography for detection of significant coronary stenosis in a prospective registry: comparison with invasive coronary angiography. *Circulation* 2005;**112**:U621.

Ehara M, Kawai M, Kato O, Matsubara T, Terashima M, Tsuchikane E, *et al*. Diagnostic accuracy of coronary angiography using 64-slice computed tomography for detection of coronary artery disease in an unselected population: reliability in the 'real world'. *Am J Cardiol* 2005;**96**:21H.

Ehara M, Kato O, Matsubara T, Trashima M, Tsuchikane E, Ito T, *et al*. Diagnostic accuracy of 64-slice computed tomography compared with invasive angiography: feasibility of this non-invasive modality on the clinical practice. *Eur Heart J* 2005;**26**:533.

Fine (2006a)[49]

Primary reference
Fine JJ, Hopkins CB, Ruff N, Newton FC. Comparison of accuracy of 64-slice cardiovascular computed tomography with coronary angiography in patients with suspected coronary artery disease. *Am J Cardiol* 2006; **97**:173–4.

Secondary reference
Fine JJ, Hall PA, Hopkins CB, Newton FC. Noninvasive coronary angiography: agreement of 64-slice cardiovascular computed tomography and selective catheter angiography. *J Am Coll Cardiol* 2006;**47**:127A.

Ghostine (2006)[52]

Primary reference
Ghostine S, Caussin C, Daoud B, Habis M, Perrier E, Pesenti-Rossi D, *et al*. Non-invasive detection of coronary artery disease in patients with left bundle branch block using 64-slice computed tomography. *J Am Coll Cardiol* 2006;**48**:1929–34.

Secondary reference
Ghostine S, Caussin C, Daoud B, Habis M, Perrier E, Rossi R, *et al*. Noninvasive detection of coronary artery disease in patients with left bundle branch block using 64-slice computed tomography. *J Am Coll Cardiol* 2006; **47**:136A.

Hoffmann (2006)[55]

Primary reference
Hoffmann U, Nagurney JT, Moselewski F, Pena A, Ferencik M, Chae CU, *et al*. Coronary multidetector computed tomography in the assessment of patients with acute chest pain. *Circulation* 2006;**114**:2251–60.

Johnson (2007)[56]

Primary reference
Johnson TR, Nikolaou K, Wintersperger BJ, Knez A, Boekstegers P, Reiser MF, *et al*. ECG-gated 64-MDCT angiography in the differential diagnosis of acute chest pain. *AJR Am J Roentgenol* 2007;**188**:76–82.

Leber (2005)[58]

Primary reference
Leber AW, Knez A, Von Ziegler F, Becker A, Nikolaou K, Paul S, *et al*. Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound. *J Am Coll Cardiol* 2005;**46**:147–54.

Secondary reference
Knez A, Leber A, Becker A, Von Ziegler F, Becker C. Non invasive coronary angiography with 64 multislice spiral CT: ready to replace diagnostic angiography in patients with suspected CAD. *Circulation* 2005;**112**:U743.

Leschka (2005)[59]

Primary reference
Leschka S, Alkadhi H, Plass A, Desbiolles L, Grunenfelder J, Marincek B, *et al*. Accuracy of MSCT coronary angiography with 64-slice technology: first experience. *Eur Heart J* 2005;**26**:1482–7.

Meijboom (2006)[65]

Primary reference
Meijboom WB, Mollet NR, Van Mieghem CAG, Kluin J, Weustink AC, Pugliese F, *et al*. Pre-operative computed tomography coronary angiography to detect significant coronary artery disease in patients referred for cardiac valve surgery. *J Am Coll Cardiol* 2006;**48**:1658–65.

Secondary reference
Meijboom WB, Van Mieghem C, Kluin J, Pugliese F, Mollet N, Cademartiri F, *et al*. Comparison of computed tomography coronary angiography with conventional coronary angiography for the detection of significant coronary lesions in the pre-operative valve surgery patient. *J Am Coll Cardiol* 2006;**47**:126A.

Mollet (2005)[66]

Primary reference
Mollet NR, Cademartiri F, Van Mieghem CA, Runza G, McFadden EP, Baks T, *et al*. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. *Circulation* 2005;**112**:2318–23.

Secondary references
Cademartiri F, Mollet N, Van Mieghem C, Runza G, Belgrano M, Baks T, *et al*. Diagnostic accuracy of non-invasive 64-slice CT coronary angiography. European Congress on Radiology, Vienna, March 2005. Abstract B-342.

Mollet NR, Cademartiri F, Van Mieghem C, Runza G, Baks T, McFadden EP, *et al*. Non-invasive 64-slice multi-detector CT coronary angiography of the entire coronary tree in patients with stable angina pectoris or an acute coronary syndrome. *J Am Coll Cardiol* 2005; **45**:267A.

Nikolaou (2006)[71]

Primary reference
Nikolaou K, Knez A, Rist C, Wintersperger BJ, Leber A, Johnson T, *et al*. Accuracy of 64-MDCT in the diagnosis of ischemic heart disease. *AJR Am J Roentgenol* 2006; **187**:111–17.

Secondary references
Nikolaou K, Rist C, Wintersperger B, Flohr T, Johnson T, Von Ziegler F, *et al*. 64-detector row computed tomography of the coronary arteries: initial experience. European Congress on Radiology, Vienna, March 2005. Abstract B-346.

Nikolaou K, Wintersperger B, Rist C, Johnson T, Reiser M, Becker C. Sixty-four-slice computed tomography in the diagnosis of ischemic heart disease: impact on clinical decision making. Radiological Society of North America, Annual Scientific Meeting, Chicago, December 2005. Abstract SSC05-05.

Ong (2006)[75]

Primary reference
Ong TK, Chin SP, Liew CK, Chan WL, Seyfarth MT, Liew HB, *et al*. Accuracy of 64-row multidetector computed tomography in detecting coronary artery disease in 134 symptomatic patients: influence of calcification. *Am Heart J* 2006;**151**:1323e1–6.

Secondary reference
Ong K, Chin SP, Chan WL, Liew CK, Seyfarth MT, Liew HB, *et al*. Feasibility and accuracy of 64-row MDCT coronary imaging from a centre with early experience: a review and comparison with established centres. *Med J Malaysia* 2005;**60**:629–36.

Pache (2006)[77]

Primary reference
Pache G, Saueressig U, Frydrychowicz A, Foell D, Ghanem N, Kotter E, *et al*. Initial experience with 64-slice cardiac CT: non-invasive visualization of coronary artery bypass grafts. *Eur Heart J* 2006;**27**:976–80.

Plass (2006)[79]

Primary reference
Plass A, Grunenfelder J, Leschka S, Alkadhi H, Eberli FR, Wildermuth S, *et al*. Coronary artery imaging with 64-slice computed tomography from cardiac surgical perspective. *Eur J Cardiothorac Surg* 2006; **30**:109–16.

Secondary reference
Plass AR, Haeussler AK, Grunenfelder J, Leschka S, Widermuth S, Zund G, *et al*. First experiences in evaluating coronary artery disease with the 64-MDCT. *Br J Surg* 2005;**92**:915.

Pugliese (2006a)[83]

Primary reference
Pugliese F, Mollet NR, Runza G, Van Mieghem C, Meijboom WB, Malagutti P, *et al*. Diagnostic accuracy of non-invasive 64-slice CT coronary angiography in patients with stable angina pectoris. *Eur Radiol* 2006; **16**:575–82.

Raff (2005)[85]

Primary reference
Raff GL, Gallagher MJ, O'Neill WW, Goldstein JA. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. *J Am Coll Cardiol* 2005;**46**:552–7.

Rist (2006)[86]

Primary reference
Rist C, Von Ziegler F, Nikolaou K, Kirchin MA, Wintersperger BJ, Johnson TR, *et al*. Assessment of coronary artery stent patency and restenosis using 64-slice computed tomography. *Acad Radiol* 2006; **13**:1465–73.

Rixe (2006)[89]

Primary reference
Rixe J, Achenbach S, Ropers D, Baum U, Kuettner A, Ropers U, *et al*. Assessment of coronary artery stent restenosis by 64-slice multi-detector computed tomography. *Eur Heart J* 2006;**27**:2567–72.

Secondary references
Rixe J, Anders K, Ropers D, Kuettner A, Baum U, Ludwig J, *et al*. Assessment of coronary artery stent patency by 64-slice multi-detector computed tomography: predictors of evaluability. World Congress

of Cardiology, Barcelona, September 2006. Abstract P2490.

Rixe J, Anders K, Ropers D, Baum U, Kuettner A, Werner GD, *et al*. Noninvasive angiographic assessment of coronary artery stent patency by 64 slice multidetector computed tomography. *Circulation* 2005; **112**:U621.

Ropers (2006a)[93]

Primary reference

Ropers D, Rixe J, Anders K, Kuttner A, Baum U, Bautz W, *et al*. Usefulness of multidetector row spiral computed tomography with 64- × 0.6-mm collimation and 330-ms rotation for the noninvasive detection of significant coronary artery stenoses. *Am J Cardiol* 2006; **97**:343–8.

Secondary references

Ropers D, Andres K, Baum U, Bautz W, Daniel WG, Achenbach S. Improved evaluability and diagnostic accuracy of noninvasive coronary artery angiography using 64-slice spiral computed tomography with 330ms gantry rotation. *Eur Heart J* 2005;**26**:436.

Ropers D, Anders K, Baum U, Bautz W, Achenbach S. Noninvasive coronary angiography by retrospectively ECG gated 64-slice spiral computed tomography: initial clinical experiences. *J Am Coll Cardiol* 2005;**45**(Suppl 1): 311A.

Ropers (2006b)[94]

Primary reference

Ropers D, Pohle FK, Kuettner A, Pflederer T, Anders K, Daniel WG, *et al*. Diagnostic accuracy of noninvasive coronary angiography in patients after bypass surgery using 64-slice spiral computed tomography with 330-ms gantry rotation. *Circulation* 2006;**114**:2334–41.

Secondary reference

Ropers D, Pflederer T, Rixe J, Anders K, Kuettner A, Baum U, *et al*. Improved diagnostic accuracy of noninvasive coronary angiography in patients after bypass surgery using 64-slice spiral computed tomography. American Heart Association Annual Scientific Sessions, Dallas, Texas, November 2005. Abstract 2651.

Schuijf (2006)[100]

Primary reference

Schuijf JD, Pundziute G, Jukema JW, Lamb HJ, van der Hoeven BL, de Roos A, *et al*. Diagnostic accuracy of 64-slice multislice computed tomography in the noninvasive evaluation of significant coronary artery disease. *Am J Cardiol* 2006;**98**:145–8.

Sheth (2006)[101]

Primary reference

Sheth TN, Rieber J, Mooyaart EAQ, Pena A, Abbara S, Cury RC, *et al*. Usefulness of coronary computed tomographic angiography to assess suitability for revascularization in patients with significant coronary artery disease and angina pectoris. *Am J Cardiol* 2006; **98**:1198–201.

Diagnostic studies (Abstracts)

Beck (2006)[37]

Primary reference

Beck T, Burgstahler C, Reimann A, Kopp AF, Schroeder S, Tuebingen U. Diagnostic accuracy of 64-slice spiral computed tomography in the detection of significant coronary artery stenoses and delayed myocardial enhancement in consecutive patients. *Int J Cardiovasc Imaging* 2006;**21**:701.

Secondary reference

Beck T, Reimann A, Burgstahler C, Heuschmid M, Kuettner A, Kopp AF, *et al*. Diagnostic accuracy of 64-slice spiral computed tomography in the detection of significant coronary artery stenoses delayed myocardial enhancement in consecutive patients. American Heart Association Annual Scientific Sessions, Dallas, Texas, November 2005. Abstract 2249.

Becker (2006)[39]

Primary reference

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Appendix 5

Characteristics of the included studies

TABLE 21 *Diagnostic studies: full text*

Study, design and methods	Participants	Tests	Outcomes summary
Ehara, 2006a[42–44,46] **Aim**: To evaluate the diagnostic accuracy of 64-slice CT in various types of patients, including those with severely calcified arteries or post-PCI, as well as detecting CAD in patients with imperfect breath-holding, or arrhythmias occurring during the scan **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Coronary arteries were classified into 14 segments. Significant stenosis was defined as >50% reduction of minimal lumen diameter **Method of recruitment**: Consecutive **Period**: October 2004 to January 2005 **Country**: Japan	**Enrolled**: 69 **Analysed**: 67 **Age (years)**: Mean 67, SD 11 **Gender**: M 52; F 17 **Previous PCI**: 46 **Previous CABG**: 2 **Indications for testing**: Suspected CAD 19; proven CAD 50 **Inclusion criteria**: NS **Exclusion criteria**: Patients with contraindications to iodinated contrast media (such as renal insufficiency with a serum creatinine >1.5 mg/dl, known allergy or thyroid disorder), chronic arrhythmias or unable to hold their breath	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: Mean 13.6 s (range 10.5–24.1) **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: At the time of the MSCT scan 15 patients were on β-blockers. No additional β-blocker medication was given to the remaining 54 patients before the scan **Heart rate during CT scan**: Mean 71.8, SD 13 (range 51–115) bpm **Invasive CA**: Quantitative CA was performed using CMS (MEDIS, The Netherlands). At least two different views were obtained for each vessel	**Prevalence of significant CAD**: 88% (61/69) **Cut-off**: >50% stenosis **Segments (*n* = 884); patients (*n* = 67):** **Sensitivity**: 90%, 98% **Specificity**: 94%, 86% **PPV**: 89%, 98% **NPV**: 95%, 86% **Image quality (all segments):** Fine: 767 (80%) Adequate: 117 (12%) Poor: 82 (8%) **CT interobserver agreement:** κ = 0.95 **CT intraobserver agreement**: κ = 0.93 **Fryback and Thornbury grading**:[a] Level 2
Fine, 2006a[47,49] **Aim**: To evaluate the accuracy of 64-slice CT and the frequency distribution of indications for MSCT to determine whether improved performance offers a low-risk and patient-friendly mode of CA, which in selected clinical situations may replace the need for catheter angiography **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Vessel-by-vessel analysis. Significant stenosis was defined as >50% reduction of minimal lumen diameter. Vessels with a diameter	**Enrolled**: 66 **Analysed**: 66 **Age (years)**: Mean 62, SD 7 **Gender**: M 32; F 34 **Previous PCI**: NS **Previous CABG**: 9 vein grafts **Indications for testing**: Chest pain 33; previous revascularisation 9; abnormal ECG 5; dyspnoea 7; abnormal calcium score 2; known coronary disease 3; abnormal cardiovascular study 7 **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 33 ms **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: Patients with high heart rates were given oral and/or i.v. metoprolol as needed to decrease their heart rate to 50–60 bpm **Heart rate during CT scan**: NS	**Prevalence of significant CAD**: NS **Cut-off**: >50% stenosis **Arteries (*n* = 245?):** **Sensitivity**: 95% **Specificity**: 96% **PPV**: 97% **NPV**: 92% **Image quality**: CT provided images of technical quality that allowed for diagnosis among 94% (62/66) of study subjects **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
<1.5 mm were excluded from correlation and technical quality analysis **Method of recruitment**: Sequential **Period**: NS **Country**: USA		**Invasive CA**: Details NS, vessels with a diameter <1.5 mm were excluded from correlation and image quality analysis	
Ghostine, 2006[51,52] **Aim**: To evaluate the diagnostic accuracy of 64-slice CT to identify CAD in patients with complete LBBB **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). AHA 15-segment model. The diagnostic accuracy of 64-slice CT was performed for lesions with mean lumen diameter reduction >50% **Method of recruitment**: Consecutive **Period**: September to November 2005 **Country**: France	**Enrolled**: 66 **Analysed**: 66 **Age (years)**: Mean 69, SD 13 **Gender**: M 40; F 26 **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: Patients with complete LBBB, sinus rhythm, without a history of CAD **Inclusion criteria**: NS **Exclusion criteria**: Suspicion of ACS, known history of CAD, arrhythmia, renal insufficiency (serum creatinine >150 μmol/l), iodine allergy, pregnancy	**64-Slice CT**: Sensation 64, Siemens, Germany **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: 12 (SD 2) s **Total examination time**: NS **Radiation dose**: 7 (SD 2) mSv **Dose modulation used**: Yes **Use of drugs to limit heart rate**: All patients received oral β-blocker medication if not contraindicated (metoprolol 100 mg, 1 hour before acquisition) to lower heart rate below 70 bpm **Heart rate during CT scan**: Mean 67, SD 13 (range 46–119) bpm **Invasive CA**: Invasive coronary angiograms were evaluated by quantitative CA, with the mean diameter reduction determined in two orthogonal views	**Prevalence of CAD at >50% luminal narrowing**: 44% (29/66) **Cut-off**: >50% stenosis **Segments (n = 94); patients (n = 29):** **Sensitivity**: 97%, 72% **Specificity**: 95%, 99% **PPV**: 93%, 91% **NPV**: 97%, 97% **Image quality**: Image quality score was good on average (3.8, SD 1.4). Score 5 (n = 32), 4 (n = 10), 3 (n = 6), 2 (n = 14) and 1 (n = 4) were for a heart rate of 60 (SD 8), 67 (SD 8), 71 (SD 3), 72 (SD 10) and 101 (SD 13) bpm, respectively. All the patients with a heart rate >90 bpm presented blurred image quality (score 1) **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Hoffmann, 2006[55] **Aim**: To assess CT angiographic patterns of CAD – any coronary atherosclerotic plaque and significant stenosis – in patients who were being admitted for chest pain and who had negative initial cardiac biomarkers and a non-diagnostic ECG on presentation **Study design**: Non-randomised comparative study in which some patients received both MSCT and invasive CA (reference standard). Modified AHA 17-segment model. The diagnostic accuracy of 64-slice CT was performed for luminal obstruction ⩾50% diameter reduction in cross-sectional images (corresponding to >~70% stenosis in planimetric invasive CA) **Method of recruitment**: Consecutive **Period**: May to July 2005 **Country**: USA	**Enrolled**: 106 **Analysed**: 103 (8 received both MSCT and invasive CA) **Age (years)**: Mean 54, SD 12 (whole group) **Gender**: M 62; F 41 (whole group) **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: Adults with acute chest pain in whom initial ED evaluation was inconclusive **Inclusion criteria**: Age >18 years, >5 minutes of chest pain within the previous 24 hours, no or non-diagnostic ECG changes, normal initial cardiac biomarkers, sinus rhythm, ability to perform a breath-hold of 10–15 seconds **Exclusion criteria**: Elevated troponin-I or creatine kinase-MB levels in the initial blood sample obtained in the ED, new diagnostic ECG changes (ST-segment elevation or depression >1 mm or T-wave inversion >4 mm in more than two anatomically contiguous leads), haemodynamic or clinical instability, known allergy to iodinated contrast agent, serum creatinine >1.3 mg/dl, metformin treatment, hyperthyroidism, inability to provide informed consent, perceived interference with standard clinical care of patients	**64-Slice CT**: Sensation 64, Siemens, Germany **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: 13.6 (SD 2.2) s **Total examination time**: Including patient preparation 12 (SD 1) minutes **Radiation dose**: 6–11 mSv **Dose modulation used**: Yes **Use of drugs to limit heart rate**: All patients with a heart rate >60 bpm received a β-blocker (i.v. metoprolol 5–20 mg) unless their systolic blood pressure was <100 mmHg or other contraindications were present **Heart rate during CT scan**: NS **Invasive CA**: NS	**Prevalence of CAD at >50% luminal narrowing**: 63% (5/8) **Cut-off**: >50% stenosis **Patients (*n* = 8):** **Sensitivity**: 100% **Specificity**: 100% **PPV**: 100% **NPV**: 100% **Image quality**: NS **CT interobserver agreement**: Detection of any plaque per patient: κ = 0.92 Detection of any plaque per segment: κ = 0.81 Detection of stenosis per patient: κ = 0.82 **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Johnson, 2007[56] **Aim**: To evaluate the diagnostic value of an ECG-gated 64 MSCT angiography protocol for simultaneous assessment of the pulmonary arteries, coronary arteries and aorta within a single breath-hold **Study design**: Non-randomised comparative study in which some patients received both MSCT and invasive CA (reference standard). AHA 15-segment model. The diagnostic accuracy of 64-slice CT was performed for lesions with luminal narrowing >50% or occlusion **Method of recruitment**: Consecutive **Period**: July 2004 to March 2005 **Country**: Germany	**Enrolled**: 55 **Analysed**: 55 (20 received both MSCT and invasive CA) **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: Patients with acute chest pain **Inclusion criteria**: Patients with acute chest pain and the origin of the pain was unclear, i.e. if ECG findings were absent or inconclusive and if the clinical appearance did not suggest a specific cause **Exclusion criteria**: Patients who could not hold their breath for at least 15 seconds. In the acute setting, relative contraindications were arrhythmia, history of severe allergic reaction to iodinated contrast media, renal insufficiency and young age (<55 years)	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: 21.4 (SD 3.2) s **Total examination time**: NS **Radiation dose**: ~6.9 mSv **Dose modulation used**: Yes **Use of drugs to limit heart rate**: β-Blockers were not administered in preparation for the scan **Heart rate during CT scan**: Mean 71, SD 15 (range 51–123) bpm **Invasive CA**: In 20 patients, X-ray coronary angiograms were available for correlation. Ten patients had undergone CA within 1 year before CT, the other ten underwent CA within 4 days after CT for confirmation of or intervention in lesions detected with CT	**Prevalence of CAD at >50% luminal narrowing**: 85% (17/20) **Cut-off**: >50% stenosis or occlusions **Patients (*n* = 20):** **Sensitivity**: 94% **Specificity**: 0% **PPV**: 84% **NPV**: 0% **Image quality**: One right coronary artery resulted in image quality insufficient for diagnosis. The overall image quality rating was 1.2 (SD 0.4) **CT interobserver agreement**: Regarding presence or absence of clinically significant stenosis in each patient κ = 0.81, regarding number of significant stenoses per patient κ = 0.62, regarding wall irregularities with stenosis <50%, κ = 0.43 **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Leber, 2005[57,58] **Aim**: To determine the diagnostic accuracy of 64-slice CT to identify and quantify atherosclerotic coronary lesions in comparison with catheter-based angiography and intravascular ultrasound **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). AHA 15-segment model. The diagnostic accuracy of 64-slice CT was performed for lesions with various degrees of luminal narrowing: >75%, >50% and <50%	**Enrolled**: 59 **Analysed**: 59 **Age (years)**: Mean 64, SD 10 **Gender**: NS **Previous PCI**: NS (stenting >1 vessel excluded) **Previous CABG**: Excluded **Indications for testing**: NS **Inclusion criteria**: NS **Exclusion criteria**: Patients with atrial fibrillation, previous bypass surgery, previous stenting of more than one vessel, an unstable clinical condition, or a	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: 8–11 s **Total examination time**: NS **Radiation dose**: Mean 10–14 mSv **Dose modulation used**: Yes **Use of drugs to limit heart rate**: Patients with heart rates >70 bpm were given 50 mg of metoprolol 60 minutes before the scheduled CT scan. In the presence of contraindications for a β-blocker, or an unsatisfactory lowering of	**Prevalence of CAD at >50% luminal narrowing**: 42% (25/59) **Cut-off**: >50% stenosis **Segments (*n* = 697), patients (*n* = 55):** **Sensitivity**: 73%, 88% **Specificity**: 97%, NS **PPV**: 60%, NS **NPV**: 98%, NS **Image quality**: Four of 59 patients had CT angiograms that were severely affected by motion artefacts or poor contrast-to-noise ratio, making an evaluation of all coronary segments impossible. In the remaining

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Method of recruitment: Consecutive **Period**: July to November 2004 **Country**: Germany	contraindication to the administration of contrast agent	the heart rate, the scan was performed even at higher heart rates **Heart rate during CT scan**: Mean 62, SD? 13 bpm **Invasive CA**: Invasive coronary angiograms were evaluated by quantitative CA, with the mean diameter reduction determined in two projections	55 patients all coronary segments were graded to provide good or intermediate image quality that was sufficient for evaluation **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Leschka, 2005[59] **Aim**: To investigate the accuracy of 64-slice CT for assessing haemodynamically significant stenosis of the coronary arteries in comparison with invasive CA **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). AHA 15-segment model. Significant stenosis was defined as vessel reduction >50%. Coronary artery analysis was performed in all vessels with a diameter down to 1.5 mm, including those vessels distal to complete occlusions **Method of recruitment**: Consecutive **Period**: October 2004 to January 2005 **Country**: Switzerland	**Enrolled**: 67 **Analysed**: 67 **Age (years)**: Mean 60.1, SD 10.5 (range 34–82) **Gender**: M 50; F 17 **Previous PCI**: NS (stenting excluded) **Previous CABG**: Excluded **Indications for testing**: Signs of unstable angina 24; prior to CABG 43 **Inclusion criteria**: Suspected CAD; prior to CABG **Exclusion criteria**: Previous allergic reactions to iodine contrast media, severe renal insufficiency (creatinine level >120 μmol/l), haemodynamic instability, atrial fibrillation, inability to follow breath-hold commands, previous percutaneous transluminal coronary stent placement, previous bypass surgery	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 0.37 s **Slice thickness**: 0.6 mm **Total scan time**: <12 s (median 11.2, range 10.7–11.9) **Total examination time**: <15 minutes (median 12, range 8–14) **Radiation dose**: NS **Dose modulation used**: No **Use of drugs to limit heart rate**: 40 patients had taken β-blockers as part of their baseline medication at the time of the CT scan. No additional β-blockers were administered before the CT scan **Heart rate during CT scan**: Mean 66.3, SD 14.7 (range 48–90) bpm **Invasive CA**: Invasive CA was performed according to standard techniques	**Prevalence of significant CAD**: 70% (47/67) **Cut-off**: >50% stenosis **Segments (n = 1005):** **Sensitivity**: 94% **Specificity**: 97% **PPV**: 87% **NPV**: 99% **Image quality (segments):** Excellent: 61% (612/1005) Good: 31% (310/1005) Adequate: 8% (83/1005) **CT interobserver agreement**: κ = 0.88 (image quality), 0.87 (calcifications), 0.95 (stenoses detection) **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Meijboom, 2006[64,65] **Aim**: To study the diagnostic performance of 64-slice CT to rule out or detect significant coronary stenosis in patients referred for valve surgery **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). 17-Segment modified AHA model. Significant stenosis was defined as lumen diameter reduction ⩾50% **Method of recruitment**: Consecutive **Period**: 6 months **Country**: The Netherlands	**Enrolled**: 70 **Analysed**: 70 **Age (years)**: Mean 63, SD 11 **Gender**: M 49; F 21 **Previous PCI**: 0 **Previous CABG**: 0 **Indications for testing**: Scheduled for valve surgery **Inclusion criteria**: Patients scheduled for valve surgery **Exclusion criteria**: Irregular heart rhythm 26, impaired renal function 5, known contrast allergy 4, hospitalisation in community hospital 4, no need for CA 4, previous coronary artery bypass surgery 1 or percutaneous coronary intervention 4, no consent 27	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: Mean 12.8, SD 1.3 s **Total examination time**: NS **Radiation dose**: 15.2–21.4 mSv for men and women, respectively **Dose modulation used**: No **Use of drugs to limit heart rate**: β-Blocker administered in 71% and 64% received lorazepam **Heart rate during CT scan**: Mean 60, SD 8 bpm **Invasive CA**: Stenoses were evaluated in two orthogonal views. Segments distal to a chronic total occlusion were excluded because of poor distal filling by collaterals	**Prevalence of significant CAD**: 26% (18/70) **Cut-off**: ⩾50% stenosis **Segments (n = 1003), patients (n = 70):** **Sensitivity**: 94%, 100% **Specificity**: 98%, 92% **PPV**: 65%, 82% **NPV**: 100%, 100% **Image quality**: NS **CT interobserver agreement**: κ = 0.71 **CT intraobserver agreement**: κ = 0.74 **Fryback and Thornbury grading**: Level 2
Mollet, 2005[40,66,67] **Aim**: To assess the diagnostic performance of 64-slice CT in detecting the extent and severity of coronary stenosis in the clinically relevant coronary tree of patients with atypical chest pain, stable or unstable angina, or non-ST-segment elevation MI referred for diagnostic invasive CA **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). 17-Segment modified AHA model. Significant stenosis was defined as mean lumen diameter reduction ⩾50% **Method of recruitment**: Consecutive **Period**: 6 weeks	**Enrolled**: 70 **Analysed**: 52 **Age (years)**: Mean 59.6, SD 12.1 **Gender**: M 34; F 18 **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: Atypical chest pain 6; stable angina pectoris 32; unstable angina pectoris 3; non-ST-segment elevation MI 11 **Inclusion criteria**: Patients scheduled for diagnostic conventional CA with sinus heart rhythm, able to hold breath for 15 seconds, and no previous PCI or CABG surgery	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: Mean 13.3, SD 0.6 s **Total examination time**: NS **Radiation dose**: 15.2–21.4 mSv for men and women, respectively **Dose modulation used**: No **Use of drugs to limit heart rate**: Patients with heart rates >70 bpm received, unless they had known overt heart failure or ECG AV conduction abnormalities, a single oral dose of 100 mg metoprolol 45 minutes before the scan. Patients with heart rates >80 bpm received an additional single oral dose of 1 mg lorazepam	**Prevalence of significant CAD**: 75% (39/52) **Cut-off**: ⩾50% stenosis **Segments (n = 725), patients (n = 51):** **Sensitivity**: 99%, 100% **Specificity**: 95%, 92% **PPV**: 76%, 97% **NPV**: 100%, 100% **Image quality (all segments):** Good: 90% Moderate: 7% Poor: 3% **CT interobserver agreement**: κ = 0.73 **CT intraobserver agreement**: κ = 0.79 **Fryback and Thornbury grading**: Level 2

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Country: The Netherlands	**Exclusion criteria**: Logistical inability to perform a CT scan before the conventional angiogram (n = 9), presence of arrhythmia (n = 4), impaired renal function (serum creatinine >120 mmol/l) (n = 4) and known contrast allergy (n = 1)	**Heart rate during CT scan**: Mean 57.8, SD 6.8 bpm **Invasive CA**: Stenoses were evaluated in two orthogonal views using a validated quantitative CA algorithm	
Nikolaou, 2006[69–71] **Aim**: To evaluate the diagnostic accuracy of 64-slice CT for detecting significant CAD in both patients with known CAD and patients without a history of CAD **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). AHA 15-segment model. Significant stenosis was defined as, on a per-patient basis, one or more stenoses >50%, independent of the segmental location **Method of recruitment**: NS **Period**: 6 months **Country**: Germany	**Enrolled**: 72 **Analysed**: 72 **Age (years)**: Mean 64, SD 10 (range 38–89) **Gender**: M 59; F 13 **Previous PCI**: 15 (24 stents) **Previous CABG**: Excluded **Indications for testing**: NS **Inclusion criteria**: NS **Exclusion criteria**: Patients with CABG. Known allergic reactions to iodine-containing contrast media, severe renal failure, pregnancy or an unstable clinical condition	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: ~8–10 mSv **Dose modulation used**: Yes **Use of drugs to limit heart rate**: i.v. administration of 5–10 mg metoprolol shortly before the CT scan in patients with heart rates >70 bpm. If contraindicated for β-blockers or with an unsatisfactory lowering of the heart rate, the scan was still performed, even at higher heart rates **Heart rate during CT scan**: Mean 61, SD 9 (range 42–87) bpm **Invasive CA**: Quantitative CA was performed for all coronary artery lesions, determining the mean diameter reduction of these lesions in two projections	**Prevalence of significant CAD**: 57% (39/68) **Cut-off**: > 50% stenosis **Segments (n = 923), patients (n = 68):** **Sensitivity**: 82%, 97% **Specificity**: 95%, 79% **PPV**: 69%, 86% **NPV**: 97%, 96% **Image quality (all segments):** High: 64% Moderate: 30% Poor: 6% **CT interobserver agreement**: κ = 0.75 (segments), 0.81 (patients) **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Ong, 2006[74,75] **Aim**: To investigate the accuracy of 64-slice CT in detecting CAD in symptomatic patients with mild and moderate-to-severe degrees of coronary calcification **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Patients were divided into those with calcium score <142 AS (group A, *n* = 68) and those with calcium score ⩾142 AS (group B, *n* = 66). 11-Segment modified AHA model. Moderate to severe stenosis was defined as ⩾50% luminal narrowing **Method of recruitment**: Consecutive **Period**: 4 months **Country**: Malaysia	**Enrolled**: 134 **Analysed**: 134 **Age (years)**: Mean 54.5, SD 8.8 **Gender**: M 98; F 36 **Previous PCI**: NS (segments with stents excluded) **Previous CABG**: Excluded **Indications for testing**: NS **Inclusion criteria**: Patients with ischaemic heart disease (defined as new or chronic stable exertional angina with typical ECG changes or positive ETT) scheduled for conventional CA. Eligibility criteria included regular heart rate, ability to hold breath for >12 seconds, and no renal impairment **Exclusion criteria**: Previous bypass graft surgery, presence of tachyarrhythmias, atrial fibrillation and other irregular heart rhythms, known allergies or contraindications to iodine contrast media and β-adrenergic antagonists and preprocedural serum creatinine >140 μmol/l	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.75 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: Yes **Use of drugs to limit heart rate**: In the absence of contraindications, all patients with a resting heart rate >60 bpm each received a 100 mg tablet of atenolol the night before the scan and another tablet 2 hours before the scan. Patients who could not tolerate β-blockade received 80 mg of oral verapamil. If the prescan rate remained >80 bpm, an additional 5-mg dose of i.v. metoprolol was given before the scan to reduce the heart rate further. Patients with resting heart rates >80 bpm after treatment were asked to continue with atenolol 100 mg daily and given a second appointment a week later for MDCT angiography **Heart rate during CT scan**: Mean 62, SD 9 bpm **Invasive CA**: Performed with a biplane digital fluoroscopy. A minimum of six orthogonal views were obtained. Assessment of diameter stenosis was by visual estimation	**Prevalence of significant CAD**: 73% (98/134) **Cut-off**: ⩾50% stenosis **Segments:** **Group A (*n* = 68), group B (*n* = 66):** **Sensitivity**: 85%, 80% **Specificity**: 98%, 93% **PPV**: 83%, 77% **NPV**: 98%, 94% **Image quality (all segments):** Evaluable segments Group A: 93.6% Group B: 86.9% **CT interobserver agreement:** Variability <5% **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Pache, 2006[77] **Aim**: To evaluate the diagnostic accuracy of 64-slice CT in the assessment of CABG compared with invasive CA **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Significant stenosis defined as a luminal diameter >50% **Method of recruitment**: NS **Period**: NS **Country**: Germany	**Enrolled**: 31 **Analysed**: 31 **Age (years)**: Mean 68.4, SD 8.4 (range 45–83) **Gender**: M 26; F 5 **Previous PCI**: NS **Previous CABG**: 31 **Indications for testing**: Suspected recurrent anginal symptoms after CABG surgery **Inclusion criteria**: Patients who had received a CT examination and who had had previous CABG surgery and had been referred to the authors' clinic for invasive CA evaluation because of suspected recurrent anginal symptoms after CABG surgery **Exclusion criteria**: Patients in whom a conventional catheter angiography had not been performed within 4 weeks (of the CT scan?)	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: Yes **Use of drugs to limit heart rate**: The β-blocker metoprolol tartrate (50–100 mg) was administered before the scan if a patient's heart rate was >65 bpm and no contraindications for β-blockade were present **Heart rate during CT scan**: Mean 63.3, SD 7.3 (range 29–164) bpm **Invasive CA**: Coronary bypass angiograms were evaluated by quantitative CA with automated vessel contour detection	**Prevalence of significant CAD**: 77% (24/31) **Cut-off**: >50% stenosis **Grafts (*n* = 93), patients (*n* = 31):** **Sensitivity**: 98%, 100% **Specificity**: 89%, 71% **PPV**: 90%, 92% **NPV**: 98%, 100% **Image quality**: NS **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Plass, 2006[79,80] **Aim**: To investigate the diagnostic accuracy of 64-slice CT with regard to coronary artery stenoses for preoperative planning of CABG when image analysis is performed by cardiovascular surgeons **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). 11-Segment modified AHA model. Significant stenosis defined as vessel lumen constriction >50% **Method of recruitment**: NS **Period**: NS	**Enrolled**: 50 **Analysed**: 50 **Age (years)**: Mean 66, SD 8 **Gender**: M 39; F 11 **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: NS **Exclusion criteria**: Patients with arrhythmia, allergy to iodinated contrast media and renal insufficiency (serum creatinine >120 mmol/l)	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 0.37 s **Slice thickness**: 0.6 mm **Total scan time**: ~12 s (range 10–13) **Total examination time**: Mean <13 minutes (range 8–14) **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: No additional β-blockers were administered before the CT scan	**Prevalence of significant CAD**: 80% (40/50) **Cut-off**: >50% stenosis **Segments (*n* = 550), patients (*n* = 50):** **Sensitivity**: 87%, 100% **Specificity**: 96%, 90% **PPV**: 86%, 98% **NPV**: 96%, 100% **Image quality (all segments):** Excellent: 506/550 (92%) Limited but still diagnostic: 27/550 (5%) Not assessable: 17/550 (3%)

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Country: Switzerland		**Heart rate during CT scan**: Mean 65, SD 11 (range 38–89) bpm **Invasive CA**: Performed according to standard techniques. Coronary arteries with diameter as large as 1.5 mm were analysed including those vessels distal to an occlusion	**CT interobserver agreement**: $\kappa = 0.93$ **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Pugliese, 2006a[83] **Aim**: To evaluate the diagnostic performance of 64-slice CT to detect significant stenoses in the entire coronary tree in a patient cohort with stable angina pectoris **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). 17-Segment modified AHA model. Significant stenosis was defined as mean lumen diameter reduction of ⩾50% **Method of recruitment**: Consecutive **Period**: NS **Country**: Italy	**Enrolled**: 35 **Analysed**: 35 **Age (years)**: Mean 61, SD 10, range 46 to 80 **Gender**: M 21; F 14 **Previous PCI**: NS (previous stenting excluded) **Previous CABG**: Excluded **Indications for testing**: NS **Inclusion criteria**: Patients with stable angina pectoris. Patients exhibiting sinus heart rhythm incapable of holding their breath for 15 seconds and/or without contraindications to the administration of iodinated contrast agents were prospectively included **Exclusion criteria**: Presence of arrhythmias, previous CABG or PCI with stent implantation	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: Average 13 s (SD 1, range 11–15) **Total examination time**: NS **Radiation dose**: 15 and 20 mSv (male and female, respectively) **Dose modulation used**: No **Use of drugs to limit heart rate**: Patients with prescan heart rates >70 bpm received a single oral dose of 100 mg metoprolol 1 hour before the CT scan **Heart rate during CT scan**: Mean 58, SD 6 bpm **Invasive CA**: The coronary lumen of all coronary segments was quantitatively evaluated on two projections using dedicated software	**Prevalence of significant CAD**: 71% (25/35) **Cut-off**: ⩾50% stenosis **Segments (n = 494), patients (n = 35):** **Sensitivity**: 99%, 100% **Specificity**: 96%, 90% **PPV**: 78%, 96% **NPV**: 100%, 100% **Image quality (all segments):** Good: 455/494 (92%) Moderate: 25/494 (5%) Poor: 14/494 (3%) **CT interobserver agreement**: $\kappa = 0.73$ **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Raff, 2005[85] **Aim**: To assess the accuracy of 64-slice CT in patients previously scheduled to undergo invasive selective CA for suspected CAD **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). 15-Segment AHA model. Significant stenosis defined as mean lumen diameter reduction of ⩾50% **Method of recruitment**: Consecutive **Period**: September 2004 to February 2006 **Country**: USA	**Enrolled**: 70 **Analysed**: 70 **Age (years)**: Mean 59, SD 11 (range 22–81) **Gender**: M 53; F 17 **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: Patients scheduled to have elective invasive CA for suspected CAD **Exclusion criteria**: Irregular heart rate, patients at risk for iodinated contrast agents (congestive heart failure, dye allergy or elevated serum creatinine >1.5 mg/dl) or contraindications to β-blocking drugs	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: 13 and 18 mSv (men and women, respectively) **Dose modulation used**: No **Use of drugs to limit heart rate**: Patients not already on β-blocking drugs received 100 mg of atenolol for heart rates >65 bpm, or 50 mg of atenolol for heart rates <65 bpm but >50 bpm, 1 hour before MSCT imaging. Additional i.v. metoprolol (5–30 mg) was administered as required to achieve a target heart rate <65 bpm. However, no patient was excluded because of a heart rate above this target. Sublingual nitroglycerin 0.4 mg was given 1 minute before image acquisition **Heart rate during CT scan**: <70 bpm 54/70 (77%); 70–80 bpm 10/70 (14%); >80 bpm 6/70 (9%) **Invasive CA**: Stenosis severity in each segment was classified according to the maximal luminal diameter stenosis present in each segment. Lesions were examined in orthogonal views, and stenosis severity was determined using an automated edge-detection system	**Prevalence of significant CAD**: 57% (40/70) **Cut-off**: ⩾50% stenosis **Segments (*n* = 935), patients (*n* = 70):** **Sensitivity**: 86%, 95% **Specificity**: 95%, 90% **PPV**: 66%, 93% **NPV**: 98%, 93% **Image quality**: NS **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Rist, 2006[86] **Aim**: To evaluate the diagnostic accuracy of high-resolution 64-slice CT in a pilot study for the assessment of the lumen of coronary artery stents **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). AHA 15-segment model. Significant stenosis was defined as stent restenosis with a luminal decrease ⩾50% or occlusion **Method of recruitment**: NS **Period**: 4 months **Country**: Germany	**Enrolled**: 25 **Analysed**: 25 **Age (years)**: Mean 59.4, SD 12 (range 40–83) **Gender**: M 23; F 2 **Previous PCI**: 25 **Previous CABG**: NS **Indications for testing**: For the majority of studied population (n = 17), the indication for conventional angiography after stent placement was the suspicion of in-stent stenosis because of new or changing clinical symptoms **Inclusion criteria**: Patients had coronary artery stent placement **Exclusion criteria**: Atrial fibrillation and over-severe arrhythmias, severe renal failure, hyperthyroidism, hypersensitivity to iodine-containing contrast agent, pregnancy, unstable clinical conditions	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: ~10 s **Total examination time**: NS **Radiation dose**: 8–10 mSv **Dose modulation used**: Yes **Use of drugs to limit heart rate**: β-Blocker treatment (metoprolol 5–10 mg) was administered i.v. to patients (n = 14) with heart rates >70 bpm shortly before the MSCT examination **Heart rate during CT scan**: Mean 62.2, SD 8 (range 49–79) bpm **Invasive CA**: Standard projections were obtained and evaluated quantitatively. Lesions in two projections were determined	**Prevalence of significant in-stent stenosis or occlusion**: 18% (8/45 stents) **Cut-off**: ⩾50% stenosis or occlusion **Stent (n = 45):** **Sensitivity**: 75% **Specificity**: 92% **PPV**: 67% **NPV**: 94% **Image quality:** High quality: 30/46 stents (65%) Moderate quality: 15/46 stents (33%) Poor quality: 1/46 stents (2%) **CT interobserver agreement:** In-stent stenosis: κ = 0.53 Proximal stenoses: κ = 0.65 Distal stenoses: κ = 0.66 **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Rixe, 2006[87–89] **Aim**: To investigate the feasibility of assessing coronary artery stent restenosis using a new generation 64-slice multidetector CT scanner in comparison to conventional quantitative angiography **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Significant stenosis was defined as stent diameter decrease >50% **Method of recruitment**: Consecutive **Period**: NS **Country**: Germany	**Enrolled**: 64 **Analysed**: 64 **Age (years)**: Mean 58, SD 10 **Gender**: M 41; F 23 **Previous PCI**: 64 **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: Patients with previously implanted coronary artery stents scheduled for invasive CA **Exclusion criteria**: Stent-in-stent implantation and renal failure, known allergy to contrast agent, possible pregnancy, non-sinus rhythm	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: NS **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: Yes **Use of drugs to limit heart rate**: Patients with a heart rate >60 bpm received 100 mg of atenolol orally 45 minutes before scanning; if heart rate remained >60 bpm at the time of MDCT investigation, up to four doses of 5 mg of metoprolol were administered i.v.	**Prevalence of significant stent stenosis**: 12% (7/59 evaluable stents) **Cut-off**: >50% stenosis **Stent (n = 59):** **Sensitivity**: 86% **Specificity**: 98% **PPV**: 86% **NPV**: 98% **Image quality:** Evaluable: 59/102 (58%) The mean diameter of unevaluable stents was 3.03 (SD 0.31) mm, whereas the mean diameter of evaluable stents was 3.28 (SD 0.4) mm (p = 0.0002); of all 13 stents

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
		Heart rate during CT scan: Mean 60, SD 5 (range 49–64) bpm **Invasive CA**: Standardised projections were obtained and evaluated using quantitative coronary angiographic software	with a diameter <3.0 mm, only one stent was evaluable **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Ropers, 2006a[90,92,93] **Aim**: To analyse the accuracy of 64-slice CT for the detection of significant coronary stenoses compared with quantitative CA **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). 17-Segment modified AHA model. Significant stenosis was defined as lesions with a luminal decrease ⩾50% **Method of recruitment**: NS **Period**: NS **Country**: Germany	**Enrolled**: 84 **Analysed**: 81 **Age (years)**: Mean 58, SD 10 (range 35–77) **Gender**: NS **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: Patients referred for a first invasive CA due to suspected CAD **Exclusion criteria**: ACS, contraindications to administration of contrast agent, cardiac arrhythmias, possible pregnancy or an unstable clinical situation	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: Average 7.45 and 10.24 mSv (men and women, respectively) **Dose modulation used**: Yes **Use of drugs to limit heart rate**: Patients with a heart rate >60 bpm received 100 mg of atenolol orally 1 hour before scanning; if heart rate remained >60 bpm at the time of MDCT investigation, up to four doses of 5 mg of metoprolol were administered i.v. to lower heart rate to ⩽60 bpm. In addition, all patients received 0.8 mg of isosorbide dinitrate sublingually immediately before MDCT scanning **Heart rate during CT scan**: Mean 59, SD 9 bpm **Invasive CA**: Standard projections were obtained and evaluated using quantitative coronary angiographic software. Proximal luminal diameters of all coronary segments were measured. Segments with a diameter <1.5 mm were excluded	**Prevalence of significant CAD**: 32% (26/81) **Cut-off**: ⩾50% stenosis **Segments (*n* = 1083), patients (*n* = 81):** **Sensitivity**: 93%, 96% **Specificity**: 97%, 91% **PPV**: 56%, 83% **NPV**: 100%, 98% **Image quality:** Evaluable: 1083/1128 (96%) Unevaluable: 45/1128 (4%) **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Ropers, 2006b[91,94] **Aim**: To assess the accuracy of 64-slice MSCT CA for the evaluation of patients after coronary artery bypass surgery **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). AHA 16-segment model. Significant stenosis was defined as lesions with a luminal decrease 50–99% **Method of recruitment**: Consecutive **Period**: NS **Country**: Germany	**Enrolled**: 50 **Analysed**: 50 **Age (years)**: Mean 67 (range 44–82) **Gender**: M 38; F 12 **Previous PCI**: NS **Previous CABG**: 50 **Indications for testing**: Patients with previous coronary artery bypass surgery who had been referred for invasive CA for clinical reasons **Inclusion criteria**: Patients in stable clinical condition, in sinus rhythm, without implanted pacemakers or valve prostheses, and without contraindications to the administration of iodinated contrast agent **Exclusion criteria**: Possible pregnancy, ACS, or stent in native coronary arteries or bypass grafts	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: Average 8.55 and 12.24 mSv (men and women, respectively) **Dose modulation used**: Yes **Use of drugs to limit heart rate**: 42 patients (84%) were on long-term medication with β-blockers. Patients with a heart rate of >60 bpm received 100 mg atenolol orally 1 hour before the scan. If the heart rate was still >60 bpm at the time of MSCT investigation, up to four doses of 5 mg metoprolol were administrated i.v. to lower the heart rate to ≤60 bpm **Heart rate during CT scan**: Mean 59, SD 9 bpm **Invasive CA**: Standard projections were obtained and evaluated using quantitative coronary angiographic software. Proximal luminal diameters of all coronary segments and bypass grafts were measured. Segments with a diameter <1.5 mm were excluded	**Prevalence of significant CAD**: Evaluable native segments: 18% (101/566); evaluable grafts: 0% (0/138) **Cut-off**: ⩾50% stenosis **Native segments (*n* = 566), grafts (*n* = 138):** **Sensitivity**: 86%, 100% **Specificity**: 76%, 94% **PPV**: 44%, 92% **NPV**: 96%, 100% **Image quality:** Evaluable native segments: 566/621 (91%) Evaluable grafts: 100% (138/138) **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Schuijf, 2006,[100] **Aim**: To determine the diagnostic accuracy of current 64-slice MSCT in the detection of significant CAD, using conventional CA as the gold standard **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). AHA-based segment model was used. Significant stenosis was defined as lesions with a luminal decrease ⩾50% **Method of recruitment**: NS **Period**: NS **Country**: The Netherlands	**Enrolled**: 61 **Analysed**: 60 **Age (years)**: Mean 60, SD 11 **Gender**: M 46; F 14 **Previous PCI**: 33 (55%) **Previous CABG**: 0 **Indications for testing**: Patients scheduled for conventional CA **Inclusion criteria**: NS **Exclusion criteria**: Patients with contraindications to MSCT	**64-Slice CT**: Toshiba Multi-Slice Aquilion 64 system (Toshiba Medical Systems, Tokyo, Japan) **Retrospective ECG gating**: Yes **Rotation time**: 0.4 s **Slice thickness**: 0.5 mm **Total scan time**: 8–10 s **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS, mentioned in a table, 43 (72%) patients were on β-blocker medication **Heart rate during CT scan**: NS, in one patient, the heart rate was >90 bpm during MSCT, resulting in the complete data set being uninterpretable **Invasive CA**: Standard projections were obtained and evaluated for the presence of ⩾50% diameter stenosis, on the basis of the evaluation of two orthogonal views	**Prevalence of significant CAD**: 52% (31/60) **Cut-off**: ⩾50% stenosis **Segments (*n* = 842), patients (*n* = 60):** **Sensitivity**: 85%, 94% **Specificity**: 98%, 97% **PPV**: 82%, 97% **NPV**: 99%, 93% **Image quality:** Evaluable segments: 842/854 (99%) **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 21 *Diagnostic studies: full text (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Sheth, 2006[101] **Aim**: To evaluate the accuracy of CT for the detection of complex lesion morphology, including the presence of severe calcium, total occlusion, and ostial or bifurcation location, and compare the results with those of invasive angiography **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Positive tests in MSCT were defined as: severe calcium, any dense vessel-calcific deposit that obscured the underlying lumen because of blooming artefact was considered severe calcium on CT; total occlusion, complete absence of contrast within the lumen at the site of significant stenosis. Significant stenosis in invasive CA was defined as lesions with a luminal decrease >70%, severe calcium was identified as radiopacities seen without cardiac motion and before contrast injection. On both CT and CA, a bifurcation lesion was defined as a lesion in which a branch vessel with a diameter >1.5 mm originated within the stenosis; an ostial lesion was a stenosis that began within 3 mm of a major coronary ostium **Method of recruitment**: NS, retrospective **Period**: December 2004 to September 2005 **Country**: USA	**Enrolled**: 29 **Analysed**: 29 **Age (years)**: Mean 60.3 **Gender**: M 24; F 5 **Previous PCI**: 2 **Previous CABG**: 0 **Indications for testing**: Patients with stable or unstable angina, who had at least one significant coronary artery stenosis as detected by invasive angiography **Inclusion criteria**: Patients with significant coronary artery stenosis who underwent coronary CT before invasive selective CA among the patients referred for coronary CT because of stable or unstable angina **Exclusion criteria**: NS	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: NS **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: All patients with a heart rate >65 bpm received 5–30 mg i.v. metoprolol before the CT scan **Heart rate during CT scan**: NS **Invasive CA**: Angiograms were quantitatively assessed	**Prevalence of ⩾1 feature of complexity (i.e. severe calcium, total occlusion, ostial or bifurcation)**: 47% (26/55 segments) **⩾1 feature of complexity:** **Segments (n = 55):** **Sensitivity**: 89% **Specificity**: 83% **PPV**: 82% **NPV**: 89% **Image quality:** Evaluable segments: 55/65 (85%) **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

NS, not stated; ED, emergency department.

[a] Fryback and Thornbury grading: level 1, technical quality of the images; level 2, diagnostic accuracy, sensitivity and specificity of the images; level 3, degree to which results influence physicians' diagnostic thinking; level 4, degree to which imaging results affect patient management; level 5, efficacy studies measuring the degree of effect on patient management; level 6, analyses of societal costs and benefits of a diagnostic imaging technology.

TABLE 22 *Diagnostic studies: abstracts*

Study, design and methods	Participants	Tests	Outcomes summary
Beck, 2006[37,38] **Aim**: NS **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). 13-Segment model. Significant stenosis was defined as >50% diameter stenoses **Method of recruitment**: Consecutive **Period**: NS **Country**: Germany	**Enrolled**: NS **Analysed**: 102 **Age (years)**: Mean 62, SD 10 **Gender**: M 82; F 20 **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: Patients with suspected obstructive coronary stenoses **Exclusion criteria**: NS	**64-Slice CT**: Sensation 64, Siemens, Germany **Retrospective ECG gating**: NS **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	**Prevalence of significant CAD**: NS **Cut-off**: >50% stenosis **Segments (*n* = 1326):** **Sensitivity**: 90% **Specificity**: 99% **PPV**: 95% **NPV**: 98% **Image quality**: NS **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Becker, 2006[39] **Aim**: To examine the possibility to improve the diagnostic accuracy by combining coronary calcium screening with non-invasive CA using 64 MSCT **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). No definition stated for significant stenosis **Method of recruitment**: NS **Period**: NS **Country**: Germany	**Enrolled**: NS **Analysed**: 199 **Age (years)**: Mean 61.3, SD 12.6 **Gender**: M 82; F 117 **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: Attended the ED with acute chest pain **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: Sensation 64, Siemens, Germany **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	**Prevalence of significant CAD**: 59% (117/199) **Sensitivity**: 97% **Specificity**: 79% **PPV**: 87% **NPV**: 94% **Image quality**: In three patients evaluation was not possible **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 22 *Diagnostic studies: abstracts (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Ehara, 2006b[45] **Aim**: To assess the diagnostic value of 64 MSCT to detect coronary in-stent stenosis **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Significant stenosis was defined as >50% stent diameter stenosis **Method of recruitment**: NS **Period**: NS **Country**: Japan	**Enrolled**: NS **Analysed**: 80 **Age (years)**: 68 **Gender**: M 62; F 18 **Previous PCI**: 80 **Previous CABG**: NS **Indications for testing**: Had previously undergone coronary stent implantation **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: Mean 13.2 s **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: Mean 69.9 bpm **Invasive CA**: quantitative CA was used	**Prevalence of significant in-stent stenosis**: 20% (22/113 stents) **Sensitivity**: 95% **Specificity**: 90% **PPV**: 70% **NPV**: 99% **Image quality**: 15 lesions (12%) were not assessable by MSCT mainly because of motion artefact and calcification **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Fine, 2006b[48] **Aim**: To determine the ability of 64-slice CT to measure the prevalence, morphology and severity of coronary plaque in high-risk patients and assess its accuracy compared with invasive CA **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Disease severity was categorised as: no disease, subclinical disease (lesions <70%), clinically significant disease (lesions >70%). Plaque morphology was stratified as either vulnerable (AHA type IV/Va lipid core) or stable [AHA type Vb (calcific) or Vc (fibrotic)] **Method of recruitment**: NS **Period**: NS **Country**: USA	**Enrolled**: NS **Analysed**: 101 **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	**Prevalence of significant (lesions >70%) CAD**: 41% diabetes group, 33% metabolic syndrome group, 15% comparator group **Cut-off**: >70% stenosis **Segments? (*n* = NS)** **Diabetes group, metabolic syndrome group, comparator group:** **Sensitivity**: 87%, 91%, 91% **Specificity**: 94%, 94%, 98% **PPV**: 87%, 87%, 93% **NPV**: 94%, 94%, 98% **Stable coronary plaque:** 52% diabetes group, 25% metabolic syndrome group, 20% comparator group **Image quality**: NS **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 22 *Diagnostic studies: abstracts (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Hausleiter, 2005[53] **Aim**: To compare the accuracy of 64-slice CT angiography with invasive CA for patency and relevant stenoses of CABG including the anastomoses and run-off vessels **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). 13-Segment model. Significant stenosis was defined as diameter reduction ⩾50% **Method of recruitment**: NS **Period**: NS **Country**: Germany	**Enrolled**: NS **Analysed**: 43 **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: 43 **Indications for testing**: NS **Inclusion criteria**: Patients with CABG **Exclusion criteria**: NS	**64-Slice CT**: NS **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: NS	**Prevalence of significant CAD**: NS **Cut-off**: ⩾50% stenosis **CABGs (*n* = 130):** **Sensitivity**: 97% **Specificity**: 98% **PPV**: 94%? **NPV**: 99% **Image quality**: NS **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Makaryus, 2006a[61a] **Aim**: To investigate the accuracy of 64-slice CT for assessing significant coronary stenoses in comparison with conventional CA **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Significant stenosis was defined as >50% **Method of recruitment**: Consecutive **Period**: May to July 2005 **Country**: USA	**Enrolled**: 374 **Analysed**: NS **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: Patients suspected of having CAD or who had experienced recurrent symptoms after prior coronary interventions and whose 64-slice CT results prompted conventional CA investigation **Exclusion criteria**: NS	**64-Slice CT**: GE Light-Speed VCT, GE Healthcare **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	**Prevalence of significant CAD**: NS **Cut-off**: >50% stenosis **Unit of analysis unclear:** **Sensitivity**: 88% **Specificity**: 97% **PPV**: NS **NPV**: NS **Image quality**: NS **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 22 *Diagnostic studies: abstracts (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Makaryus, 2006b[60a] **Aim**: NS **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Significant stenosis was not defined **Method of recruitment**: NS **Period**: May to July 2005 **Country**: USA	**Enrolled**: 18 **Analysed**: 18 **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: 18 **Indications for testing**: NS **Inclusion criteria**: Patients with a history of CABG **Exclusion criteria**: NS	**64-Slice CT**: GE Light-Speed VCT, GE Healthcare **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	**Prevalence of significant CAD**: NS **Cut-off**: Graft occlusion **Bypass grafts (*n* = 43):** **Sensitivity**: 90% **Specificity**: 97% **PPV**: NS **NPV**: NS **Image quality**: NS **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Malagutti, 2006[62,63] **Aim**: To evaluate the performance of 64-slice MSCT angiography in patients who had previously undergone CABG, for detection of graft obstruction and native coronary artery stenosis **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Significant stenosis was defined as >50% luminal narrowing **Method of recruitment**: NS **Period**: NS **Country**: The Netherlands	**Enrolled**: NS **Analysed**: 52 **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: 52 **Indications for testing**: Symptomatic post-CABG **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: Siemens Sensation 64, Germany **Retrospective ECG gating**: NS **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Conventional quantitative CA was used	**Prevalence of significant CAD**: 96% (50/52) **Cut-off**: >50% luminal narrowing **Coronary artery grafted segments (*n* = 182), patients (*n* = 52):** **Sensitivity**: 99%, 100% **Specificity**: 96%, 50% **PPV**: 95%, 98% **NPV**: 99%, 100% **Image quality**: NS **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 22 *Diagnostic studies: abstracts (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Motoyama, 2006[68] **Aim**: To compare the diagnostic accuracy of 256-slice CT angiography with conventional, invasive CA **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Segments >2 mm were examined. Significant stenosis was defined as >50% **Method of recruitment**: Consecutive **Period**: NS **Country**: Japan	**Enrolled**: 10 **Analysed**: 10 **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: NS **Exclusion criteria**: NS	**256-Slice CT**: Prototype, Toshiba, Japan **Retrospective ECG gating**: NS **Rotation time**: 500 ms **Slice thickness**: 0.5 mm **Total scan time**: 3 s **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: NS, segments ⩽2 mm diameter were not examined	**Prevalence of significant CAD**: NS **Cut-off**: >50% stenosis **Segments (*n* = NS) with severe calcification excluded, severe calcification assumed as stenosis:** **Sensitivity**: 100%, 100% **Specificity**: 96%, 90% **PPV**: 73%, 61% **NPV**: 100%, 100% **Image quality**: No segments were excluded due to motion artefact **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Oncel, 2006[72,73] **Aim**: To assess the role of MSCT in the evaluation of coronary stent patency and in-stent restenosis **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Significant in-stent stenosis was defined as >50% **Method of recruitment**: NS **Period**: NS **Country**: Turkey	**Enrolled**: NS **Analysed**: 43 **Age (years)**: NS **Gender**: NS **Previous PCI**: 43 **Previous CABG**: NS **Indications for testing**: Patients suspected for in-stent restenosis and scheduled for conventional angiography **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: Sensation 64, Siemens, Germany **Retrospective ECG gating**: Yes **Rotation time**: 0.33 s **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: NS	**Prevalence of significant in-stent stenosis**: 58% (25/43 stents) **Cut-off**: >50% stenosis **Sensitivity**: 92% **Specificity**: 94% **PPV**: 96% **NPV**: 89% **Image quality**: In all patients, the image quality was eligible for the evaluation of stent patency **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 22 *Diagnostic studies: abstracts (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Onuma, 2006[76] **Aim**: To assess the accuracy of 64-slice CT to detect CAD **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). 17-Segment modified AHA model with segment 17 being the intermediate branch of the left coronary artery. Significant stenosis was defined as >50% **Method of recruitment**: Consecutive **Period**: November 2004 to June 2005 **Country**: Japan	**Enrolled**: NS **Analysed**: 29 **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: NS **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Traditional CA	**Prevalence of significant CAD**: NS **Cut-off**: >50% stenosis **Segments (*n* = 430):** **Sensitivity**: 94% **Specificity**: 99% **PPV**: 93% **NPV**: 99% **Image quality**: 430/442 (97.2%) segments were judged visible **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Pinto, 2006[78] **Aim**: To evaluate the accuracy of 64-slice MSCT to evaluate the presence of in-stent restenosis and the minimal lumen diameter **Study design**: Non-randomised comparative study in which patients received exercise treadmill testing, 64-slice CT and invasive CA (reference standard). Definition of significant stenosis NS **Method of recruitment**: NS **Period**: NS **Country**: Brazil	**Enrolled**: NS **Analysed**: 30 **Age (years)**: NS **Gender**: NS **Previous PCI**: 30 **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: Patients completed 9-month follow-up after the implantation of bare metal stents **Exclusion criteria**: NS	**64-Slice CT**: NS **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: β-Blockers were used in all patients with heart rate >70 bpm **Heart rate during CT scan**: NS **Invasive CA**: Details NS	**Prevalence of significant in-stent restenosis**: 10% (3/30) **Patients (*n* = 30):** **Sensitivity**: 100% **Image quality**: NS **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 22 *Diagnostic studies: abstracts (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Pugliese, 2006b[81,82] **Aim**: To compare the diagnostic accuracy of 64-slice MSCT in the assessment of CAD with conventional CA as the reference standard **Study design**: Non-randomised comparative study in which patients received exercise treadmill testing, 64-slice CT and invasive CA (reference standard). Definition of significant stenosis NS **Method of recruitment**: Consecutive **Period**: NS **Country**: The Netherlands	**Enrolled**: 51 **Analysed**: 51 **Age (years)**: NS **Gender**: NS **Previous PCI**: 0 **Previous CABG**: 0 **Indications for testing**: Patients referred for conventional angiography for suspected CAD **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: NS **Retrospective ECG gating**: NS **Rotation time**: 330 ms **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	**Prevalence of significant CAD**: NS **Presence of CAD: >2 mm segments; all segments:** **Sensitivity**: 99%, 99% **Specificity**: 96%, 95% **PPV**: 80%, 76% **NPV**: 99%, 99% **Image quality**: All segments >2 mm diameter were evaluable **CT inter-observer agreement**: NS **CT intra-observer agreement**: NS **Fryback and Thornbury grading**: Level 2
Pugliese, 2006c[84] **Aim**: To test the feasibility and accuracy of 64-slice MSCT in patients with ACS **Study design**: Non-randomised comparative study in which patients received exercise treadmill testing, 64-slice CT and invasive CA (reference standard). Definition of significant stenosis NS **Method of recruitment**: NS **Period**: NS **Country**: The Netherlands	**Enrolled**: NS **Analysed**: 25 **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: Patients with unstable angina or suspected acute MI **Inclusion criteria**: Patients with unstable angina or suspected acute MI underwent CT within 24 hours before cardiac catheterisation **Exclusion criteria**: Patients with heart/renal failure or allergy to contrast agent	**64-Slice CT**: NS **Retrospective ECG gating**: NS **Rotation time**: 330 ms **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: β-Blockers were administered to 15 patients with heart rates >65 bpm **Heart rate during CT scan**: Mean 58 bpm **Invasive CA**: Details NS	**Prevalence of significant CAD**: 96% (24/25) **Presence of CAD: patients (n = 25):** **Sensitivity**: 100% **Specificity**: 100% **PPV**: 100% **NPV**: 100% **Image quality**: NS **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 22 *Diagnostic studies: abstracts (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Rubinshtein, 2006a[50,95] **Aim**: To assess the additional benefit of 64-slice multidetector CT scanning for detection of obstructive coronary disease **Study design**: Non-randomised comparative study in which patients received exercise treadmill testing, 64-slice CT and invasive CA (reference standard). Significant stenosis was defined as ⩾50% stenosis (arterial segments proximal to functional bypass grafts excluded) **Method of recruitment**: Consecutive **Period**: NS **Country**: Israel	**Enrolled**: NS **Analysed**: 133 **Age (years)**: Mean 58.2, SD 11.8 **Gender**: M 88; F 45 **Previous PCI**: NS **Previous CABG**: NS (49 patients had prior myocardial revascularisation) **Indications for testing**: Suspected ACS (n = 54) or chronic stable angina (n = 79) **Inclusion criteria**: Patients with chest pain and negative/equivocal ETT (<1 mm horizontal, or upsloping, ST segment depression) **Exclusion criteria**: NS	**64-Slice CT**: Brilliance 64, Philips **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	**Prevalence of significant CAD**: 30% (40/133) **Patients (n = 133):** **Sensitivity**: 100% (CT), 55% (ETT) **Specificity**: 96% (CT), 62% (ETT) **PPV**: 91% (CT), 39% (ETT) **NPV**: 100% (CT), 76% (ETT) **Image quality**: NS **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Rubinshtein, 2006b[96] **Aim**: To use 64-slice MSCT to examine the prevalence of significant stenosis in coronary arteries supplying myocardial territories with low-grade myocardial perfusion defects on SPECT **Study design**: Non-randomised comparative study in which patients received exercise treadmill testing, 64-slice CT and invasive CA (reference standard). Significant stenosis was defined as >50% stenosis **Method of recruitment**: NS **Period**: NS **Country**: Israel	**Enrolled**: NS **Analysed**: 40 **Age (years)**: Mean 59, SD 11 **Gender**: M 24; F 16 **Previous PCI**: 9 **Previous CABG**: NS **Indications for testing**: Significant stenosis in coronary arteries supplying myocardial territories with low-grade myocardial perfusion defects on SPECT **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: Brilliance 64, Philips **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	**Prevalence of significant CAD**: 23% (9/40) **Cut-off**: >50% stenosis **Stents (n = 51), patients (n = 40):** **Sensitivity**: 100%, 100% **Specificity**: 88%, 84% **PPV**: 67%, 64% **NPV**: 100%, 100% **Image quality**: NS **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 22 *Diagnostic studies: abstracts (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Savino, 2006[41,54,97,104] **Aim**: To investigate the diagnostic accuracy of 64-slice MSCT in the assessment of CAD **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Significant stenosis was defined as >50% of the lumen diameter **Method of recruitment**: NS **Period**: NS **Country**: USA	**Enrolled**: NS **Analysed**: 55 **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: Patients with suspected CAD **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: NS **Retrospective ECG gating**: Yes **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	**Prevalence of significant CAD**: 35% (19/55) **Cut-off**: >50% stenosis **Segments (n = 826), patients (n = 55):** **Sensitivity**: 82%, 100% **Specificity**: 97%, 83% **PPV**: 69%, 76% **NPV**: 99%, 100% **Image quality**: All CT angiograms were considered of diagnostic quality **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Schlosser, 2006[98,99] **Aim**: To evaluate the value of 64-detector CT for ruling out high-grade coronary stenoses in patients with a low to moderate pretest probability of significant CAD **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Significant stenosis was defined as ⩾50% of the lumen diameter by visual assessment. Only those patients in whom significant stenoses could not be ruled out underwent invasive CA (n = 61) **Method of recruitment**: NS **Period**: NS **Country**: Germany	**Enrolled**: 179 **Analysed**: 61 **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: Atypical angina, ambiguous findings in non-invasive stress testing and a class II indication for invasive CA **Inclusion criteria**: Patients with a low to moderate pretest probability of CAD **Exclusion criteria**: NS	**64-Slice CT**: NS **Retrospective ECG gating**: NS **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: Patients with heart rates >60 bpm received β-blockers, and all patients received nitrates **Heart rate during CT scan**: Mean 57 bpm, SD 4 **Invasive CA**: Details NS	**Prevalence of significant CAD**: NS **Cut-off**: ⩾50% stenosis **Segments (n = 915):** **Sensitivity**: 100% **Specificity**: 97% **PPV**: 55% **NPV**: 100% **Image quality**: 11 segments in five patients showed severe calcifications resulting in an insufficient assessment of the segment. Because high-grade stenoses could not be ruled out in these segments, they were classified as severely stenotic **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

continued

TABLE 22 *Diagnostic studies: abstracts (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Sirol, 2006[102] **Aim**: To evaluate the diagnostic accuracy of 64-slice spiral CT angiography for the detection of significant coronary stenoses in a non-selected population of cardiac patients typically seen by a cardiologist on consultation **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Significant stenosis was defined as >50% stenosis **Method of recruitment**: NS **Period**: NS **Country**: Germany	**Enrolled**: NS **Analysed**: 38 **Age (years)**: Mean 59, SD 14 **Gender**: M 24, F 14 **Previous PCI**: NS **Previous CABG**: NS, 19 patients had prior stent implantation or CABG **Indications for testing**: NS **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: NS **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: 10–15 mg i.v. metoprolol immediately, before the scan if heart rate was >70 bpm **Heart rate during CT scan**: Mean 61 bpm, SD 7 **Invasive CA**: Quantitative CA was used	**Prevalence of significant CAD**: 20% (103/521 evaluable segments) **Cut-off**: >50% stenosis **Segments (*n* = 521), patients (*n* NS):** **Sensitivity**: 75%, 75% **Specificity**: 77%, 89% **PPV**: 88%, 88% **NPV**: 94%, 76% **Image quality**: 11.1% of the segments were not evaluable due to the presence of calcification (4.9%), stents (3.4%) or motion artefacts (2.6%) **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2
Wang, 2006,[103] **Aim**: To evaluate the diagnostic accuracy of 64-slice spiral CT angiography for the assessment of coronary artery stenosis **Study design**: Non-randomised comparative study in which patients received both MSCT and invasive CA (reference standard). Significant stenosis was defined as >50% stenosis. Image quality was assessed using a three-point grading scale from excellent (1) to non-assessable (3) **Method of recruitment**: NS **Period**: NS **Country**: China	**Enrolled**: 100 **Analysed**: 48 **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: Patients with suspected obstructive coronary stenoses **Exclusion criteria**: NS	**64-Slice CT**: Sensation 64, Siemens **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: Mean 11.9 s, SD 0.9 **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: Patients with a heart rate >70 bpm received oral β-blockers before the scan **Heart rate during CT scan**: Mean 61 bpm, SD 8 **Invasive CA**: Details NS	**Prevalence of significant CAD**: NS **Cut-off**: >50% stenosis **Arteries (*n* = 192):** **Sensitivity**: 95% **Specificity**: 93% **PPV**: 86% **NPV**: 98% **Image quality**: 1.2, SD 0.47. Visibility of distal arteries and small branches: LAD distal 92%, LCX distal 98%, first obtuse marginal 93%, cone branch 86% **CT interobserver agreement**: NS **CT intraobserver agreement**: NS **Fryback and Thornbury grading**: Level 2

[a] Makaryus (2006a) and Makaryus (2006b) have been treated as two separate studies, although their patients are drawn from the same patient population (*n* = 374) and there may also be some overlap of patients between the studies. Makaryus (2006a) assessed the accuracy of 64-slice CT for assessing significant coronary stenoses in comparison with conventional CA in patients suspected of having CAD or who had experienced recurrent symptoms after prior coronary interventions and whose 64-slice CT results prompted conventional CA investigation. In Makaryus (2006b) the patient population consisted of those with a history of CABG and the study assessed the accuracy of 64-slice CT compared with conventional CA in assessing graft occlusion in bypass grafts.

TABLE 23 *Prognostic study: full text*

Study, design and methods	Participants	Tests	Outcomes summary
Hoffmann, 2006[55] **Aim**: In patients who were being admitted for chest pain and who had negative initial cardiac biomarkers and a non-diagnostic ECG on presentation, to examine whether CT angiography characteristics were associated with risk of ACS and whether they provided incremental value to standard cardiovascular risk factors and standard clinical risk assessment **Study design**: Prospective observational cohort study with multivariate regression analysis performed to determine whether information on the extent of coronary atherosclerotic plaque added incremental value to information available at initial triage to predict ACS in patients who had any atherosclerotic plaque on MSCT **Method of recruitment**: Consecutive **Period**: May to July 2005 **Follow-up**: Mean 5.2 months (SD 0.3) **Country**: USA	**Enrolled**: 106 **Analysed**: 103 **Age (years)**: Mean 54, SD 12 **Gender**: M 62; F 41 **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: Adults with acute chest pain in whom initial ED evaluation was inconclusive **Inclusion criteria**: Age >18 years, >5 minutes of chest pain within the previous 24 hours, no or non-diagnostic ECG changes, normal initial cardiac biomarkers, sinus rhythm, ability to perform a breath-hold of 10–15 seconds **Exclusion criteria**: Elevated troponin-I or creatine kinase-MB levels in the initial blood sample obtained in the emergency department, new diagnostic ECG changes (ST-segment elevation or depression >1 mm or T-wave inversion >4 mm in more than two anatomically contiguous leads), haemodynamic or clinical instability, known allergy to iodinated contrast agent, serum creatinine >1.3 mg/dl, metformin treatment, hyperthyroidism, inability to provide informed consent, perceived interference with standard clinical care of patients	**64-Slice CT**: Sensation 64, Siemens, Germany **Retrospective ECG gating**: Yes **Rotation time**: 330 ms **Slice thickness**: 0.6 mm **Total scan time**: 13.6 (SD 2.2) s **Total examination time**: Including patient preparation 12 (SD 1) minutes **Radiation dose**: 6–11 mSv **Dose modulation used**: Yes **Use of drugs to limit heart rate**: All patients with a heart rate >60 bpm received a β-blocker (i.v. metoprolol, 5–20 mg) unless their systolic blood pressure was <100 mmHg or other contraindications were present **Heart rate during CT scan**: NS **Invasive CA**: NS	Of the 103 patients, 14 were diagnosed with ACS (five with an acute MI and nine with unstable angina pectoris). In multivariate logistic regression analyses both initial models containing either traditional risk factors or the categorised clinical estimates of probability of ACS did not predict ACS (LR 8.41, $p = 0.13$; LR 1.94, $p = 0.38$). Adding the extent of coronary atherosclerotic plaque on 64-slice CT as a continuous variable provided incremental information and improved both the model with traditional risk factors (LR 23.27, $p = 0.0007$) and the model with the categorised clinical estimates of probability of ACS (LR 19.1, $p = 0.0003$) In 81 (91%) of 89 patients diagnosed as not having an ACS during hospitalisation, telephone follow-up was conducted at a mean of 5.2 months (SD 0.3) after hospital discharge, with no patient having suffered a major cardiovascular event **Fryback and Thornbury grading**: Level 3

TABLE 24 *Prognostic studies: abstracts*

Study, design and methods	Participants	Tests	Outcomes summary
Auseon, 2006[105] **Aim**: To analyse the first year of use of cardiac multidetector CT in a major university hospital and determine its impact on invasive angiographic procedures to diagnose and treat atherosclerotic heart disease **Study design**: The findings from 1056 cardiovascular MSCT examinations were recorded along with subsequent cardiac catheterisations and cardiac surgeries. In addition, the yearly procedural volumes in the cardiac catheterisation laboratories were tabulated and assessed for change after the introduction of MSCT **Method of recruitment**: NS **Period**: 2005 calendar year **Follow-up**: NS **Country**: USA	**Enrolled**: NS **Analysed**: 1056 **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: NS **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	After MSCT, 94/1056 (8.9%) patients subsequently went on to require an invasive diagnostic CA, of whom 69% were found to have disease in the native coronary arteries, 29% in both native vessels and pre-existing bypass grafts and 2% in peripheral arteries. 24 of these patients went on to have a cardiovascular operative procedure. 23 patients required PCI in the coronary (92%), carotid (4%) and renal arteries (4%). Of the 21 coronary interventions, 47.6% had only native vessel disease and 52.4% also had prior bypass grafts **Average yearly increase in (a) diagnostic cardiac volume and (b) PCIs**: 2000–2004: 8.7%, 15.2% 2005 (64-slice CT): 7%, 15% **Fryback and Thornbury grading**: Level 4
Danciu, 2006[106] **Aim**: To review the initial experience with 64-slice CT angiography used in day-to-day practice in a single 20-physician cardiology group **Study design**: All records of studies performed during the first 6 months of 64-slice CT usage were reviewed. Charts were abstracted for demographic data, referral patterns and indications, prior cardiac testing, results of 64-slice CT and clinical decisions based on these. 17-Segment AHA model. Short-term follow-up was obtained in all patients	**Enrolled**: NS **Analysed**: 486 **Age (years)**: Mean 62, SD 12 **Gender**: M 282; F 204 **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: Abnormal stress test 228, unexplained symptoms after stress test 170, high risk for CAD 46, cardiomyopathy 16, other 26, including congenital heart disease and post-transplant **Inclusion criteria**: NS **Exclusion criteria**: NS	**64-Slice CT**: NS **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	CT ruled out CAD in 30% of patients without prior known disease. Invasive CA was recommended in 88 patients (18%) and saved in 398 patients (82%). CT missed six moderate stenoses, but no severe stenosis, and overestimated six lesions. 51 patients (10.5%) had revascularisation, by stent (n = 40, 8.5%) or CABG (n = 11, 2%). During 300 patient-years of follow-up two hospitalisations for minor CAD-related issues were noted in the medically treated patients **Image quality**: Adequate diagnostic quality was achieved in 99% of cases. All 17 AHA segments were seen in 89.5% of patients. All vessels were analysed in 98% of

continued

TABLE 24 *Prognostic studies: abstracts (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Method of recruitment: NS **Period**: NS **Follow-up**: NS **Country**: USA			patients. Three cases required rescanning because of artefact **Fryback and Thornbury grading**: Level 4
Gallagher, 2005[107] **Aim**: To compare the accuracy of MSCT with stress MPI in low-risk ED chest pain patients **Study design**: Prospective cross-sectional study. All patients received rest/stress MPI and 64-slice CT. Patients with positive MPI (inducible ischaemia or submaximal heart rate response) and/or positive MSCT (calcium score >400, stenosis >50%, or uninterpretable images defined by severe calcification or motion artefacts) were considered for catheterisation. Patients with negative results were discharged. 30-Day MACE were identified by follow-up telephone calls and chart review. Reference outcomes were defined as ACS, revascularisation, coronary stenosis >50% and 30-day MACE (death, acute MI, hospitalisation for angina or heart failure) **Method of recruitment**: NS **Period**: NS **Follow-up**: 30 days **Country**: USA	**Enrolled**: 97 **Analysed**: 93 **Age (years)**: NS **Gender**: NS **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: ED chest pain patients identified as low or very low risk (Reilly/Goldman criteria) **Exclusion criteria**: Positive cardiac enzymes or ECGs, known CAD, elevated creatinine, or contraindications to iodinated contrast or β-blockers	**64-Slice CT**: NS **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	MSCT and MPI were both negative in 52 patients, who were subsequently discharged without undergoing invasive CA During the 30-day follow-up 13 patients underwent cardiac catheterisation, seven had coronary stenoses >50% (six required coronary revascularisation). There were no additional 30-day adverse events **Fryback and Thornbury grading**: Level 4

continued

TABLE 24 *Prognostic studies: abstracts (cont'd)*

Study, design and methods	Participants	Tests	Outcomes summary
Rubinshtein, 2005[108–110] **Aim**: To examine the role of 64-slice CT angiography in the emergency room assessment of patients presenting with chest pain of uncertain aetiology **Study design**: MSCT was performed and presumptive diagnosis, decision to hospitalise and intended management (intensive therapy/early intervention vs medical management) were made and recorded. Following MSCT, change in diagnosis, need for early intervention and/or hospitalisation were noted **Method of recruitment**: NS **Period**: NS **Follow-up**: 30 days **Country**: Israel	**Enrolled**: NS **Analysed**: 40 **Age (years)**: Mean 56, SD 10.7 **Gender**: M 26; F 14 **Previous PCI**: NS **Previous CABG**: NS **Indications for testing**: NS **Inclusion criteria**: Emergency room patients presenting with chest pain of uncertain aetiology **Exclusion criteria**: NS	**64-Slice CT**: Brilliance 64, Philips **Retrospective ECG gating**: NS **Rotation time**: NS **Slice thickness**: NS **Total scan time**: NS **Total examination time**: NS **Radiation dose**: NS **Dose modulation used**: NS **Use of drugs to limit heart rate**: NS **Heart rate during CT scan**: NS **Invasive CA**: Details NS	**Pain of cardiac origin:** Before MSCT: 28/40 (70%) After MSCT: 14/40 (35%) Change in diagnosis/management: 14/28 (50%) *p*-Value: 0.002 **Hospitalisation recommended:** Before MSCT: 34/40 (85%) After MSCT: 19/40 (48%) Change in diagnosis/management: 15/34 (44%) *p*-Value: 0.0004 **Early intervention planned:** Before MSCT: 24/40 (60%) After MSCT: 9/40 (23%) Change in diagnosis/management: 17/40 (43%) *p*-Value: 0.0007 In 15 patients discharged from the emergency room as a result of negative/low-risk MSCT findings, there were no adverse cardiac events at 30-day follow-up **Fryback and Thornbury grading**: Level 4

MACE, major adverse cardiac events.

Appendix 6

Quality assessment results for individual studies

TABLE 25 *Quality assessment results*

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Ehara, 2006a[46]	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fine, 2006a[49]	+	+	+	+	+	+	+	+	?	+	+	+	–	–
Ghostine, 2006[52]	–	+	+	+	+	+	+	+	+	+	+	+	–	+
Hoffmann, 2006[55]	–	+	+	+[a]	+[a]	+	+	?	+	–	+	+	+	+
Johnson, 2007[56]	–	+	–	+[a]	+[a]	+	+	+	?	+	+	+	+	–
Leber, 2005[58]	+	+	+	+	+	+	?	?	?	+	+	+	–	+
Leschka, 2005[59]	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Meijboom, 2006[65]	–	+	+	+	+	+	+	+	?	–	+	+	+	+
Mollet, 2005[66]	+	+	+	+	+	+	+	+	?	+	+	+	+	–
Nikolaou, 2006[71]	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ong, 2006[75]	+	+	+	+	+	+	+	+	?	+	+	+	+	+
Pache, 2006[77]	–	+	+	+	+	+	+	?	?	+	+	+	–	+
Plass, 2006[79]	–	+	?	+	+	+	+	?	+	+	+	+	+	–
Pugliese, 2006a[83]	–	+	+	+	+	+	+	+	?	–	+	+	+	+
Raff, 2005[85]	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Rist, 2006[86]	–	+	+	+	+	+	+	+	?	+	+	+	+	+
Rixe, 2006[89]	–	+	+	+	+	+	?	+	+	+	+	+	–	+
Ropers, 2006a[93]	+	+	+	+	+	+	+	?	+	+	+	+	–	–
Ropers, 2006b[94]	–	+	+	+	+	+	+	?	+	+	+	+	–	+
Schuijf, 2006[100]	+	+	+	+	+	+	+	+	?	+	+	+	–	+
Sheth, 2006[101]	–	+	?	+	+	+	–[b]	+	?	+	+	–	+	–

+, Yes to the question; –, no to the question; ?, unclear.

[a] In the study by Hoffmann and colleagues[55] eight of 103 patients received 64–slice CT and invasive CA and in the study by Johnson and colleagues[56] 20 of 55 patients received 64–slice CT and invasive CA. Both studies were checked Yes for Q4 and Q5 as if only some patients in the studies received both tests, then it was only those who were considered to be the patient sample and included in the review.

[b] 64–Slice CT readers were given the segment in which severe stenosis was located on invasive CA, but were unaware of other invasive CA data.

Appendix 7

Studies included in the pooled estimates for different levels of analysis

TABLE 26 *Studies included in the pooled estimates for analysis*

Study	Level of analysis								
	Patient	**Segment**	**Left main artery**	**LAD artery**	**Proximal LAD artery**	**LCX artery**	**RCA**	**Stent**	**CABG**
Full-text studies									
Ehara, 2006[46]	✓	✓	✓	✓	✓	✓	✓		
Ghostine, 2006[52]	✓	✓	✓	✓	✓	✓	✓		
Hoffmann, 2006[55]	✓								
Leber, 2005[58]		✓						✓	
Leschka, 2005[59]		✓	✓	✓	✓	✓	✓		
Meijboom, 2006[65]	✓	✓		✓		✓	✓		
Mollet, 2005[66]	✓	✓							
Nikolaou, 2006[71]	✓	✓	✓	✓		✓	✓		
Ong, 2006[75]		✓	✓	✓	✓	✓	✓		
Pache, 2006[77]	✓								✓
Plass, 2006[79]	✓	✓							
Pugliese, 2006a[83]	✓	✓		✓	✓	✓	✓		
Raff, 2005[85]	✓	✓							
Rist, 2006[86]								✓	
Rixe, 2006[89]								✓	
Ropers, 2006a[93]	✓	✓							
Ropers, 2006b[94]	✓	✓							✓
Schuijf, 2006[100]	✓	✓						✓	
Abstracts									
Becker, 2006[39]	✓								
Ehara, 2006b[45]								✓	
Hausleiter, 2005[53]									✓
Malagutti, 2006[62]	✓								✓
Oncel, 2006[72]								✓	
Onuma, 2006[76]		✓							
Rubinshtein, 2006a[95]	✓								
Rubinshtein, 2006b[96]	✓								
Savino, 2006[97]	✓	✓							
Schlosser, 2006[99]		✓							

Appendix 8

Results of 64-slice or higher CT diagnostic studies

TABLE 27 *64-Slice or higher CT diagnostic studies: full text*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Ehara, 2006a[42–44,46] (patients with suspected and proven CAD, including 46 post-PCI)	>50% reduction of minimal lumen diameter Prevalence: 91% (61/67) Not evaluated: 3% (2/69) patients 8% (82/966) segments	All coronary artery segments	884	275	35	29	545	90	94	89	95
		RCA overall	265	90	9	10	156	90	95	91	94
		RCA proximal	65	27	1	3	34	96	92	90	97
		RCA mid	66	28	2	3	33	93	92	90	94
		RCA distal	68	23	5	2	38	82	95	92	88
		Posterior descending artery	66	12	1	2	51	86	98	92	96
		Left main trunk	64	19	0	2	43	100	96	90	100
		LAD overall	313	102	8	10	193	93	95	91	96
		LAD proximal	65	42	2	2	19	95	90	95	90
		LAD mid	60	18	0	3	39	100	93	86	100
		LAD distal	64	2	1	0	61	67	100	100	98
		First diagonal	62	25	2	3	32	93	91	89	94
		Second diagonal	62	15	3	2	42	83	95	88	93
		LCX overall	242	64	11	14	153	85	92	82	93
		LCX proximal	62	19	1	4	38	95	90	83	97
		LCX distal	64	27	5	8	24	84	75	77	83
		First obtuse marginal artery	64	14	3	1	46	82	98	93	94
		Second obtuse marginal artery	52	4	2	1	45	67	98	80	96
		Patients	67	59	1	1	6	98	86	98	86
Fine, 2006a[47,49] (all patients with suspected CAD)	>50% stenosis Prevalence: NS Not evaluated: 6% (4/66) patients	Arteries	NS	NS	NS	NS	NS	95	96	97	92

continued

TABLE 27 *64-Slice or higher CT diagnostic studies: full text (cont'd)*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Ghostine, 2006[51,52] (all patients LBBB)	>50% stenosis Prevalence: 44% (29/66) Not evaluated: 0% (0/66) patients 0% (0/990) segments	All segments	990	68	7	26	889	72	99	91	97
		Left main	66	5	0	0	61	100	100	100	100
		LAD	330	37	0	5	288	88	100	100	98
		LAD proximal	66	15	0	1	50	94	100	100	98
		LAD mid	66	16	0	3	47	84	100	100	94
		LAD distal	66	0	0	0	66		100		100
		First diagonal	66	6	0	1	59	86	100	100	98
		Second diagonal	66	0	0	0	66		100		100
		LCX	264	13	3	9	239	59	99	81	96
		LCX proximal	66	5	3	0	58	100	95	63	100
		LCX distal	66	3	0	2	61	60	100	100	97
		First obtuse marginal	66	4	0	4	58	50	100	100	94
		Second obtuse marginal	66	1	0	3	62	25	100	100	95
		RCA	330	13	4	12	301	52	99	76	96
		RCA proximal	66	2	1	2	61	50	98	67	97
		RCA mid	66	7	3	3	53	70	95	70	95
		RCA distal	66	2	0	1	63	67	100	100	98
		Right posterior descending	66	1	0	3	62	25	100	100	95
		Posterolateral artery	66	1	0	3	62	25	100	100	95
		Patients	66	28	2	1	35	97	95	93	97
Hoffmann, 2006[55] (eight of 103 patients with acute chest pain received CA)	⩾50% stenosis Prevalence: 63% (5/8) Not evaluated: 0% (0/8) patients	Patients	8	5	0	0	3	100	100	100	100
Johnson, 2007[56] (all patients with acute chest pain)	>50% stenosis Prevalence: 85% (17/20) Not evaluated: 0% (0/20) patients	Patients	20					94	77	84	91

continued

TABLE 27 *64-Slice or higher CT diagnostic studies: full text (cont'd)*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Leber, 2005[57,58a] (all patients with stable angina pectoris, including ten post-PCI)	>50% stenosis Prevalence: 42% (25/59) Not evaluated: 7% (4/59) patients 8% (74/885) segments	All segments	798	59	23	16	700	79	97	72	98
		Patients	55	22	NS	3	NS	88	NS	NS	NS
	>75% stenosis Not evaluated: As above	All segments	798	28	11	7	752	80	99	72	99
		Patients	45	NS	3	NS	17	NS	85	NS	NS
	Stenosis that subsequently required either PCI or CABG	Patients	18	17		1		94			
	In-stent restenosis >50%	Stents	13	2	4	2	5	50	56	33	71
Leschka, 2005[59] (patients with suspected CAD or prior to CABG)	Narrowing of the coronary lumen >50% Prevalence: 70% (47/67) Not evaluated: 0% (0/67) patients 0% (0/1005) segments	All vessel segments	1005	165	24	11	805	94	97	87	99
		Left main	67	6	0	0	61	100	100	100	100
		LAD (proximal, middle, distal)	201	54	7	3	137	95	95	89	98
		LAD proximal	67	28	0	0	39	100	100	100	100
		LAD middle	67	25	5	2	35	93	88	83	95
		LAD distal	67	1	2	1	63	50	97	33	98
		LCX (proximal, distal)	134	32	8	2	92	94	92	80	98
		LCX proximal	67	18	5	0	44	100	90	78	100
		LCX distal	67	14	3	2	48	88	94	82	96
		Left posterior descending artery	67	0	0	1	66	0	100	NA	99
		Right posterior descending artery	67	2	0	0	65	100	100	100	100
		RCA (proximal, middle, distal)	201	41	6	3	151	93	96	87	98
		RCA proximal	67	18	0	0	49	100	100	100	100
		RCA middle	67	19	4	1	43	95	91	83	98
		RCA distal	67	4	2	2	59	67	97	67	97
		Diagonal branch 1	67	7	1	2	57	78	98	88	97
		Diagonal branch 2	67	8	0	0	59	100	100	100	100
		Obtuse marginal branches	67	2	0	0	65	100	100	100	100
		Posterolateral branches	67	13	2	0	52	100	96	87	100

continued

TABLE 27 *64-Slice or higher CT diagnostic studies: full text (cont'd)*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Meijboom, 2006[64,65] (all patients referred for cardiac valve surgery)	⩾50% stenosis Prevalence: 26% (18/70) Not evaluated: 0% (0/70) patients 0% (0/280) arteries 0% (0/1003) segments	All segments	1003	34	18	2	949	94	98	65	100
		Segments: calcium score 0–10	338	0	0	0	338		100		100
		Segments: calcium score 11–400	465	15	7	0	443	100	98	68	100
		Segments: calcium score 401–1000	146	16	5	1	124	94	96	76	99
		Segments: calcium score >1000	54	3	6	1	44	75	88	33	98
		Arteries	280	26	8	0	246	100	97	76	100
		RCA	70	10	2	0	58	100	97	83	100
		Left main	70	0	0	0	70		100		100
		LAD	70	10	6	0	54	100	90	63	100
		Circumflex	70	6	0	0	64	100	100	100	100
		Patients	70	18	4	0	48	100	92	82	100
		Patients with angina pectoris	21	8	1	0	12	100	92	89	100
		Patients with no angina pectoris	49	10	3	0	36	100	92	77	100
		Patients with aortic stenosis	31	9	3	0	19	100	86	75	100
		Patients with no aortic stenosis	39	9	1	0	29	100	97	90	100
Mollet, 2005[40,66,67] (patients with atypical chest pain, stable or unstable angina pectoris, or non-ST segment MI)	⩾50% stenosis Prevalence: 76% (39/51) Not evaluated: 2% (1/52) patients 18% (159/884) segments (of which 142 could not be visualised on conventional angiogram)	All segments	725	93	30	1	601	99	95	76	100
		Proximal segments	204	NS	NS	NS	NS	100	97	83	100
		Mid segments	142	NS	NS	NS	NS	97	94	81	99
		Distal segments	121	NS	NS	NS	NS	100	97	73	100
		Side branches	258	NS	NS	NS	NS	100	94	65	100
		Left main	51	NS	NS	NS	NS	100	100	100	100
		LAD	230	NS	NS	NS	NS	97	92	69	99
		LCX	235	NS	NS	NS	NS	100	97	83	100
		RCA	209	NS	NS	NS	NS	100	95	77	100
		Patients	51	38	1	0	12	100	92	97	100

continued

TABLE 27 *64-Slice or higher CT diagnostic studies: full text (cont'd)*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Nikolaou, 2006[69–71] (patients with suspected or known CAD)	>50% stenosis Prevalence: 57% (39/68) Not evaluated: 6% (4/72) patients 10% (97/1020) segments	All segments	923	97	43	21	762	82	95	69	97
		Left main	68	4	0	0	64	100	100	100	100
		LAD	311	47	19	13	232	78	92	71	95
		RCA	251	26	9	4	212	87	96	74	98
		LCX	293	20	15	4	254	83	94	57	98
		All patients	68	38	6	1	23	97	79	86	96
		Patients with known CAD	29	NS	NS	NS	NS	100	75	85	100
		Patients with suspected CAD	39	NS	NS	NS	NS	95	82	88	93
	>75% stenosis	All segments	56	48	NS	8	NS	86	NS	NS	NS
		Left main	3	3	NS	0	NS	100	NS	NS	NS
		LAD	30	25	NS	5	NS	83	NS	NS	NS
		RCA	13	12	NS	1	NS	92	NS	NS	NS
		LCX	10	8	NS	2	NS	80	NS	NS	NS
Ong, 2006[74,75*b*] (all patients with ischaemic heart disease)	Diseased segments were graded as 1 = none or mild stenosis, or 2 = moderate to severe stenosis ⩾50% Prevalence (patients with significant lesions): 73% (98/134) Not evaluated: 10% (143/1474) segments	All segments (all patients)	1331	185	45	32	1069	85	96	80	97
		Left main	128	5	0	0	123	100	100	100	100
		Proximal LAD	125	39	7	4	75	91	91	85	90
		Mid LAD	122	38	7	1	76	97	92	84	99
		Distal LAD	112	4	1	0	107	100	99	80	100
		Main diagonal branch	115	20	2	4	89	83	98	91	96
		LCX overall	256	18	14	7	217	72	94	56	97
		Proximal circumflex	129	12	8	3	106	80	93	60	97
		Distal circumflex	127	6	6	4	111	60	95	50	97
		Main obtuse marginal	113	5	2	7	99	42	98	71	93
		RCA overall	360	56	12	9	283	86	96	82	97
		Proximal RCA	128	37	3	1	87	97	97	93	99
		Mid RCA	117	9	7	6	95	60	93	56	94
		Distal RCA	115	10	2	2	101	83	98	83	98
		All segments (patients with calcium score <142 AS)	700	64	12	5	619	93	98	84	99
		Left main	65	0	0	0	65		100		100
		Proximal LAD	63	13	3	0	47	100	94	81	100
		Mid LAD	63	16	1	1	45	94	98	94	98
		Distal LAD	61	1	0	0	60	100	100	100	100

continued

TABLE 27 *64-Slice or higher CT diagnostic studies: full text (cont'd)*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
		Main diagonal branch	63	10	0	1	52	91	100	100	98
		LCX overall	132	2	3	1	126	67	98	40	99
		Proximal circumflex	66	2	2	1	61	67	97	50	98
		Distal circumflex	66		1		65		99		100
		Main obtuse marginal	61	1	1	1	58	50	98	50	98
		RCA overall	192	21	4	1	166	95	98	84	99
		Proximal RCA	66	16	0	0	50	100	100	100	100
		Mid RCA	63	2	3	1	57	67	95	40	98
		Distal RCA	63	3	1	0	59	100	98	75	100
		All segments (patients with calcium score ⩾142 AS)	631	121	33	27	450	82	93	79	94
		Left main	63	5	0	0	58	100	100	100	100
		Proximal LAD	62	26	4	4	28	87	88	87	88
		Mid LAD	59	22	6	0	31	100	84	79	100
		Distal LAD	51	3	1	0	47	100	98	75	100
		Main diagonal branch	52	10	2	3	37	77	95	83	93
		LCX overall	124	16	11	6	91	73	89	59	94
		Proximal circumflex	63	10	6	2	45	83	88	63	96
		Distal circumflex	61	6	5	4	46	60	90	55	92
		Main obtuse marginal	52	4	1	6	41	40	98	80	87
		RCA overall	168	35	8	8	117	81	94	81	94
		Proximal RCA	62	21	3	1	37	95	93	88	97
		Mid RCA	54	7	4	5	38	58	90	64	88
		Distal RCA	52	7	1	2	42	78	98	88	95
Pache, 2006[77] (all patients post CABG)	>50% stenosis Prevalence: 77% (24/31) Not evaluated: 0% (0/93) grafts	All grafts	93	45	5	1	42	98	89	90	98
		Arterial grafts	22	5	4	1	12	83	75	56	92
		Venous grafts	71	40	1	0	30	100	97	98	100
		Patients	31	24	2	0	5	100	71	92	100

continued

TABLE 27 *64-Slice or higher CT diagnostic studies: full text (cont'd)*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Plass, 2006[79,80] (patients with CAD and patients with valve disease)	>50% stenosis Prevalence: 80% (40/50) 3% (17/550) segments rated not assessable but included in the analysis: three significant lesions missed with CT in unassessable segments were classed as FN	All segments	550	111	18	17	404	87	96	86	96
		Segments classed as reliable	506	106	11	8	381	93	97	91	98
		Segments – valvular disease patients	110		1		109		99		
		Patients	50	40	1	0	9	100	90	98	100
		Patients with valvular disease	10		1		9		90		
Pugliese, 2006a[83] (all patients with stable angina pectoris)	⩾50% stenosis Prevalence: 71% (25/35) Not evaluated: 0% (0/35) patients 0% (0/494) segments	All segments	494	66	19	1	408	99	96	78	100
		RCA, posterior descending artery, posterolateral artery	138	20	5	0	113	100	96	80	100
		RCA	90	17	4	0	69	100	95	81	100
		RCA 1	35	10	1	0	24	100	96	91	100
		RCA 2	28	5	1	0	22	100	96	83	100
		RCA 3	27	2	2	0	23	100	92	50	100
		Posterior descending artery	27	1	0	0	26	100	100	100	100
		Distal RCA/posterolateral artery	21	2	1	0	18	100	95	67	100
		Left main	35		0		35		100		100
		LAD, diagonal branches	156	25	9	1	121	96	93	74	99
		LAD	101	18	3	1	79	95	96	86	99
		LAD 1	35	8	1	0	26	100	96	89	100
		LAD 2	33	9	2	1	21	90	91	82	95
		LAD 3	33	1	0	0	32	100	100	100	100
		Diagonal branches	55	7	6	0	42	100	88	54	100
		Diagonal branch 1	33	6	5	0	22	100	81	55	100
		Diagonal branch 2	22	1	1	0	20	100	95	50	100
		LCX, MO, intermediate branch	165	21	5	0	139	100	97	81	100
		LCX	92	10	2	0	80	100	98	83	100
		LCX 1	35	4	0	0	31	100	100	100	100
		LCX 2	34	5	2	0	27	100	93	71	100
		LCX 3	23	1	0	0	22	100	100	100	100

continued

TABLE 27 *64-Slice or higher CT diagnostic studies: full text (cont'd)*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
		MO	60	9	2	0	49	100	96	82	100
		MO 1	35	7	2	0	26	100	93	78	100
		MO 2	25	2	0	0	23	100	100	100	100
		Intermediate branch	13	2	1	0	10	100	91	67	100
		Patients	35	25	1	0	9	100	90	96	100
Raff, 2005[85] (all patients with suspected CAD)	>50% stenosis Prevalence: 57% (40/70) Not evaluated: 0% (0/70) patients 0.4% (1/280) arteries 12% (130/1065) segments	Segments	935	79	41	13	802	86	95	66	98
		Calcium rating: segments: none	709	27	14	8	660	77	98	66	99
		Calcium rating: segments: mild	89	13	5	2	69	87	93	72	97
		Calcium rating: segments: moderate	48	11	6	1	30	92	83	65	97
		Calcium rating: segments: severe	88	28	16	2	42	93	72	64	95
		Arteries	279	63	16	6	194	91	92	80	97
		Calcium rating: arteries: none	172	22	3	3	144	88	98	88	98
		Calcium rating: arteries: mild	36	10	4	1	21	91	84	71	95
		Calcium rating: arteries: moderate	30	10	3	1	16	91	84	77	94
		Calcium rating: arteries: severe	40	21	6	1	12	95	67	78	92
		Patients	70	38	3	2	27	95	90	93	93
		Calcium score 0–100	35	15	1	1	18	94	95	94	95
		Calcium score 101–400	17	9	1	0	7	100	88	90	100
		Calcium score 401–1804	18	14	1	1	2	93	67	93	67
		BMI normal (<25 kg/m^2)	10	5	0	0	5	100	100	100	100
		BMI overweight (25–29.9 kg/m^2)	25	14	1	0	10	100	91	93	100
		BMI obese (⩾30 kg/m^2)	35	19	2	2	12	90	86	90	86
		Heart rate <70 bpm	54	31	1	1	21	97	95	97	95
		Heart rate 71–85 bpm	15	7	2	1	5	88	71	78	83
		Heart rate >85 bpm	1		0		1		100		100
Rist, 2006[86] (all patients post-PCI)	⩾50% restenosis Not evaluated: 2% (1/46) stents	Stents	45	6	3	2	34	75	92	67	94
		Stenosis proximal <3 mm to stent	45	3	2	1	39	75	95	60	98
		Stenosis distal to stent	45	2	6	1	36	67	86	25	97
		Significant disease, not occluded		4		2		67			
	Occluded	Stents		2		0		100			

continued

TABLE 27 *64-Slice or higher CT diagnostic studies: full text (cont'd)*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Rixe 2006[87–89] (all patients post-PCI)	⩾50% restenosis Not evaluated: 42% (43/102) stents 48% (31/64) patients	Stents	59	6	1	1	51	86	98	86	98
		Stents ⩾3.0 mm	25?	100	100	100	100				
		Stents 3.0 mm	33	83	96	83	96				
		Stents <3.0 mm	1		0		1		100		100
		Patients	33	83	46	10	96				
Ropers, 2006a[90,92,93] (all patients with suspected CAD)	⩾50% stenosis Prevalence: 32% (26/81) Not evaluated: 4% (45/1128) segments 4% (15/336) arteries 4% (3/84) patients	Segments	1083	39	31	3	1010	93	97	56	100
		Arteries	321	36	20	2	263	95	93	64	99
		Patients	81	25	5	1	50	96	91	83	98
Ropers, 2006b[91,94] (all patients post-CABG)	> 50% stenosis	Bypass grafts	138	54	5	0	79	100	94	92	100
	Occluded	Bypass grafts	138	38	0	0	100	100	100	100	100
	50–99% stenosis	Bypass grafts classed as patent by CA	100	16	5	0	79	100	94	76	100
	>50% stenosis	Segments (evaluable)	566	87	111	14	354	86	76	44	96
	Prevalence: 72% (36/50)	Segments (unevaluable classed as positive)	621	97	156	14	354	87	69	38	96
		Non-grafted arteries and run-off vessels distal to bypass graft anastomoses	378	38	32	6	302	86	90	54	98
	Not evaluated: 0% (0/138) bypass grafts 9% (55/621) native segments 7% (29/407) non-grafted arteries and run-off vessels distal to bypass graft anastomoses 0% (0/50) patients	Non-grafted arteries and run-off vessels distal to bypass graft anastomoses (unevaluable classed as positive)	407	42	57	6	302	88	84	42	98
		Patients: bypass grafts	50	31	2	0	17	100	89	94	100
		Patients: non-grafted arteries and the distal run-off vessels	33	18	2	1	12	95	86	90	92
		Patients: non-grafted arteries and the distal run-off vessels (unevaluable classed as positive)	50	35	2	1	12	97	86	95	92

continued

TABLE 27 *64-Slice or higher CT diagnostic studies: full text (cont'd)*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
		Patients: bypass grafts, distal run-off vessels and non-grafted coronary arteries	33	18	2	1	12	95	86	90	92
		Patients: bypass grafts, distal run-off vessels and non-grafted coronary arteries (unevaluable classed as positive)	50	35	2	1	12	97	86	95	92
Schuijf, 2006[100] (patients scheduled for invasive CA)	⩾50% stenosis Prevalence: 52% (31/60) Not evaluated: 1% (12/854) segments 0.4% (1/240) arteries 2% (1/61) patients	Segments	842	62	14	11	755	85	98	82	99
		Arteries	239	46	7	7	179	87	96	87	96
		Patients	60	29	1	2	28	94	97	97	93
		Stented segments	44	3	0	0	41	100	100	100	100
Sheth, 2006[101] [all patients with significant (>70%) stenosis]	Lesions with ⩾1 feature of complexity	Segments with lesions that were >70% stenosed	55	23	5	3	24	88	83	82	89
	Lesions with severe calcium		55	5	7	0	43	100	86	42	100
	Lesions totally occluded		49	13	1	1	34	93	97	93	97
	Ostial lesions		49	3	1	2	43	60	98	75	96
	Bifurcation lesions		49	4	0	1	44	80	100	100	98
	Prevalence of stenosis >70%: 100% (29/29) Not evaluated: 15% (10/65) segments										

MO, marginal obtuse branch.

[a] Non-evaluable segments: four of 59 (60 segments) patients had CT angiograms that were severely affected by motion artefacts. Potentially evaluable segments from 59 patients = 885, – 60 segments = 825, – 14 distally located segments not evaluable because of an occlusion of four vessels = 811, – 13 segments containing a stent that were separately analysed = 798. Therefore, 10% (87/885) of segments were not evaluated.

[b] The data for LCX overall were calculated by adding the true positives, false positives, false negatives and true negatives for proximal circumflex and distal circumflex. The data for RCA overall were calculated by adding the true positives, false positives, false negatives and true negatives for proximal RCA, mid RCA and distal RCA.

TABLE 28 *64-Slice or higher CT diagnostic studies: abstracts*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Beck, 2006[37,38] (all patients with suspected CAD)	>50% stenosis	Segments	1326	NS	NS	NS	NS	90	99	95	98
Becker, 2006[39] (all patients with acute chest pain)	Significant CAD Prevalence: 59% (117/199)	Patients	199	113	17	4	65	97	79	87	94
Ehara, 2006b[45] (all patients post-PCI)	>50% stenosis	Stented segments	113	21	9	1	82	95	90	70	99
	Not evaluated: 12% (15/128)	Patients	80?					89	87	71	96
Fine, 2006b[48] (three groups of high-risk patients: diabetes, metabolic syndrome, comparison group)	Subclinical disease (lesions <70%), clinically significant disease (lesions >70%) Prevalence (lesions >70%): 41% diabetes, 33% metabolic syndrome, 15% comparison group	Diabetes group	101 in total	NS	NS	NS	NS	87	94	87	94
		Metabolic syndrome group		NS	NS	NS	NS	91	94	87	94
		Comparison group		NS	NS	NS	NS	91	98	93	98
Hausleiter, 2005[53] (all patients post-CABG)	⩾50% stenosis	CABGs	130	34	2	1	93	97	98	94	99
		Graft anastomosis	142	10	0			100			
		Run-off vessels of grafts	NS	NS	NS	NS	NS	100	98	80	100

continued

TABLE 28 *64-Slice or higher CT diagnostic studies: abstracts (cont'd)*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Makaryus, 2006a[61a] (patients with suspected CAD or recurrent symptoms after prior coronary interventions)	>50% stenosis	Unclear	NS	8	NS	2	NS	88%	97%	NS	NS
Makaryus 2006b[60a] (all patients post-CABG)	> 50% stenosis	Bypass grafts	43	NS	NS	NS	NS	90%	97%	NS	NS
Malagutti, 2006[62,63] (all patients post-CABG and symptomatic)	>50% stenosis Prevalence: 96% (50/52)	Grafted segments	182	71	4	1	106	99	96	95	99
		Obstructed run-offs		8		1		89			
		Non-grafted coronary branches	288	62	32	2	192	97	86	66	99
		Patients	52	50	1	0	1	100	50	98	100
		Graft disease	52	36	1	0	15	100	94	97	100
		Distal run-off disease	51	7	6	1	37	88	86	54	97
		Non-grafted CAD	47	28	8	0	11	100	58	78	100
Motoyama, 2006[68] (type of patients NS)	>50% stenosis	Segments with severe calcification excluded	101	NS	NS	NS	NS	100	96	73	100
		Segments with severe calcification assumed as stenosis	101	NS	NS	NS	NS	100	90	61	100
Oncel, 2006[72,73] (all patients post-PCI)	>50% stenosis	Coronary stents	43	23	1	2	17	92	94	96	89
Onuma, 2006[76] (type of patients NS)	>50% stenosis	Segments	430	51	4	3	372	94	99	93	99

continued

TABLE 28 *64-Slice or higher CT diagnostic studies: abstracts (cont'd)*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Pinto, 2006[78] (all patients post-PCI)	In-stent restenosis	Coronary stents	30?	3		0		100			
Pugliese, 2006b[81,82] (all patients with suspected CAD)	Cut-off not defined Not evaluated: 0% (0/*N* NS) segments >2 mm diameter 74% (*n*/*N* NS) coronary branches <2 mm diameter	Segments >2 mm diameter Segments >2 mm diameter plus assessable segments < 2 mm diameter						99 99	96 95	80 76	99 99
Pugliese, 2006c[84] (patients with unstable angina or suspected acute MI)	One or more vessel disease Prevalence: 96% (24/25)	Patients	25	24	0	0	1	100	100	100	100
Rubinshtein, 2006a[50,95] (all patients with chest pain and negative/equivocal ETT)	MSCT: ⩾50% stenosis Prevalence: 30% (40/133) ETT: equivocal (<1 mm horizontal, or upsloping, ST segment depression) Prevalence: 30% (40/133)	Patients, MSCT 64-slice Patients, ETT	133 133	40 22	4 35	0 18	89 58	100 55	96 62	91 39	100 76

continued

TABLE 28 *64-Slice or higher CT diagnostic studies: abstracts (cont'd)*

Study	Cut-off, prevalence	Unit of analysis	No. analysed	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Rubinshtein, 2006b[96] (patients with low-grade reversible perfusion defects on SPECT)	>50% stenosis Prevalence: 23% (9/40)	Vessels	51	10	5	0	36	100	88	67	100
		Patients	40	9	5	0	26	100	84	64	100
Savino, 2006[41,54,97,104] (all patients with suspected CAD)	>50% stenosis Prevalence: 35% (19/55) Not evaluated: 0% (0/55) patients	Segments	826	50	22	11	743	82	97	69	99
		Arteries	165	32	11	4	118	89	91	74	97
		Patients	55	19	6	0	30	100	83	76	100
Schlosser, 2006[98,99] (all patients with suspected CAD)	⩾50% stenosis	Segments	915	34	28	0	853	100	97	55	100
Sirol, 2006[102] (patients with suspected and known CAD)	>50% stenosis Not evaluated: 11% (65/586) segments	Segments	521					75	97	88	94
		Patients	38					75	89	88	76
Wang, 2006[103] (all patients with suspected CAD)	>50% stenosis	Arteries	192	56	9	3	124	95	93	86	98

[a] Makaryus (2006a) and Makaryus (2006b) have been treated as two separate studies, although their patients are drawn from the same patient population (n = 374) and there may also be some overlap of patients between the studies. Makaryus (2006a) assessed the accuracy of 64-slice CT for assessing significant coronary stenoses in comparison with conventional CA in patients suspected of having CAD or who had experienced recurrent symptoms after prior coronary interventions and whose 64-slice CT results prompted conventional CA investigation. In Makaryus (2006b) the patient population consisted of those with a history of CABG and the study assessed the accuracy of 64-slice CT compared with conventional CA in assessing graft occlusion in bypass grafts.

Appendix 9

Illustrative longer term modelling

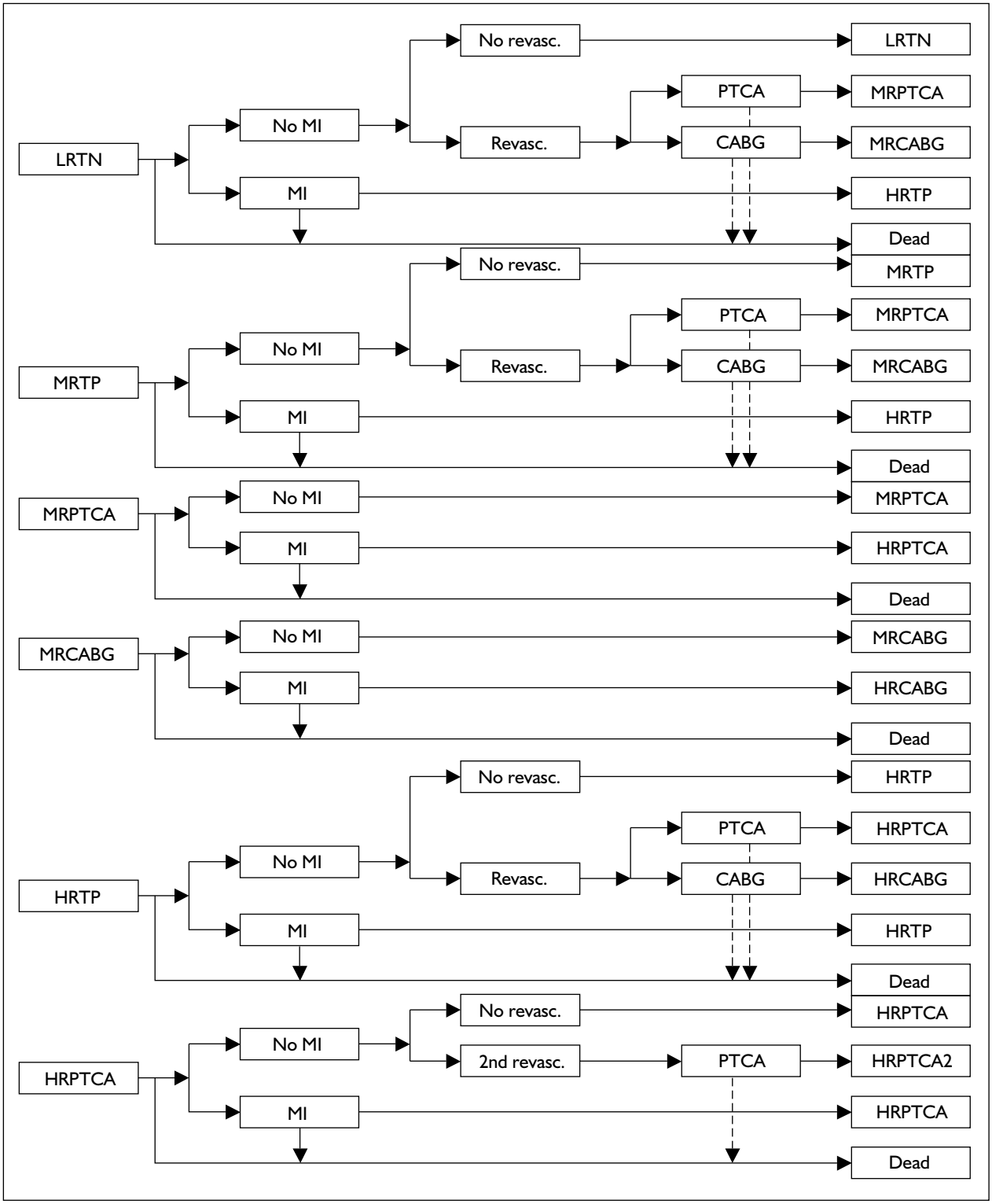

FIGURE 19 *Longer term modelling. FN, false negative; HR, high risk; LR, low risk; MR, medium risk; Rediag., rediagnosis; Revasc., revascularisation; TN, true negative; TP, true positive.*

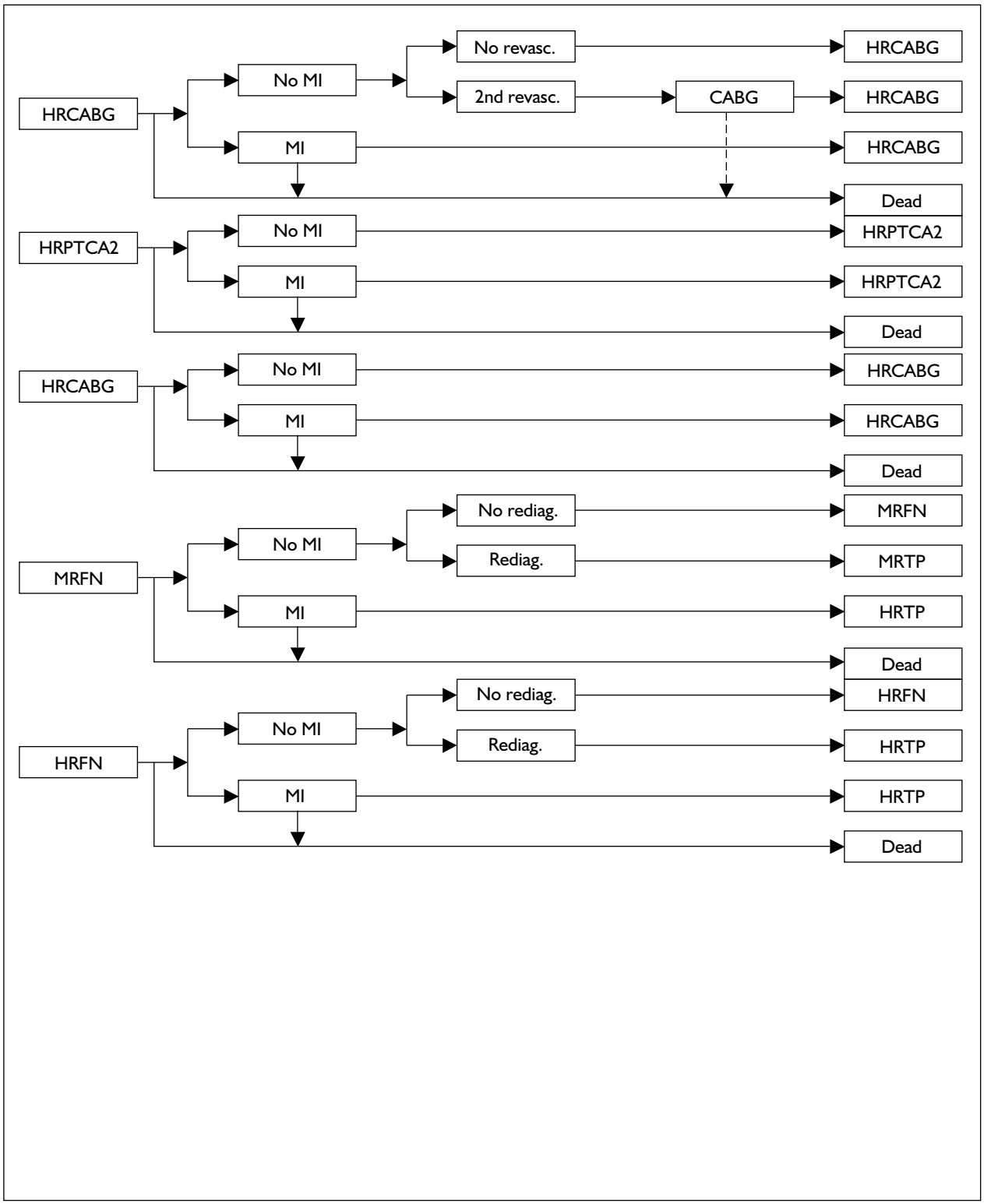

FIGURE 19 *Continued*

Appendix 10

Long-term model variables

TABLE 29 *Long-term model variables*

Discount rates					
Costs	3.50%				
Benefits	3.50%				
Cohort					
Cohort age	50				
% Male	100%				
Utilities					
Low risk	0.87				
Medium risk	0.81				
High risk	0.67				
MI	–0.10				
Revascularisation	–0.10				
Medication and other ongoing costs					
Low risk	£0				
Medium risk	£350				
High risk	£350				
General mortality multipliers					
Medium risk	2.3				
High risk	3.6				
Procedure mortality rates					
PTCA	3.10%				
CABG	0.75%				
Likelihood of HR second revascularisation					
From HR-PTCA	2.50%				
From HR-CABG	2.50%				
MI relative risk					
PTCA	17.00%				
CABG	40.00%				
MI fatality rate					
Fatal male	44.84%				
Fatal female	51.08%				
MI rates		**Cost**			
Low risk	2.50%	£1055			
Med risk	5.00%	£1055			
High risk	9.00%	£1055			
Revascularisation rates	**Base**	**PTCA**	**CABG**	**PTCA**	**CABG**
Low risk	5%	90.00%	10.00%	£3141	£6320
Med risk	50%	61.00%	39.00%	£3141	£6320
High risk	100%	10.00%	90.00%	£3141	£6320

Source: Mowatt *et al*. (2004).[113]

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