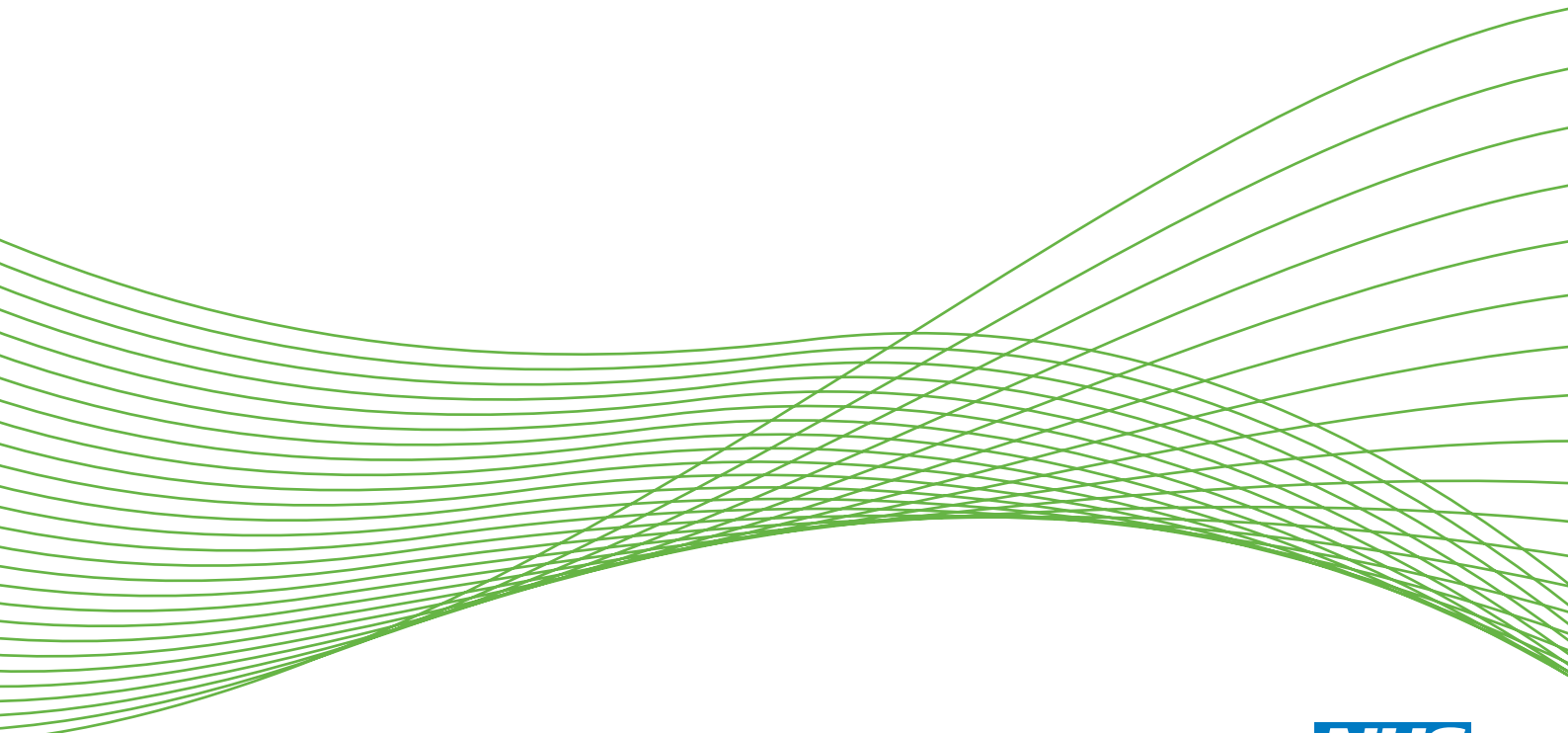A systematic review and economic evaluation of new-generation computed tomography scanners for imaging in coronary artery disease and congenital heart disease: Somatom Definition Flash, Aquilion ONE, Brilliance iCT and Discovery CT750 HD

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This report

Abstract

A systematic review and economic evaluation of new-generation computed tomography scanners for imaging in coronary artery disease and congenital heart disease: Somatom Definition Flash, Aquilion ONE, Brilliance iCT and Discovery CT750 HD

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Background: Computed tomography (CT) is important in diagnosing and managing many conditions, including coronary artery disease (CAD) and congenital heart disease. Current CT scanners can very accurately diagnose CAD requiring revascularisation in most patients. However, imaging technologies have developed rapidly and new-generation computed tomography (NGCCT) scanners may benefit patients who are difficult to image (e.g. obese patients, patients with high or irregular heart beats and patients who have high levels of coronary calcium or a previous stent or bypass graft).

Objective: To assess the clinical effectiveness and cost-effectiveness of NGCCT for diagnosing clinically significant CAD in patients who are difficult to image using 64-slice computed tomography and treatment planning in complex congenital heart disease.

Data sources: Bibliographic databases were searched from 2000 to February/March 2011, including MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) database and Science Citation Index (SCI). Trial registers and conference proceedings were searched.

Review methods: Systematic review methods followed published guidance. Risk of bias was assessed using QUADAS-2. Results were stratified by patient group. Summary sensitivity and specificity were calculated using a bivariate summary receiver operating characteristic, or random effects model. Heterogeneity was assessed using the chi-squared statistic and I^2-statistic. Cost-effectiveness of NGCCT was modelled separately for suspected and known CAD, evaluating invasive coronary angiography (ICA) only, ICA after positive NGCCT (NGCCT–ICA), and NGCCT only. The cost-effectiveness of NGCCT, compared with 64-slice CT, in reducing imaging-associated radiation in congenital heart disease was assessed.

Results: Twenty-four studies reported accuracy of NGCCT for diagnosing CAD in difficult-to-image patients. No clinical effectiveness studies of NGCCT in congenital heart disease were identified. The pooled per-patient estimates of sensitivity were

97.7% [95% confidence interval (CI) 88.0% to 99.9%], 97.7% (95% CI 93.2% to 99.3%) and 96.0% (95% CI 88.8% to 99.2%) for patients with arrhythmias, high heart rates and previous stent, respectively. The corresponding estimates of specificity were 81.7% (95% CI 71.6% to 89.4%), 86.3% (95% CI 80.2% to 90.7%) and 81.6% (95% CI 74.7% to 87.3%), respectively. In patients with high coronary calcium scores, previous bypass grafts or obesity, only per-segment or per-artery data were available. Sensitivity estimates remained high (>90% in all but one study). In patients with suspected CAD, the NGCCT-only strategy appeared most cost-effective; the incremental cost-effectiveness ratio (ICER) of NGCCT–ICA compared with NGCCT only was £71,000. In patients with known CAD, the most cost-effective strategy was NGCCT–ICA (highest cost saving, dominates ICA only). The ICER of NGCCT only compared with NGCCT–ICA was £726,230. For radiation exposure only, the ICER for NGCCT compared with 64-slice CT in congenital heart disease ranged from £521,000 for the youngest patients to £90,000 for adults.

Limitations: Available data were limited, particularly for obese patients and patients with previous bypass grafts. All studies of the accuracy of NGCCT assume that the reference standard (ICA) is 100% sensitive and specific; however, there is some evidence that ICA may sometimes underestimate the extent and severity of stenosis. Patients with more than one criterion that could contribute to difficulty in imaging were often excluded from studies; the effect on test accuracy of multiple difficult to image criteria remains uncertain.

Conclusions: NGCCT may be sufficiently accurate to diagnose clinically significant CAD in some or all difficult-to-image patient groups. Economic analyses suggest that NGCCT is likely to be considered cost-effective for difficult-to-image patients with CAD, at current levels of willingness to pay in the NHS. For patients with suspected CAD, NGCCT only would be most favourable; for patients with known CAD, NGCCT–ICA would be most favourable. No studies assessing the effects of NGCCT on therapeutic decision making, or subsequent patient outcomes, were identified. The ideal study to address these questions would be a large multi-centre RCT. However, one possible alternative might be to establish a multicentre tracker study. High-quality test accuracy studies, particularly in obese patients, patients with high coronary calcium, and those with previous bypass grafts are needed to confirm the findings of our systematic review. These studies should include patients with multiple difficult to image criteria.

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Contents

Glossary

Acute chest pain Chest pain/discomfort which has occurred recently and may still be present, is of suspected cardiac origin and may be due to acute myocardial infarction or unstable angina.

Calcium scoring A technique by which the extent of calcification in the coronary arteries is measured and scored. This does not necessarily reflect the degree of stenosis.

Congenital heart defect A defect in the structure of the heart and great vessels that is present at birth.

Coronary angiography An invasive diagnostic test that provides anatomical information about the degree of stenosis (narrowing) in a coronary artery. It involves manipulation of cardiac catheters from an artery in the arm or top of the leg. A contrast medium is injected into the coronary arteries, and the flow of contrast in the artery is monitored by taking a rapid series of radiographs. It is considered the reference standard for providing anatomical information and defining the site and severity of coronary artery lesions.

Coronary artery An artery that supplies the myocardium.

Coronary artery disease A condition in which atheromatous plaque builds up inside the coronary artery, leading to narrowing of the arteries, which may be sufficient to restrict blood flow and cause myocardial ischaemia.

Cost-effectiveness analysis An economic analysis that converts effects into health terms and describes the costs for additional health gain.

Decision modelling A theoretical construct that allows the comparison of the relationship between costs and outcomes of alternative health-care interventions.

False-negative Incorrect negative test result – number of diseased persons with a negative test result.

False-positive Incorrect positive test result – number of non-diseased persons with a positive test result.

Gantry Found in computed tomography machines, a gantry rotates around a patient for cross-sectional views.

Incremental cost-effectiveness ratio The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.

Index test The test of which performance is being evaluated.

Major aortopulmonary collateral arteries Arteries that develop to supply blood to the lungs when native pulmonary circulation is underdeveloped. Instead of coming from the pulmonary trunk, blood supply usually develops from the aorta and other systemic arteries.

Markov model An analytic method particularly suited to modelling repeated events, or the progression of a chronic disease over time.

Material separation The contrast resolution of the image between the iodine agent and the soft tissues. Improved material separation enables a lower dose of contrast agent to be used.

Meta-analysis Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.

Meta-regression Statistical technique used to explore the relationship between study characteristics and study results.

Multislice computed tomography coronary angiography A non-invasive investigation that provides coronary calcium scoring and anatomical information about the degree of stenosis (narrowing) in the coronary arteries. The scanner has a special X-ray tube and rotation speed, and as the technology has advanced the number of slices in each rotation has increased. A dual-source scanner has two pairs of X-ray sources and multislice detectors mounted at 90° to each other.

Myocardial perfusion scintigraphy with single-photon emission computed tomography Myocardial perfusion scintigraphy involves injecting small amounts of radioactive tracer to evaluate perfusion of the myocardium via the coronary arteries at stress and at rest. The distribution of the radioactive tracer is imaged using a gamma camera. In single-photon emission computed tomography (SPECT) the camera rotates round the patient and the raw data processed to obtain tomographic images of the myocardium. Cardiovascular stress may be induced by either pharmacological agents or exercise.

Opportunity costs The cost of forgone outcomes that could have been achieved through alternative investments.

Patent ductus arteriosus The ductus arteriosus is a duct or passage in the heart that is meant to close shortly after birth. In cases of patent ductus arteriosus, the duct fails to completely close, which means that some oxygen-rich blood leaks through the duct, into the pulmonary valve and into the lungs.

Publication bias Bias arising from the preferential publication of studies with statistically significant results.

Pulmonary artery sling A rare condition in which the left pulmonary artery anomalously originates from a normally positioned right pulmonary artery.

Quality of life An individual's emotional, social and physical well-being, and his or her ability to perform the ordinary tasks of living.

Quality-adjusted life-year A measure of health gain, used in economic evaluations, in which survival duration is weighted or adjusted by the patient's quality of life during the survival period.

Receiver operating characteristic curve A graph that illustrates the trade-offs between sensitivity and specificity, which result from varying the diagnostic threshold.

Reference standard The best currently available diagnostic test(s), against which the index test is compared.

Scimitar syndrome　A rare congenital heart defect characterised by anomalous venous return (partial or total) from the right lung. The name scimitar syndrome refers to the curvilinear pattern, seen on a chest radiograph, of the pulmonary veins that drain into the inferior vena cava.

Sensitivity　Proportion of people with the target disorder who have a positive test result.

Septal defects (atrial or ventricular)　A group of common congenital anomalies consisting of a hole in the septum (the wall) between the chambers of the heart. The hole may be between the left and right atria or the left and right ventricles. The result is that the blood cannot circulate as it should and the heart has to compensate by working harder.

Specificity　Proportion of people without the target disorder who have a negative test result.

Stable angina　There are no case definitions of stable angina that have been agreed internationally. The working definition of angina is a symptom of myocardial ischaemia that is recognised clinically by its character, its location and its relation to provocative stimuli. Angina is usually caused by obstructive coronary artery disease that is sufficiently severe to restrict oxygen delivery to the cardiac myocytes. Generally speaking, angiographic luminal obstruction estimated at ≥ 70% is regarded as 'severe' and likely to be a cause of angina, but this will depend on other factors.

Stenosis　A narrowing of the arteries leading to a reduction in blood flow. May be due to the build-up of atherosclerotic deposits of fibrous and fatty tissue or may be a congenital defect.

Stress echocardiography　An ultrasound examination of the heart. Exercise or pharmacological stress may be used to look for reversible systolic regional wall motion abnormalities consistent with the development of myocardial ischaemia.

Stress magnetic resonance imaging　Magnetic resonance imaging (MRI) is a diagnostic procedure that uses radio waves in a strong magnetic field. The pattern of electromagnetic energy released is detected and analysed by a computer to generate detailed images of the heart. Stress MRI is a specific application in which a contrast agent is used to detect myocardial blood flow at stress and at rest. Pharmacological stress is used to induce cardiovascular stress.

Tetralogy of Fallot　A complex congenital heart defect condition comprising a ventricular septal defect, pulmonary obstruction, a displaced aorta and an enlarged right ventricle.

Total anomalous pulmonary venous drainage　A rare cyanotic congenital heart defect in which all four pulmonary veins are incorrectly positioned and make anomalous connections to the systemic venous circulation. All pulmonary veins, draining blood from the lungs, should normally be connected to the left atrium; in total anomalous pulmonary venous drainage they drain into the right atrium, usually via systemic venous circulation.

Transposition of great arteries　A congenital heart defect in which the aorta and pulmonary artery are transposed so that the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. This leads to oxygen-low blood being pumped around the body.

True-negative　Correct negative test result – number of non-diseases persons with a negative test result.

True-positive　Correct positive test result – number of diseased persons with a positive test result.

Vascular ring A congenital defect in which there is abnormal formation of the aorta and/or its surrounding blood vessels. The trachea and oesophagus are completely encircled by a ring formed by these vessels, which can lead to breathing and digestive problems.

Unstable angina New onset chest pain/discomfort, or abrupt deterioration in previously stable angina, with chest pain/discomfort occurring frequently and with little or no exertion, and often with prolonged episodes. This often presents in the same way as myocardial infarction but without biomarker evidence of myocardial necrosis.

z-**axis** The direction that the scanning table travels in (i.e. head to toe).

List of abbreviations

ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
BCIS	British Cardiovascular Intervention Society
BMI	body mass index
b.p.m.	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society
CEP	Centre for Evidence-based Purchasing
CI	confidence interval
CMR	cardiovascular magnetic resonance
CRD	Centre for Reviews and Dissemination
CT	computed tomography
CTA	computed tomography angiography
CTCA	computed tomography coronary angiography
CV	cardiovascular
DLP	dose–length product
DSCT	dual-source computed tomography
ECG	electrocardiogram
EQ-5D	European Quality of Life-5 Dimensions
ESC	European Society of Cardiology
FN	false-negative
FP	false-positive
HCS	high calcium score
HDCT	high-definition computed tomography
HHR	high heart rate
HPA	Health Protection Agency
HR	hazard ratio
HRF	heart rate frequency
HRQoL	health-related quality of life
HRV	heart rate variability
ICA	invasive coronary angiography
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
MAPCA	major aortopulmonary collateral arteries
MI	myocardial infarction
MRI	magnetic resonance imaging
MSCT	multislice computed tomography
N/A	not available
NA	not applicable
NFE	non-fatal event
NGCCT	new-generation cardiac computed tomography
NGCCT–ICA	ICA after positive NGCCT
NR	not reported
OR	odds ratio
PCI	percutaneous coronary intervention
PSA	probabilistic sensitivity analysis

PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
SCCT	Society of Cardiovascular Computed Tomography
SD	standard deviation
SE	standard error
SPECT	single photon emission computed tomography
SROC	summary receiver operating characteristic
TAPVD	total anomalous pulmonary venous drainage
TIA	transient ischaemic attack
TN	true-negative
TP	true-positive
YRM	York Radiation Model

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

Executive summary

Background

Medical imaging, including computed tomography (CT), is important in diagnosing and managing many conditions. However, some potential disadvantages are associated with imaging [e.g. CT requires exposure to potentially harmful radiation, and invasive coronary angiography (ICA) is associated with increased risk of stroke, heart attack and death]. Imaging technologies have developed rapidly and new-generation computed tomography (NGCCT) scanners may offer advantages over CT and other imaging methods currently used (e.g. shorter imaging times, reduced radiation, increased accuracy). The development of NGCCT has focused on assessment of patients with coronary artery disease (CAD) and congenital heart disease. Current CT scanners can very accurately diagnose CAD requiring revascularisation in most patients. However, NGCCT may benefit patients who are difficult to image (e.g. obese patients, patients with high or irregular heart rates, and patients who have high levels of coronary calcium or a previous stent or bypass graft). Similarly, although patients with congenital heart disease can be diagnosed using existing technologies, NGCCT may provide additional information to help plan surgery in patients who have complex abnormalities.

Objectives

To assess the clinical effectiveness and cost-effectiveness of NGCCT, using Discovery CT750 HD (GE Healthcare), Brilliance iCT (Philips Healthcare), Somatom Definition Flash (Siemens Healthcare) or Aquilion ONE (Toshiba Medical Systems) for:

■ diagnosis of clinically significant CAD in patients who are difficult to image using (64-slice) CT
■ treatment planning in complex congenital heart disease.

Methods

A systematic review was conducted to assess the clinical effectiveness of NGCCT to diagnose clinically significant CAD in difficult-to-image patients [obese patients, patients with high heart rates (HHRs), arrhythmias, intolerance to beta-blockers, previous stent implantation(s) or bypass graft(s)], and for treatment planning in patients with complex congenital heart disease. Search strategies were based on target condition and intervention, as recommended in published guidance [Centre for Reviews and Dissemination (CRD). *Systematic reviews: CRD's guidance for undertaking reviews in health care*. York: University of York; 2009. URL: www.york. ac.yk/inst/crd/systematic_reviews_book.htm (accessed 12 January 2010); Cochrane Diagnostic Test Accuracy Working Group. *Handbook for DTA Reviews*: Cochrane Collaboration, 2011. URL: http://srdta.cochrane.org/handbook-dta-reviews (accessed 12 January 2011); Whiting P, Westwood M, Beynon R, Burke M, Sterne JA, Glanville J. Inclusion of methodological filters in searches for diagnostic test accuracy studies misses relevant studies. *J Clin Epidemiol* 2011;**64**:602–7]. Eight bibliographic databases were searched (2000 to February/March 2011). Research registers and conference proceedings were also searched. Systematic review methods followed published guidance [Centre for Reviews and Dissemination (CRD). *Systematic reviews: CRD's guidance for undertaking reviews in health care*. York: University of York; 2009. URL:

www.york.ac.yk/inst/crd/systematic_reviews_book.htm (accessed 12 January 2010); National Institute for Health and Clinical Excellence (NICE). *Diagnostics Assessment Programme: interim methods statement (version 2)*. London: NICE; 2010. URL: www.nice.org.uk/media/164/3C/DAPInterimMethodsStatementProgramme.pdf (accessed 12 January 2011)]. The risk of bias in included studies was assessed using the QUADAS-2. Results were summarised in tables and text, stratified by patient group. Where four or more data sets were available, summary receiver operating characteristic (SROC) curves and summary estimates of sensitivity and specificity, with 95% confidence intervals (CIs) were calculated using a bivariate model (Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;**58**:982–90; Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JA. Unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics* 2006;**1**:1–21).Where a bivariate model could not be fitted, pooled estimates of sensitivity and specificity, with 95% CIs, were estimated using a random-effects model. Between-study heterogeneity was assessed using the chi-squared test and inconsistency was quantified using the I^2-statistic (Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–58).

The health economic analysis assessed the cost-effectiveness of NGCCT in two populations (NGCCT vs ICA in difficult-to-image patients with CAD, and NGCCT vs 64-slice CT in patients with congenital heart disease).

For the CAD population, five models were combined:

1. decision tree modelling the diagnostic pathway [Walker S. Email regarding CE-MARC model (Walker S, University of York, March 2011, personal communication)]
2. alive–dead Markov model for 'healthy' patients without CAD [Office of Population Censuses and Surveys, Government Statistical Service, Office for National Statistics. *Mortality statistics (Cause). Review of the Registrar General on deaths by cause, sex, and age, in England and Wales.* Series DH2. London: HMSO; 2006]
3. stroke model estimating the impact of test- and treatment-related stroke
4. model for prognosis of patients with CAD [the EURopean trial On recluction of cardiovascular events with Perindopril in stable coronary Artery disease (EUROPA) model] (Briggs A, Mihaylova B, Sculpher M, Hall A, Wolstenholme J, Simoons M, *et al.* Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study. *Heart* 2007;**93**:1081–6)
5. model assessing the impact of imaging radiation on cancer morbidity and mortality (McKenna C, Wade R, Faria R, Yang H, Stirk L, Gummerson N, *et al. EOS 2D/3D X-ray Imaging System: a Diagnostics Assessment Report.* York: Centre for Reviews and Dissemination/Centre for Health Economics, University of York; 2011. URL: http://guidance.nice.org.uk/DT/1/AssessmentReport/pdf/English).

Model 5, the York Radiation Model (YRM), was also used to assess the cost-effectiveness of using NGCCT to lower imaging-associated radiation in patients with congenital heart disease.

The difficult-to-image CAD population was divided into two subgroups (suspected and known CAD). NGCCT has different purposes in these two populations (to diagnose CAD and to determine if revascularisation is necessary).

Three imaging strategies were evaluated: ICA only, ICA following a positive NGCCT (NGCCT–ICA) and NGCCT only. ICA was assumed to have 100% sensitivity and specificity; however, ICA has a risk of serious complications, including stroke, non-fatal myocardial infarction (MI) and death.

The diagnostic decision tree identifies patients as true-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN), depending on performance of the test or test strategy and prior likelihood of test outcome. Estimates of sensitivity and specificity of NGCCT varied between difficult-to-image patient groups, but were assumed to be equal for the suspected and known CAD populations within these groups.

Two versions of the diagnostic model were created because the known (treatment options coronary artery bypass graft and percutaneous coronary intervention) and suspected CAD (treatment options as for known CAD or drug treatment) populations are treated differently after a positive test. Patients without the disease (TN and FP from the suspected CAD population) were modelled with a simple alive–dead Markov model based on UK life tables. The costs and health expectancy of patients who experienced a stroke due to initial ICA or revascularisation were modelled using a simple alive-dead stroke model. Life expectancy was based on updated UK life tables, combined with a multiplier for age-specific mortality among stroke patients. Patients with CAD, who have not experienced a stroke due to initial ICA or revascularisation, enter the EUROPA model. This model predicts the probability of cardiovascular events [cardiac arrest, (non-)fatal MI], mortality, decrease in quality of life, and costs associated with these events. The impact of radiation reduction on lifetime cancer risk and subsequent life expectancy, health-related quality of life (HRQoL) and costs was assessed using the YRM. Each CAD population, while going through the various models, accumulates costs and quality-adjusted life-years (QALYs). The impact of uncertainty about the various input parameters on the outcomes was explored through sensitivity analyses.

The YRM was used to compare the costs and QALYs of NGCCT and 64-slice CT in the congenital heart disease population. In this model, only the effect of reduced radiation was assessed; other potential benefits of NGCCT in costs or QALYs were not explored, owing to lack of data.

Results

Twenty-four studies, reporting data on the accuracy of NGCCT for the diagnosis of clinically significant CAD in difficult-to-image patients, were included in the systematic review. No study reported data on changes to patient management or outcomes, test-related adverse events or patient preferences. No clinical effectiveness studies of NGCCT in patients with congenital heart disease were identified.

Most included studies were judged at low risk of bias with respect to the reference standard domain of QUADAS-2; the inclusion criteria of the review specified a single reference standard (ICA). Risk of bias with respect to patient selection was frequently unclear because of uncertainty regarding the potential impact of inappropriate exclusions; difficult-to-image patient groups (e.g. obese patients) were often reported with prior exclusion of patients with one or more additional criteria which may contribute further to difficulty in imaging and the proportions of participants excluded in this way were frequently unclear. Inclusion of multiple measurements per patient (per-arterial segment, per-artery or per-stent data) was also common. Where studies excluded non-diagnostic arterial segments from analyses, the potential impact of this was frequently unclear because their distribution between patients was not reported.

Where per-patient estimates of test accuracy were possible, these were generally high. The pooled estimates of sensitivity were 97.7% (95% CI 88.1% to 99.9%), 97.7% (95% CI 93.2% to 99.3%) and 96.0% (95% CI 88.8% to 99.2%), for patients with arrhythmias, HHRs and previous stent implantation(s), respectively. The corresponding estimates of specificity were 81.7%

(95% CI 71.6% to 89.4%), 86.3% (95% CI 80.2% to 90.7%) and 81.6% (95% CI 74.7% to 87.3%), respectively. The high per-patient estimates of sensitivity (>95%) indicate that NGCCT could be used to reliably rule out significant stenosis, potentially avoiding some invasive investigations (ICA) in these patient groups. Although there were no data for beta-blocker-intolerant patients, it should be noted that no study reporting per-patient data for patients with HHRs used additional beta-blockers before scanning. It may therefore be inferred that NGCCT could be used to image patients who are intolerant to beta-blockers who could not otherwise be reliably imaged by 64-slice CT. With the exception of one small study, data on the accuracy of NGCCT in patients with high coronary calcium scores, previous bypass grafts, or obesity were limited to per-arterial segment or per-artery data. Sensitivity estimates remained high (>90% in all but one study).

A further important consideration, when assessing the practical utility of a new diagnostic technology, is the proportion of patients in whom the results of testing are likely to be non-diagnostic. Few studies reported numbers of non-diagnostic images; where these data were reported, they were often for the whole study population, rather than the difficult-to-image subgroup. Three studies did report subgroup-specific non-diagnostic image rates; these were 5% for patients with arrhythmias, 6.8% for patients with HHRs and 9% for patients with previous stent implantation. These results indicate that the proportions of otherwise difficult-to-image patients in whom imaging would remain non-diagnostic, even with NGCCT, are likely to be low; further studies are needed to confirm this.

The health economic analysis showed that the use of NGCCT in difficult-to-image CAD patients may be considered cost-effective. In patients with suspected CAD, the NGCCT-only strategy might be considered the most attractive; although NGCCT–ICA is slightly more effective, the additional costs are such that the resulting incremental cost-effectiveness ratio (ICER), £71,000, is so high that it is unlikely (given the conventional willingness-to-pay threshold range of £20,000–30,000) that commissioners of health care would consider this a cost-effective use of NHS resources. Likewise, ICA only is slightly more effective than NGCCT–ICA, but again the additional costs are high enough (ICER £83,000) that it is unlikely to be considered cost-effective. In patients with known CAD, the most attractive strategy would be NGCCT–ICA; this scenario yields the highest cost saving and dominates ICA only. The ICER of NGCCT only compared with NGCCT–ICA is so high (£726,230) that it is unlikely to be considered cost-effective. When taking uncertainty into account, these findings were confirmed. In the suspected population, in the range of thresholds of <£70,000, the NGCCT-only strategy has the highest probability of being cost-effective. For thresholds of >£70,000, the three different strategies are similar. For the known CAD patients, the NGCCT–ICA strategy has the highest probability of being cost-effective, over the whole range of thresholds, whereas the ICA-only strategy always has the smallest probability of being cost-effective.

The key drivers behind these results are percentage of patients misclassified (a function of both diagnostic accuracy and prior likelihood) and complication rates for ICA and revascularisation. Overall, in the population with suspected CAD, the NGCCT-only strategy has the lowest overall procedure-induced mortality rate, less than half that of ICA only. To some extent, the same results apply for the known CAD population; here the overall procedure-induced mortality and morbidity is lowest in the NGCCT–ICA strategy. ICA only has the highest overall procedure-induced mortality and morbidity rate. There is currently uncertainty about the estimate of cost for an NGCCT scan. Therefore, a scenario analysis was performed; increasing cost from £150 to £207 per scan did not alter our findings. Including the effects of reduced radiation had minimal impact on outcomes.

Analysis showed that, when only considering radiation exposure, the use of NGCCT instead of 64-slice CT is unlikely to be considered cost-effective in patients with congenital heart disease.

The ICER ranged from £521,000 per QALY gained for the youngest patients to £90,000 per QALY gained for adults. The reduction in radiation by replacing a single 64-slice CT scan with NGCCT is small, and leads to only a minor decrease in radiation-related cancer incidence. Therefore, it cannot justify the additional costs of the NGCCT scan. Various scenarios were explored to assess the impact of the main assumptions. Only in the most unlikely scenario, i.e. an average radiation dose of 25 millisieverts for a 64-slice CT, do the ICERs decrease significantly.

Conclusions

The results of our systematic review suggest that NGCCT may be sufficiently accurate to diagnose anatomically significant CAD in some, or all, difficult-to-image patient groups. These technologies may be particularly useful in ruling out patients from further invasive investigations. However, data were sparse, particularly for obese patients, patients with high coronary calcium and those with previous bypass grafts.

The limited available data indicate that the proportions of difficult-to-image patients, in whom imaging would remain 'non-diagnostic', even using NGCCT, are likely to be low; further studies are needed to confirm this.

The results of the economic evaluation suggest that NGCCT is likely to be considered cost-effective for difficult-to-image patients with CAD, at current levels of willingness to pay in the NHS. Although ICA can diagnose these patients, this comes at the cost of procedure-induced mortality and morbidity. Overall, taking uncertainty into account, we may conclude that strategies including NGCCT are cost saving while yielding approximately the same amount of QALYs. For the population of patients with suspected CAD the scenario with only NGCCT would be most favourable, whereas for the known CAD patients the combination of NGCCT with ICA would be most favourable.

Suggested research priorities

Test accuracy cannot provide information on the contribution of NGCCT to therapeutic decision-making, or subsequent impact on patient outcomes. The ideal study to address these questions would be a large multicentre RCT. However, one possible alternative might be to establish a multicentre tracker study. Such a study should enable the collection of data comparing numbers of misdiagnoses, clinical outcomes, and HRQoL resulting from alternative imaging strategies.

High-quality test accuracy studies – particularly in obese patients, patients with high coronary calcium and those with previous bypass grafts – are needed to confirm the findings of our systematic review. Studies should include and fully report details of patients with more than one difficult-to-image criterion, so that the potential cumulative impact on accuracy of multiple criteria can be assessed. Studies should also report the numbers of patients in whom imaging is non-diagnostic.

If NGCCT is introduced on the basis of evidence in patients with CAD and is opportunistically used in patients with congenital heart disease, before-and-after population survey studies could be considered to investigate the impact of this change upon treatment decisions and/or outcomes. Such studies might also inform the cost-effectiveness of NGCCT in this population.

The data on which the estimated likelihood of CAD are currently based date from 1979, in a US population, and may not be applicable to contemporary UK populations. The establishment of a national registry of people undergoing initial assessment for stable angina, as recommended in the National Institute for Health and Clinical Excellence clinical guideline *Chest pain of recent onset* [National Institute for Health and Clinical Excellence. *Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. Clinical Guidelines 95*. London: NICE, 2010 URL: http://guidance.nice.org.uk/CG95 (accessed 20 April 2011)] could provide data to increase robustness of the health economic findings.

Funding

Chapter 1

Background and definition of the decision problem(s)

Conditions and aetiologies

This assessment concerns the clinical effectiveness and cost-effectiveness of cardiac computed tomography (CT), using the instruments described below (see *Description of technologies under assessment*) and hereafter to be referred to as 'new-generation cardiac computed tomography (NGCCT)'. The assessment was conducted in two distinct populations. These populations were patients with known or suspected coronary artery disease (CAD), who are difficult to image using current 64-slice CT technology, and patients with complex congenital heart disease requiring additional information for treatment planning.

Coronary artery disease

Coronary artery disease is a major cause of cardiovascular (CV) disability and death in the UK. In 2007 coronary heart disease caused around 91,000 deaths in the UK (approximately 19% of deaths in men and 13% of deaths in women).[1] It is caused by narrowing of the coronary arteries, most commonly by atherosclerotic deposits of fibrous and fatty tissue, leading to a reduction in the flow of blood to the heart, angina and, ultimately, myocardial infarction (MI).

The National Institute for Health and Clinical Excellence (NICE) clinical guideline CG95 (*Chest pain of recent onset*) defines significant CAD as ≥ 70% diameter narrowing (stenosis) of at least one major epicardial artery segment or ≥ 50% diameter stenosis in the left main coronary artery.[2] Some factors intensify ischaemia and allow less-severe lesions (e.g. ≥ 50% diameter stenosis of one major epicardial artery segment) to produce angina, for example reduced oxygen delivery, increased oxygen demand, large mass of ischaemic myocardium or longer lesion length. Similarly, some factors reduce ischaemia and may render lesions (≥ 70% diameter stenosis of one major epicardial artery segment) asymptomatic, for example a well-developed collateral supply or small mass of ischaemic myocardium.

Invasive coronary angiography (ICA) or computed tomography coronary angiography (CTCA) are used to assess the state of the arteries and to identify significant stenosis as recommended by NICE clinical guideline CG95.[2] The guideline recommends use of a 64-slice (or above) CT scanner in patients with an estimated probability of CAD of 10–29%, who have undergone calcium scoring and who have a calcium score of between 0 and 400. The diagnostic performance of 64-slice CT has been well established; recent systematic reviews have estimated the sensitivity and specificity of 64-slice CT, for the detection of ≥ 50% coronary artery stenosis, to be 92–99% and 89–92%, respectively.[3–5] For most patients, it is therefore unlikely that the use of NGCCT would offer significant benefit over the use of a 64-slice CT scanner. However, NGCCT scanners may be beneficial in specific groups of patients who are currently difficult to image, for example those who cannot hold their breath, have an irregular or fast heartbeat or are obese, or in whom artefacts produced by high levels of coronary calcium or existing stents may reduce image quality. These patients are not currently candidates for CT imaging in routine practice, although some may be imaged in specialist centres.

In addition to enabling the assessment of otherwise difficult-to-image patients, NGCCT may reduce the radiation exposure associated with scanning. However, the benefits of reduced radiation exposure are likely to be limited in this population as patients with known or suspected CAD tend to be older adults.

Congenital heart disease

Congenital heart disease is a general term that describes birth defects that affect the heart. There are many different types of congenital heart defect. The most common simple lesions are ventricular or atrial septal defects, pulmonary or aortic stenosis and patent ductus arteriosus; more complex lesions include tetralogy of Fallot, transposition of the great arteries and even more complex single-ventricle morphologies. The incidence rate for congenital heart disease in the UK is estimated to be 1 in every 150 babies born and approximately 85% of children born with congenital heart disease respond well to treatment and will survive into adulthood.[6] Adequate visualisation of the defect is important to surgical/treatment planning, and diagnostic work-up currently comprises multiple imaging modalities, including echocardiography, invasive angiography, cardiac magnetic resonance imaging (MRI) and cardiac CT. It is likely that NGCCT would provide additional information in only a small proportion of patients with congenital heart disease, those whose conditions are particularly complex. Expert input from paediatric cardiologists has indicated that these will primarily involve lesions with a major extracardiac component that is not well imaged by echocardiography, for example pulmonary atresia with major aortopulmonary collateral arteries (MAPCA), variants of anomalous pulmonary venous drainage [total anomalous pulmonary venous drainage (TAPVD), scimitar syndrome, etc.], aortic arch abnormalities (double aortic arch, vascular ring, etc.) and lesions with both a vascular and an airway component (pulmonary artery sling, tracheal stenosis, right aortic arch with aberrant subclavian artery, etc.). Additionally, as with CAD, patients who have previously treated lesions, in whom stents or pacemakers make imaging with MRI or 64-slice CT difficult, may benefit from NGCCT.

Although there is some evidence that NGCCT may provide accurate initial diagnoses for a range of congenital heart conditions,[7,8] diagnostic accuracy is not considered a relevant outcome for this assessment, as existing imaging strategies can provide accurate initial diagnoses, without the need for radiation exposure.

One further potential advantage of NGCCT over current CT scanners is the fast image acquisition time, which may allow babies and infants to be scanned without the need for a general anaesthetic. Reduced radiation dose also has the potential to decrease rates of radiation-induced cancer and infertility in later life. However, as CT scanning is most likely to be used in a single instance for treatment planning, rather than for ongoing monitoring, this impact may be reduced.

Description of technologies under assessment

This assessment has focused upon specialised cardiac applications, where NGCCT is claimed to offer potential advantages over current imaging modalities, for example decreased failure rates and improved accuracy in difficult-to-image patients. However, it should be noted that NGCCT can also be used for all routine imaging procedures in which earlier generations of CT technology are currently applied.

A detailed comparison of the technical characteristics of three of the four CT scanners included in this assessment [Brilliance iCT (Phillips Healthcare), Somatom Definition Flash (Siemens

Healthcare) and Aquilion ONE (Toshiba Medical Systems)] is provided as part of a market review of advanced CT scanners for coronary angiography, by the NHS Purchasing and Supply Agency Centre for Evidence-based Purchasing (CEP).[9] There follows a brief summary of the key technical features and manufacturers' claims for each of these scanners, as well as Discovery CT750 HD, GE Healthcare (not included in the CEP report), as they may relate to the applications considered in this assessment. Summaries are presented in alphabetical order, by manufacturer name and are based largely upon product information supplied by the manufacturers.

Discovery CT750 HD, GE Healthcare

The Discovery CT750 HD is a 2×64-slice dual source CT scanner. There is a 40-mm-wide detector array with 64 rows of 0.625-mm elements. The Discovery CT750 HD has a gantry aperture of 70 cm, a gantry tilt of $\pm 30°$ and a gantry rotation speed of 0.35 seconds. The table has a maximum load of 227 kg and a horizontal speed of 137.5 mm/second. The maximum scan field is 50 cm.

The Discovery CT750 HD can provide a spatial resolution of 0.23 mm. It has a Gemstone™ detector that uses a fast scintillator made of a complex rare earth-based oxide with a chemical structure of garnet crystal. It has a single X-ray source, which switches between two energy levels, allowing two data sets – high energy and low energy – to be acquired simultaneously. This imaging technique is claimed to detect very small concentrations of contrast agent and be able to deliver non-contrast-like images by subtracting the detected agent from the images. It can also give a cardiac temporal resolution of 0.44 milliseconds.

The SnapShot Pulse™, a prospectively gated axial scanning technique, allows a complete picture of the heart to be captured in three or four 'snapshots' taken at precise patient table positions and timed to correspond to a specific phase of the cardiac cycle.

An adaptive statistical iterative reconstruction algorithm is used to enhance low contrast detection at a reduced level of radiation and to give a reduction in image noise. Other features claimed to reduce radiation dose are:

- dynamic z-axis tracking to provide automatic and continuous correction of the X-ray beam position to block unused radiation at the beginning and end of a helical scan
- filters to reduce noise providing dose reduction while maintaining image quality and spatial resolution
- three-dimensional dose modulation to facilitate dose protocol medication to individual patients.

Brilliance iCT, Philips Healthcare

The Philips Brilliance iCT is a new-generation, 256-slice multidetector CT scanner. It has 128×0.625 mm detector rows providing a total z-axis coverage of 80 mm per rotation. Each detector row is double sampled to increase spatial resolution. In cardiac step and shoot mode the Brilliance iCT can capture an image of the heart in two heart beats. It has a gantry rotation time of 0.27 seconds, a gantry aperture of 70 cm, a maximum table load of 204 kg (with an option to increase to maximum load to 295 kg) and a 50-cm scan field.

The Brilliance iCT has several features designed to manage radiation dose. It uses filters to reduce dose through absorption of unwanted X-rays and to provide a uniform dose delivery across the scan field. It uses automatic current selection to enable individualised dose optimisation. It has a collimator which is claimed to lower patient exposure during helical scanning by removing radiation at the beginning and end, which would not contribute to image formation.

Additional technical features and claims:

- It is claimed that the X-ray tube gives improved image quality and spatial resolution, particularly in patients with high BMIs.
- A 120-kW generator is claimed to maximise the image quality of short scans.
- NanoPanel detectors, claimed to reduce electronic noise, enabling fast, low-dose scans with high spatial resolution (up to 24 line pairs per centimetre).
- iDose iterative reconstruction technique, claimed to facilitate low-dose imaging and provide faster data reconstruction.
- It is claimed that when using low-dose step-and-shoot imaging, patients with heart rates of up to 75 beats per minute (b.p.m.) can be imaged successfully.

Somatom Definition Flash, Siemens Healthcare

The Somatom Definition Flash is a second-generation, dual-source 128-slice CT scanner designed to provide high-resolution images at a fast scanning speed with low-dose radiation. The scanner has two X-ray tubes and two detector arrays mounted at 95° to each other. There are 64×0.6 mm detector rows, giving a total z-axis coverage of 38.4 mm per rotation. Each detector row is double sampled to give 128 data channels.

The gantry opening measures 78 cm and the table has a maximum load of 220 kg as standard, with an option to increase maximum load to 300 kg. The maximum scan field is 50 cm, with an option to increase the scan field to 78 cm. The gantry has a rotation time of 0.28 seconds, which, combined with the fast table feed, results in a maximum scan speed of 458 mm/s. It is claimed that fast acquisition times may benefit uncooperative patients, such as young children and patients for whom a breath hold is difficult.

The use of two source–detector assemblies is designed to facilitate dual-energy scanning by operating the two tubes at different peak kilovoltages. The dual-energy data are acquired at the same time, which enables a temporal resolution of 75 milliseconds and allows scanning in a high-pitch helical 'flash' mode.

Somatom Definition Flash also has a number of features aimed to reduce the radiation load associated with imaging: 'Flash' mode scanning (recommended by the manufacturer for heart rates of up to 65 b.p.m.), in which it is claimed that data projections of the entire heart can be captured in approximately 250 milliseconds with a radiation dose of < 1 millisievert (mSv); selective photon shield, which filters the high-kilovoltage X-rays; and iterative reconstruction in image space (IRIS) to reconstruct an image from raw data.

To scan patients with heart rates of > 65 b.p.m. without the use of beta-blockers, the manufacturer recommends different scan modes, which are said to result in higher acquisition times and radiation doses.

Aquilion ONE, Toshiba Medical Systems

The Toshiba Aquilion ONE is a 640-slice CT scanner with 320×0.5 mm detector rows giving z-axis coverage of 160 mm. It is claimed that this specification allows an image of the heart can be captured within a single heart beat and reduces radiation and contrast dose. In helical scanning mode the z-axis coverage is 80 mm from 160×0.5 mm detector rows.

Additional technical features and claims:

- Adaptive iterative dose reduction, claimed to produce diagnostic images with low noise levels and minimal operator input.

- Automated parameter selection, claimed to provide consistent image quality for all patients, regardless of size.
- PhaseXact, which automatically selects the cardiac phase that displays the least amount of motion and is claimed to improve temporal accuracy and reduce review time.
- ConeXact volume reconstruction, which removes artefacts that are related to the wide cone angle.
- Automatic arrhythmia rejection software, which terminates radiation exposure if abnormal heart beat is detected and acquires the next normal beat for image reconstruction.
- Adaptive multisegment reconstruction: claimed to improve temporal resolution in patients with high or variable heart rates.
- It is also claimed that the Aquilion ONE can perform cardiac functional analysis and anatomical analysis in one scan, reducing the need to perform multiple examinations using different modalities.

Comparators

Patients with coronary artery disease who are difficult to image using 64-slice computed tomography

In patients in whom 64-slice CT is not a viable option, NGCCT may be used to rule out significant stenosis, or to confirm significant stenosis requiring coronary artery bypass graft (CABG) and thus avoid ICA; where a percutaneous coronary intervention (PCI), i.e. balloon angioplasty with or without stent implantation, is indicated, ICA is frequently performed at the same time as the intervention. The only relevant comparator for patients with CAD is ICA.

Invasive coronary angiography is an invasive imaging technique that uses a contrast dye and X-rays to provide anatomical information about the degree of stenosis in the coronary arteries. A catheter is generally inserted into an artery in the groin and is moved up the aorta and into the coronary arteries. Once in place, the dye is injected through the catheter, and a rapid series of X-ray images are taken to show how the dye moves through the branches of the coronary arteries. Any narrowing of the arteries will show up on the X-ray images. In babies and children a general anaesthetic would be required to perform the procedure.

Despite some limitations [see *Chapter 5*, *Strengths and limitations (clinical effectiveness)*], ICA is considered the reference standard for providing anatomical information and defining the site and severity of coronary artery lesions. There are serious complications associated with the technique. However, a 1990 survey by the Society for Cardiovascular Angiography and Interventions (SCAI) included approximately 60,000 patients and indicated that the total risk, for all major complications from ICA (mortality, MI, cerebrovascular accident, arrhythmia, vascular complications, allergic reaction to contrast media, haemodynamic complications, perforation of heart chamber), is < 2%.[10,11]

Invasive coronary angiography was the reference standard in our assessment of diagnostic accuracy.

Patients with congenital heart disease

In these patients, cardiac CT is likely to be used for treatment/surgical planning following diagnosis and as an add-on to imaging with echocardiography, invasive angiography and MRI. Thus, 64-slice CT is the only relevant comparator.

Multislice CT scanners (64-slice CT) combine the use of X-rays with computed analysis of a series of two-dimensional X-ray images to create three-dimensional images. The technology has

been rapidly advancing, with four-slice CT scanners first appearing in 1998, 16-slice scanners in 2001 and 64-slice scanners at the end of 2004. Multislice CTCA is a minimally invasive investigation that uses a contrast dye injected through a cannula in the forearm and provides anatomical information about the degree of stenosis in the coronary arteries. Cardiac CT has particular challenges owing to the continuous motion of the heart.

Studies that compared the treatment plan and/or patient outcome, in the same group of patients, with and without CT (high definition or 64-slice), or studies that randomised patients to receive treatment based on assessment with or without CT, were considered relevant to this assessment. Diagnostic accuracy data were not considered relevant, as existing imaging strategies can provide accurate initial diagnosis.

Care pathways

Coronary artery disease
Diagnosis
NICE clinical guideline CG95 details the care pathway recommended to make a diagnosis of stable angina in people with chest pain.[2] The guideline suggests that a diagnosis of significant CAD can be made using anatomical imaging and a diagnosis of reversible myocardial ischaemia can be made using functional imaging. Both significant CAD and reversible myocardial ischaemia are treated as a diagnosis of stable angina.

The imaging strategy recommended is dependent upon the estimated pre-test probability of significant CAD. The guideline states that:

■ People with chest pain who have an estimated probability of CAD of 10–29% should be offered calcium scoring followed by CTCA if the calcium score is between 1 and 400; people with high calcium scores (> 400) are considered difficult to image using current CT technologies (64-slice CT) and are included in this assessment as one of the specified categories of 'difficult-to-image' CAD patients. For patients with calcium scores > 400, CG95 recommends ICA if this is considered clinically appropriate.
■ People with chest pain who have an estimated probability of CAD of 30–60% should be offered non-invasive functional imaging for myocardial ischaemia.
■ People with chest pain who have an estimated probability of CAD of 61–90% should be offered ICA if clinically appropriate and coronary revascularisation is being considered.

Where non-invasive functional imaging is to be offered the following strategies are recommended by CG95:

■ myocardial perfusion scintigraphy with single-photon emission computed tomography *or*
■ stress echocardiography *or*
■ first-pass contrast-enhanced magnetic resonance perfusion *or*
■ MRI for stress-induced wall motion abnormalities.

As the guideline on chest pain of recent onset is relatively new and technology advances have been occurring rapidly, it has been noted that the guideline on chest pain of recent onset has not been implemented in all cardiac centres across the UK.

Clinical management

Patients diagnosed as having significant CAD should be initially managed as having stable angina. NICE guideline CG126 provides recommendations on the management of stable angina.[12]

Key recommendations from the guideline state:

- Optimal drug treatment consists of one or two antianginal drugs as necessary plus drugs for secondary prevention of cardiovascular disease.
- A short-acting nitrate should be offered for preventing and treating episodes of angina.
- Aspirin 75 mg daily should be considered for the secondary prevention of CV disease, taking into account the risk of bleeding and co-morbidities.
- Treatment with one or two antianginal drugs should be offered for the initial management of stable angina.
- First-line treatment options for stable angina are beta-blockers and/or calcium channel blockers.
- For people who cannot tolerate beta-blockers or calcium channel blockers, or these drugs are contraindicated, monotherapy with a long-acting nitrate – ivabradine, nicorandil or ranolazine – can be considered.
- For people on beta-blocker or calcium-channel blocker monotherapy, whose symptoms are not controlled and the other option is contraindicated or not tolerated, one of the following can be considered as an additional drug: a long-acting nitrate, ivabradine, nicorandil or ranolazine.
- A third drug can be considered when symptoms are not controlled with two antianginal drugs and the person is waiting for revascularisation or it is not considered appropriate or acceptable.

Management by revascularisation

The NICE clinical guideline on stable angina recommends considering revascularisation for people whose symptoms are not controlled by drug treatment. Results of any functional and/or anatomical tests performed at diagnosis should be reviewed when revascularisation is being considered. ICA to guide the revascularisation strategy should be offered if not recently completed during diagnosis. Additional non-invasive or invasive functional testing may be required.

Two revascularisation strategies are available. The first strategy, CABG, involves major cardiac surgery. The second strategy, PCI, involves non-surgical widening from within the artery using a balloon catheter and may be performed with or without stent implantation. NICE technology appraisal (TA) 71 (*Guidance on the use of coronary artery stents*)[13] and NICE TA152 (*Drug-eluting stents for the treatment of CAD*)[14] provide recommendations on the use of stents for revascularisation in CAD.

The NICE clinical guideline on stable angina states that, where revascularisation is considered appropriate, PCI should be offered where CABG is not considered appropriate and CABG should be offered where PCI is not considered appropriate. When either procedure would be appropriate, relative risks and benefits should be explained to the patient, and where no preference is expressed it should be explained that PCI may be the more cost-effective option. Further, when either procedure would be appropriate, the potential survival advantage of CABG for people with complex multivessel disease, who are aged > 65 years and/or have diabetes, should be considered.

NICE TA71[13] recommends that stents should be routinely used in patients in whom PCI is indicated. Further, NICE TA152[14] states that drug-eluting stents are recommended for use in PCI for the treatment of CAD only if:

- the target artery to be treated is of > 3 mm in calibre or the lesion is longer than 15 mm, *and*
- the price difference between drug-eluting stents and bare-metal stents is no more than £300.

Congenital heart disease

Diagnosis

We are not aware of any nationally accepted guidelines on the diagnosis and management of newborns, infants and children with congenital heart disease. Other sources of information, such as NHS Choices and Patient UK, provide limited information.[15,16] They suggest that if congenital heart disease is suspected then a full clinical history of the pregnancy and the mother's health should be taken prior to investigations. This should be followed by echocardiography, which is a non-invasive procedure without ionising radiation that can provide information on the anatomy and function of the heart. Other tests such as electrocardiography (ECG), chest radiography and pulse oximetry may also be used, as clinically appropriate. Invasive angiography, CT imaging or MRI may be used, in some instances, to provide further anatomical information and to prepare for correction or palliation of the defect.

The main disadvantage of using MRI in this population is the procedure length and the need to gate the scan to both the ECG and phase of respiration; this requires babies and young children to be under general anaesthetic; however, there is no associated radiation exposure. CT imaging has the advantage of rapid acquisition time, potentially removing the need for general anaesthetic. In addition, CT images allow easier examination of the lungs and airways than is the case for MRI. The main disadvantage of CT imaging is that it is associated with radiation exposure. Further, small children may have heart rates that are too high to benefit from the low radiation modes of scanning in NGCCT.

Cardiac catheterisation and invasive angiography, which would require a general anaesthetic, is avoided whenever possible but may be required for certain lesions particularly when intravascular and intracardiac pressures and oxygen saturations are required or in preparation for catheter intervention.

As the majority of babies born with congenital heart disease now survive into adulthood, long-term monitoring and care is essential. In addition, some congenital defects may be diagnosed for the first time in adult life. The European Society of Cardiology (ESC) has recently updated its Guidelines on the Management of Adult Congenital Heart Disease.[17] Recommendations are similar to those suggested for children (above): a clinical examination followed by an ECG and pulse oximetry. Chest radiography may be performed when indicated, but is not routinely recommended. Further investigation of anatomy and physiology has shifted away from invasive studies to non-invasive protocols involving cardiovascular magnetic resonance (CMR) and CT. Cardiac catheterisation and invasive angiography is reserved for the resolution of specific anatomical and physiological questions, or for intervention.[17]

Treatment and monitoring

Once congenital heart disease is diagnosed, watchful waiting, medical management, catheter intervention, invasive surgery or heart transplantation may be used to treat the condition, depending on the type of heart anomaly identified. There are several NICE Interventional Procedure Guidelines relating to the treatment of various heart defects; these are listed in *Appendix 6*.

For adults with congenital heart disease, medical management generally focuses on prevention or control of cardiac problems, for example heart failure, arrhythmias, hypertension, thromboembolic events and endocarditis. Sudden cardiac death is a particular concern. Further intervention may be required in people who have undergone procedures in childhood but have residual or new complications. In addition, new interventions may be required in people with conditions not previously diagnosed, or not considered severe enough to require surgery in childhood. Care of adults with congenital heart disease also needs to take into account a number of issues not directly related to treatment of the cardiac condition, including recommendations for exercise and sports, and issues around pregnancy, contraception and genetic counselling.[17]

Owing to the range of conditions covered by the term 'congenital heart defects', a variety of different treatment and follow-up strategies may be appropriate for different conditions. For example, people with an atrial septal defect successfully treated with surgery can usually be discharged from indefinite follow-up. Patients with more complicated defects or sequelae following interventional treatment will require lifelong regular follow-up, with frequencies usually ranging from yearly to once every 5 years.[17]

Chapter 2

Definition of decision problem

Overall aim of the assessment

To assess the clinical effectiveness and cost-effectiveness of cardiac CT, using Discovery CT750 HD (GE Healthcare), Brilliance iCT (Philips Healthcare), Somatom Definition Flash (Siemens Healthcare), or Aquilion ONE (Toshiba Medical Systems) in specified groups of cardiac patients.

Objectives

To determine the clinical effectiveness and cost-effectiveness of NGCCT for the diagnosis of clinically significant CAD in patients with suspected CAD (defined as those who have chest pain or have other symptoms suggestive of CAD) or known CAD (defined as those who have previously been diagnosed with CAD and whose symptoms are no longer controlled by drug treatment and/or are being considered for revascularisation), who are difficult to image accurately using 64-slice CT technology.

To determine the clinical effectiveness and cost-effectiveness of NGCCT for treatment planning in babies, infants, children and adults who are diagnosed with complex congenital heart defects.

Chapter 3

Assessment of clinical effectiveness

A systematic review was conducted to summarise the evidence on the clinical effectiveness of NGCCT, for the diagnosis of clinically significant coronary artery stenosis in difficult-to-image patient groups with known or suspected CAD, and for treatment planning in patients with complex congenital heart disease. Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the NICE Diagnostic Assessment Programme interim methods statement.[18,19]

Inclusion and exclusion criteria

Participants

Study populations eligible for inclusion were:

- Adults ($\geq$ 18 years) with known (previously diagnosed who have symptoms that are no longer controlled by drug treatment and/or who are being considered for revascularisation) or suspected (chest pain or other suggestive symptoms) CAD, who are difficult to image (not currently candidates for CT imaging). Difficult-to-image patient groups defined a priori were:
  - obesity [body mass index (BMI) of $\geq$ 30 kg/m^2]
  - high levels of coronary calcium (calcium score > 400)
  - arrhythmias [including, but not limited to, atrial fibrillation (AF)]
  - high heart rate (HHR) (> 65 b.p.m.)
  - intolerance of beta-blockers
  - previous stent implantation
  - previous bypass graft(s).

[Difficult-to-image patients were not limited to these patient groups, but no other groups were identified during the review process. Following consultation with clinical experts, the definition of HHR (> 70 b.p.m.) specified in the protocol was broadened to avoid potential loss of relevant data, as identified studies frequently defined HHR as > 65 b.p.m.]

- Infants, children and adults diagnosed with complex congenital heart disease, including but not limited to:
  - pulmonary atresia with MAPCA
  - variants of anomalous pulmonary venous drainage (TAPVD, scimitar syndrome, etc.)
  - aortic arch abnormalities (double aortic arch, vascular ring, etc.)
  - lesions with both a vascular and airway component (pulmonary artery sling, tracheal stenosis, right aortic arch with aberrant subclavian artery, etc.)
  - previously treated lesions where stents or pacemakers make MRI an unsuitable imaging strategy.

Setting

Relevant settings were secondary or tertiary care.

Interventions

Included interventions, described as 'NGCCT' throughout, were the following CT scanners:

- Discovery CT750 (GE Healthcare)
- Brilliance iCT (Philips Healthcare)
- Somatom Definition Flash (Siemens Healthcare)
- Aquilion ONE (Toshiba Medical systems).

No additional equivalent technologies were identified during the review process.

Comparators

The only relevant comparator for the assessment of difficult-to-image patients with CAD was ICA.

Relevant comparators, for the assessment of complex congenital heart disease, were 64-slice CT and conventional imaging (without CT).

Reference standard

Studies reporting the diagnostic accuracy of NGCCT for the detection of significant CAD were required to use ICA as the reference standard. Diagnostic accuracy was not considered a relevant outcome for studies of congenital heart disease.

Outcomes

Studies reporting the following outcomes were considered relevant for both clinical applications (CAD and congenital heart disease):

- impact of testing on treatment plan (e.g. surgical or medical management), where information on the appropriateness of the final treatment plan was also reported
- impact of testing on clinical outcome (e.g. angina, MI, CV mortality).

Studies reporting the following outcomes were considered relevant only for difficult-to-image patients with CAD:

- test accuracy
- indeterminacy (the number of patients in whom imaging failed to provide diagnostic information).

For included studies reporting any of the above outcome measures, the following outcomes were also recorded, if reported:

- acceptability of tests to patients
- adverse events associated with testing
- radiation dose associated with imaging.

Study design

The following study designs were eligible for inclusion:

- randomised or non-randomised controlled trials, in which participants were assigned to the intervention or comparator tests, for treatment planning, and outcomes were compared at follow-up

■ randomised or non-randomised controlled trials in which participants were assigned to conventional imaging only, or conventional imaging plus high definition or 64-slice CT (congenital heart disease only).

No randomised or non-randomised controlled trials were identified. Therefore, the following observational study types were considered eligible for inclusion:

■ cross-sectional test accuracy studies, where the intervention was compared with the reference standard (CAD only)
■ observational studies reporting change to treatment plan or clinical outcome subsequent to high-definition CT (CAD and congenital heart disease) or 64-slice CT (congenital heart disease only).

Cross-sectional test accuracy studies were required to report the absolute numbers of true-positive (TP), false-negative (FN), false-positive (FP) and true-negative (TN) test results, or sufficient information to allow their calculation.

The following study/publication types were excluded:

■ pre-clinical, animal and phantom studies
■ reviews, editorials, and opinion pieces
■ case reports
■ studies reporting only technical aspects of the test, or image quality
■ studies with < 10 participants.

Search strategy

Search strategies were based on target condition and intervention, as recommended in the CRD guidance for undertaking reviews in health care and the Cochrane handbook for diagnostic test accuracy reviews.[18,20,21]

The following databases were searched for relevant studies from 1 January 2000 to 9 March 2011:

■ MEDLINE (2000 to February week 2 2011) (OvidSP)
■ MEDLINE In-Process and Other Non-Indexed Citations and Daily Update (2000 to 16 February 2011) (OvidSP)
■ EMBASE (2000 to week 6 2011) (OvidSP)
■ Cochrane Database of Systematic Reviews (CDSR) (The Cochrane Library Issue 1 : 2011) (Wiley)
■ Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1 : 2011) (Wiley)
■ Database of Abstracts of Reviews of Effects (DARE) (2000 to 9 March 2011) (CRD website)
■ NHS Economic Evaluation Database (NHS EED) (2000 to 9 March 2011) (CRD website)
■ Health Technology Assessment database (HTA) (2000 to 9 March 2011) (CRD website)
■ Science Citation Index (SCI) (2000 to 5 March 2011) (Web of Science).

Supplementary searches were undertaken on the following resources to identify grey literature, completed and ongoing trials:

■ National Institutes of Health Clinicaltrials.gov (2000 to 9 March 2011) (Internet): www.clinicaltrials.gov/

- Current Controlled Trials (2000 to 9 March 2011) (Internet): www.controlled-trials.com/
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (2000 to 9 March 2011) (Internet): www.who.int/ictrp/en/

Searches were undertaken to identify studies of NGCCT in the diagnosis of CAD and assessment of congenital heart disease. Search strategies were developed specifically for each database and the keywords associated with CAD and congenital heart defects were adapted according to the configuration of each database. Searches took into account generic and other product names for the intervention. No restrictions on language or publication status were applied. Limits were applied to remove animal studies. Full search strategies are reported in *Appendix 1*.

Electronic searches were undertaken for the following conference abstracts:

- American College of Cardiology (ACC) (2006–10) (Internet): www.cardiosource.org/ Meetings/Previous-Meetings-OLD.aspx
- Society of Cardiovascular Computed Tomography (SCCT) (2006–10) (Internet): www.scct. org/annualmeeting/2010/index.cfm
- European Society of Cardiology (ESC) (2006–10) (Internet): www.escardio.org/congresses/ past_congresses/Pages/past-ESC-congresses.aspx
- American Heart Association (AHA) (2007–10) (Internet):
    - 2010: http://circ.ahajournals.org/content/vol122/21_MeetingAbstracts/
    - 2009: http://circ.ahajournals.org/content/vol120/18_MeetingAbstracts/
    - 2008: http://circ.ahajournals.org/content/vol118/18_MeetingAbstracts/
    - 2007: http://circ.ahajournals.org/content/vol116/16_MeetingAbstracts/

Identified references were downloaded in EndNote X4 software (Thomson Reuters, CA, USA) for further assessment and handling.

References in retrieved articles were checked for additional studies.

Inclusion screening and data extraction

Two reviewers (MW and HR) independently screened the titles and abstracts of all reports identified by searches and any discrepancies were discussed and resolved by consensus. Full copies of all studies deemed potentially relevant, after discussion, were obtained and the same two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus. Details of studies excluded at the full-paper-screening stage are presented in *Appendix 5*.

Studies listed in submissions from the manufacturers of NGCCT were first checked against the project reference database, in EndNote X4; any studies not already identified by our searches were screened for inclusion following the process described above. Studies referenced by manufacturers and excluded at the full-paper-screening stage are noted in *Appendix 5*. *Appendix 5* also includes a list of studies, referenced by manufacturers, which were excluded at title and abstract screening.

Where there was uncertainty regarding possible overlap between study populations, authors were contacted for clarification.

Data were extracted on study details (study design, participant recruitment, setting, funding, stated objective, and categories of participants relevant to this assessment for whom data were

reported); study participants (total number of participants, number of participants in each relevant group, study inclusion criteria, study exclusion criteria, and participant characteristics relevant to CV risk for the relevant participant groups or the whole study population); assessed technology and reference standard (technical details of the test, any use of beta-blockers prior to scanning, details of who interpreted tests and how, threshold used to define a positive test); and study results. All studies included in the review were diagnostic accuracy studies and the results extracted were unit of analysis (patient, artery or arterial segment); numbers of TP, FN, FP and TN test results; numbers of patients, arteries or segments classified as non-diagnostic by NGCCT; and radiation exposure associated with imaging. All data were extracted by one reviewer, using a piloted, standard data extraction form and checked by a second; any disagreements were resolved by consensus. Full data extraction tables are provided in *Appendix 4*.

Quality assessment

All studies included in the systematic review were test accuracy studies. The QUADAS tool,[22] is recommended for assessing the methodological quality of test accuracy studies.[18,20] However, a revised version of QUADAS (QUADAS-2) has recently been published.[23] QUADAS-2 more closely resembles the approach and structure of the Cochrane risk of bias tool. It is structured into four key domains covering participant selection, index test, reference standard, and the flow of patients through the study (including timing of tests). Each domain is rated for risk of bias (low, high or unclear) and the tool provides signalling questions, in each domain, to aid reviewers in reaching a judgement. The participant selection, index test and reference standard domains are also, separately, rated for concerns regarding the applicability of the study to the review question (low, high or unclear). Thus, QUADAS-2 separates bias from external validity (applicability) and does not include any items which assess only reporting quality. Guidance for the use of QUADAS-2 will emphasise the need to tailor the tool to specific projects and the need to avoid the use of summary quality scores. Further information on QUADAS-2 is available at the QUADAS website: www.bris.ac.uk/quadas/quadas-2.

Review-specific guidance was produced for the use of QUADAS-2 in this assessment and is reported in *Appendix 2*. The version of QUADAS-2 used in this assessment included only the risk of bias components, as it was considered that the inclusion criteria matched the review question and that questions of applicability were, therefore, not relevant.

The results of the quality assessment are summarised and presented in tables and graphs in the results of the systematic review (see *Chapter 3*, *Results*) and are presented in full, by study, in *Appendix 3*. No diagnostic accuracy data set included in this assessment was of sufficient size to allow statistical exploration of between-study heterogeneity based on aspects of risk of bias. The findings of the quality assessment were also used to inform recommendations for future research.

Methods of analysis/synthesis

All studies included in the systematic review were test accuracy studies in difficult-to-image patients with CAD. Results were summarised by patient group (e.g. obese, HHR, high coronary calcium score, etc.) and further stratified by unit of analysis (patient, artery or arterial segment). For all included studies, the absolute numbers of TP, FN, FP and TN test results, as well as sensitivity and specificity values, with 95% confidence intervals (CIs), were presented in results tables, for each patient group reported. Data on the numbers of non-diagnostic tests and radiation exposure were also included in the results tables and described in text summaries.

Where groups of similar studies (same patient group and unit of analysis) included four or more data sets, summary receiver operating characteristic (SROC) curves and summary estimates of sensitivity and specificity, with 95% CIs, were calculated using the bivariate modelling approach;[24,25] four data sets is the minimum requirement to fit models of this type. Analyses were conducted in Stata 10 (StataCorp LP, College Station, TX, USA), using the 'metandi' function.[26] In two cases, a bivariate model could not be fitted because the number of studies was small (four), 2×2 data contained one or more zero values, and between-study heterogeneity was low. In these cases, pooled estimates of sensitivity and specificity, with 95% CIs, were calculated using a random-effects model; these analyses were conducted using Meta-DiSc 1.4 (Hospital Ramon y Cajal and Universidad, Madrid, Spain)[27] and forest plots were constructed, showing the sensitivity and specificity estimates from each study together with pooled estimates. No distinction was made between patients with known or suspected CAD as per-patient data sets were generally small, with low to moderate between-study heterogeneity. In addition, 'known' and 'suspected' CAD were often poorly defined by the included studies.

Between-study heterogeneity was assessed using the chi-squared test and inconsistency was quantified using the I^2-statistic.[28] There were no data sets of sufficient size (minimum 10) to allow statistical exploration of sources of heterogeneity by including additional co-variables in the SROC model.

Where meta-analysis was considered unsuitable for the data identified (e.g. because of the heterogeneity and/or small numbers of studies), studies were summarised using a narrative synthesis. Text and tables were stratified by patient group.

No data were identified on the effects of NGCCT on treatment planning and/or clinical outcome, adverse events associated with testing, or acceptability of tests to patients.

Results

The literature searches of bibliographic databases identified 3986 references. After initial screening of titles and abstracts, 119 were considered to be potentially relevant and ordered for full-paper screening. A further 11 papers were ordered based on screening of submissions from industry and two studies cited in trials registry entries were also obtained. Of the total of 132 publications considered potentially relevant, five[29–33] could not be obtained within the timescale of this assessment; these were held in British Library stacks, which are currently closed for asbestos removal or they were not held by the British Library. *Figure 1* shows the flow of studies through the review process, and *Appendix 5* provides details, with reasons for exclusions, of all publications excluded at the full-paper-screening stage.

Based on the searches and inclusion screening described above, 23 publications of 21 studies were included in the review. Hand-searching of conference proceedings resulted in the inclusion of a further three studies, which were published in abstract form only (see *Figure 1*).[34–36] A total of 24 studies in 26 publications were, therefore, included in the review (see *Table 1*).

All included studies were test accuracy studies conducted in patients with known or suspected CAD. No study reported data on changes to patient management or outcomes, test-related adverse events or patient preferences. No studies were identified, of patients with congenital heart disease, which met the inclusion criteria of the review.

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                    ┌─────────────────────────────────┐
                    │ Titles and abstracts identified  │
                    │ from bibliographic databases     │
                    │ and screened for potential       │
                    │ relevance                        │
                    │ n = 3986                         │
                    └─────────────────────────────────┘
                                   │
        ┌──────────────────────┐   │
        │ Excluded at title    │◄──┤
        │ and abstract         │   │
        │ screening            │   │
        │ n = 3867             │   │
        └──────────────────────┘   │
                                   ▼
                    ┌─────────────────────────────────┐
                    │ Potentially relevant publications│
                    │ n = 119                          │
                    └─────────────────────────────────┘
                                   │        ┌──────────────────────────┐
                                   │◄───────│ Full papers ordered after│
                                   │        │ screening industry       │
                                   │        │ submissions              │
                                   │        │ n = 11                   │
                                   │        └──────────────────────────┘
                                   │        ┌──────────────────────────┐
                                   │◄───────│ Full papers ordered after│
        ┌──────────────────────┐   │        │ screening trial registry │
        │ Could not be obtained│◄──┤        │ entries                  │
        │ n = 5                │   │        │ n = 2                    │
        └──────────────────────┘   │        └──────────────────────────┘
                                   ▼
                    ┌─────────────────────────────────┐
                    │ Total potentially relevant       │
                    │ publications obtained as full text│
                    │ n = 127                          │
                    └─────────────────────────────────┘
                                   │
        ┌──────────────────────┐   │        ┌──────────────────────────┐
        │ Excluded at full     │◄──┤◄───────│ Conference abstracts      │
        │ paper screening      │   │        │ included after screening  │
        │ n = 104              │   │        │ n = 3                     │
        └──────────────────────┘   │        └──────────────────────────┘
                                   ▼
                    ┌─────────────────────────────────┐
                    │ Total number of studies included │
                    │ in the review                    │
                    │ n = 24 (26 publications)         │
                    └─────────────────────────────────┘
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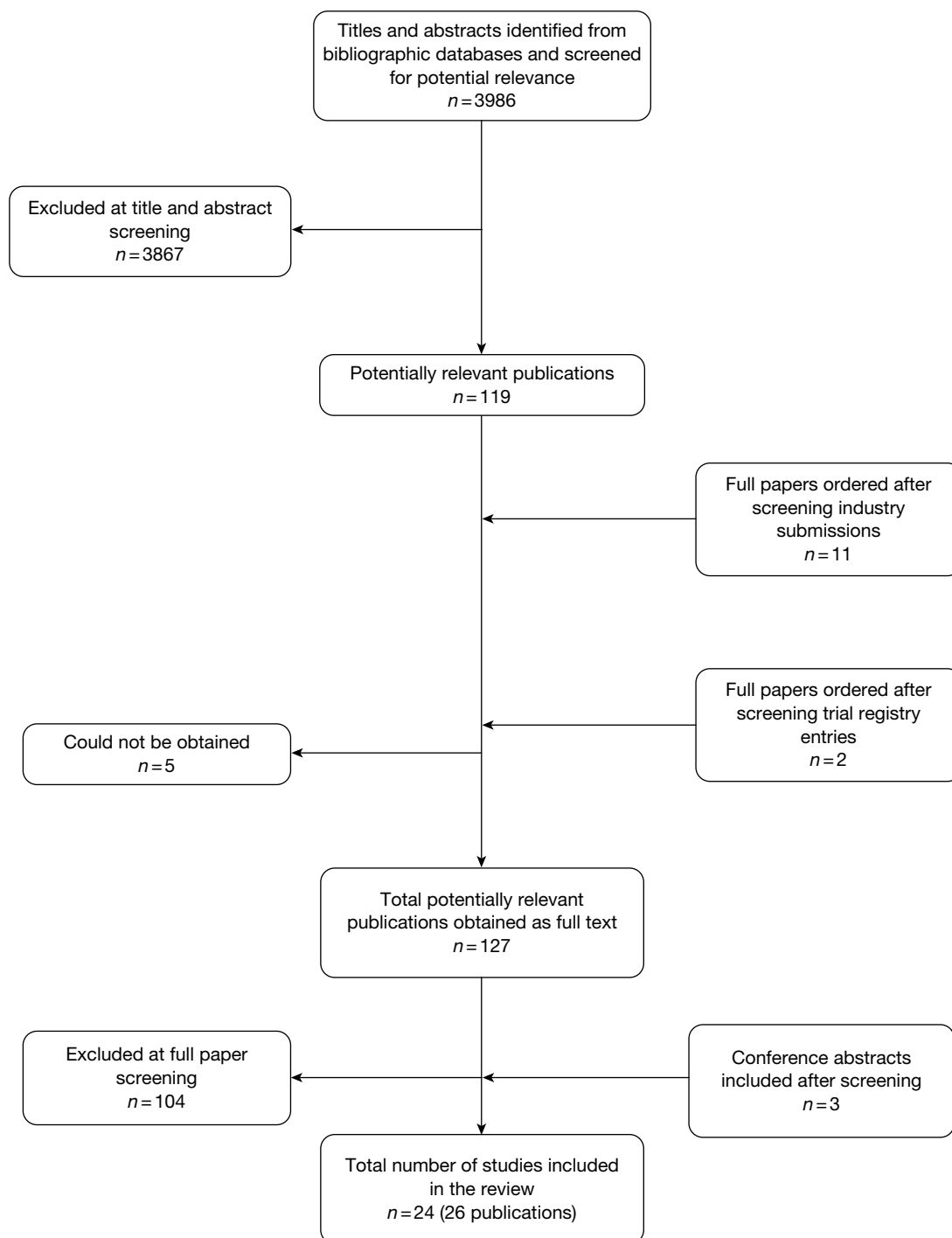
FIGURE 1 Flow of studies through the review process.

Nineteen of the 24 included studies reported using Somatom Definition (a similar previous model of Somatom Definition Flash), and one study used Somatom Definition Flash.[34] Three studies did not specify the instrument used;[36–38] the authors of one of these[37] had used Somatom Definition in an earlier study, which was also included in this review,[39] and another study was later confirmed by the manufacturer to have used Discovery CT750 HD.[38] The remaining study

TABLE 1 Included studies

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >65 b.p.m.	Stent(s)	Bypass	Beta-blocker intolerance
Alkadhi 2010[41]	Prospective diagnostic cohort Consecutive recruitment (Dates not reported) Single centre Switzerland Supported by the National Centre of Competence in Research, Computer Aided and Image Guided Medical Interventions of the Swiss National Science Foundation	To prospectively investigate the diagnostic accuracy of dual-source CTCA in relation to BMI, vessel wall calcifications, and average HR as compared with the reference standard ICA				✓			
Brodoefel 2008[42]	Prospective diagnostic cohort Recruitment not described (September 2006 to July 2007) Single centre Germany Funding not reported	To prospectively evaluate the effect of BMI on DSCT image quality and to assess diagnostic accuracy for coronary artery stenosis, using ICA as the reference standard	✓						
Brodoefel 2008[46]	Prospective diagnostic cohort Recruitment not described (September 2006 to March 2007) Single centre Germany Funding not reported	To prospectively evaluate the effect of heart rate, heart rate variability, and calcification on DSCT image quality and to prospectively assess diagnostic accuracy for coronary artery stenosis, using ICA as the reference standard		✓		✓			
De Graaf 2010[40]	Prospective? diagnostic cohort Recruitment not described (Dates not reported) Multicentre Netherlands Supported by the Dutch Technology Foundation, Applied Science Division of NWO, and the Technology Program of the Ministry of Economic Affairs; the Netherlands Heart Foundation; Boston Scientific; Biotronik; Medtronic; BMS Medical Imaging; St Jude Medical; GE Healthcare; Edwards Lifesciences	To evaluate the diagnostic accuracy of 320-row CTA in the evaluation of significant in-stent re-stenosis. A second purpose of the study was to assess CTA stent image quality and diagnostic accuracy vs stent characteristics and heart rate during CTA image acquisition				✓			

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >65 b.p.m.	Stent(s)	Bypass	Beta-blocker intolerance
LaBounty 2010[38]	Prospective diagnostic cohort, abstract only Consecutive recruitment (Dates not reported) Multicentre USA and Canada Funding not reported	To evaluate the diagnostic accuracy of high-definition (HD)-CTCA in an intent-to-diagnose analysis					✓		
Leber 2007[43]	Prospective? diagnostic cohort Consecutive recruitment (July 2006 to January 2007) Single centre Germany NR	To assess the clinical performance of a dual X-ray source MSCT with high temporal resolution to assess coronary status in patients with an intermediate pre-test likelihood for significant CAD without using negative chronotropic pre-treatment			✓[a]	✓[a]			
Lin 2010[44]	Retrospective diagnostic cohort Selected patients from a consecutive series (October 2006 to June 2007) Multicentre Taiwan Funding not reported	To evaluate the ability of DSCT CA to diagnose CAD in a heterogeneous population referred to an imaging centre, including patients with irregular heart rates and significant calcification of the coronary arteries				✓			
Marwan 2010[47]	Prospective? diagnostic cohort Consecutive recruitment (Dates not reported) Single centre Germany One author received support from Siemens and Bayer Schering Pharma. The study was supported by Bundesministerium für Bildung und Forschung, Bonn, Germany	To determine the diagnostic accuracy of DSCT to identify significant coronary stenosis in patients with AF referred for ICA			✓				

TABLE 1 Included studies (*continued*)

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >65 b.p.m.	Stent(s)	Bypass	Beta-blocker intolerance
Meng 2009[48]	Prospective? diagnostic cohort Consecutive recruitment (November 2006 to November 2007) Multicentre China (PRC) Funding not reported	To evaluate the diagnostic accuracy of DSCT coronary angiography, with particular focus on the effect of heart rate and calcifications		✓		✓			
Oncel 2007[49]	Prospective diagnostic cohort Consecutive recruitment (September 2006 to January 2007) Single-centre Turkey Funding not reported	To evaluate the sensitivity and specificity of dual-source CT for significant coronary stenosis (>50% narrowing) in patients with AF, using conventional coronary angiography as the reference standard			✓				
Oncel 2008[50]	Prospective diagnostic cohort Consecutive recruitment (September 2006 to August 2007) Single centre Turkey Funding not reported	To assess the diagnostic performance of dual-source CT in the evaluation of coronary stent patency to determine whether or not improved temporal resolution aid in visualisation of coronary stents					✓		
Pflederer 2009[51]	Prospective? diagnostic cohort Consecutive recruitment (Dates not reported) Multicentre Germany and USA Work supported by the Bundesministerium für Bildung und Forschung, Berlin Germany. One author supported by research grants from Siemens Healthcare, Erlangen, and Bayer Schering Pharma, Berlin, Germany	To evaluate the accuracy of DSCT for the assessment of coronary in-stent re-stenosis					✓		

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >65 b.p.m.	Stent(s)	Bypass	Beta-blocker intolerance
Pflederer 2010[34]	Diagnostic cohort, abstract only Recruitment not described (Dates not reported) Single centre Germany Funding not reported	To assess the accuracy of DSCT to detect coronary artery stenosis in patients with previous coronary revascularisation who were scheduled for ICA					✓	✓	
Pugliese 2008[52] and 2007[53]	Prospective diagnostic cohort Recruitment not described (April 2006 to January 2007) Single centre Netherlands Funding not reported	To evaluate the diagnostic performance of DSCT-CA for the detection of in-stent re-stenosis in patients with angina symptoms after stent implantation				✓b	✓		
Rist 2009[54]	Prospective? diagnostic cohort Recruitment not described (Dates not reported) Single centre Germany Funding not reported	To assess the image quality and diagnostic accuracy of coronary angiograms using DSCT in patients with AF			✓				
Rixe 2009[35]	Prospective? Diagnostic cohort, abstract only Consecutive recruitment (Dates not reported) Single centre Germany Funding not reported	To investigate the feasibility of DSCT with a temporal resolution of 83 milliseconds for the detection of CAD in patients with AF compared with conventional quantitative coronary angiography			✓				
Ropers 2007[39]	Prospective? diagnostic cohort Consecutive recruitment (Dates not reported) Single centre Germany Funding not reported	To assess the influence of heart rate on diagnostic accuracy of DSCT coronary angiography without beta-blocker pre-medication				✓			

TABLE 1 Included studies (continued)

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >65 b.p.m.	Stent(s)	Bypass	Beta-blocker intolerance
Ropers 2008[37]	Diagnostic cohort, abstract only Recruitment not described (Dates not reported) Single centre Germany Funding not reported	To assess the ability of DSCT to evaluate CABG patients for the presence of significant stenoses in bypass grafts and native coronary arteries						✓	
Scheffel 2006[55]	Prospective diagnostic cohort Recruitment not described (Dates not reported) Single centre Switzerland Supported by the National Centre of Competence in Research, Computer Aided and Image Guided Medical Interventions of the Swiss National Science Foundation	To assess the diagnostic accuracy of DSCT for evaluation of CAD in a population with extensive coronary artery calcifications without heart rate control		✓		✓			
Tsiflikas 2010[56] and Drosch[57]	Prospective? diagnostic cohort Recruitment not described (July 2006 to January 2008) Multicentre Netherlands Funding not reported	To evaluate the diagnostic accuracy of DSCT to detect significant coronary stenoses (>50% luminal narrowing) in patients without stable sinus rhythm in a clinical setting			✓				
Van Mieghem 2007[36]	Diagnostic cohort, abstract only Recruitment not described (Dates not reported) Single centre Netherlands Funding not reported	To compare 'traditional work-up', using exercise stress testing, myocardial perfusion imaging, stress echo or direct referral for ICA, with a CT-based strategy for the assessment of patients with recurrent chest pain after PCI					✓		

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >65 b.p.m.	Stent(s)	Bypass	Beta-blocker intolerance
Weustink 2009[58]	Prospective? diagnostic cohort Consecutive recruitment (Dates not reported) Single centre Netherlands Funding not reported	To evaluate the contribution of non-invasive dual-source CTA in the comprehensive assessment of symptomatic patients after CABG				✓c		✓	
Weustink 2009[45]	Prospective? diagnostic cohort Consecutive recruitment (April 2006 to October 2008) Single centre Netherlands Funding not reported, statement of 'no financial relationships'	To determine the effect of HRF and HRV on radiation exposure and image quality in a large cohort of patients undergoing DS CTCA with adaptive ECG pulsing, and to evaluate the impact of HRF and HRV on the diagnostic performance of DS CTCA to help detect or rule out significant stenoses in a subgroup of patients who underwent additionally conventional coronary angiography				✓			
Zhang 2010[59]	Prospective diagnostic cohort Consecutive recruitment (December 2006 to September 2008) Multicentre China and USA Funding not reported	To prospectively evaluate the accuracy of DS CTCA in diagnosing coronary artery stenosis according to CAG, and the effect of average heart rate, heart rate variability, and calcium score on the accuracy of CTCA		✓		✓			

✓, Difficult-to-image patient group for which the study reports data; CAG, conventional coronary angiography; CTA, computed tomography angiography; CTCA, computed tomography coronary angiography; DSCT, dual-source computed tomography; HCS, high calcium score; HR heart rate; HRF, heart rate frequency; HRV, heart rate variability; MSCT, multislice computed tomography.
a Combined data (patients with HHR or arrhythmia).
b Combined data (patients with HHR and previous stent implantation).
c Combined data (patients with HHR and previous bypass).

used Aquilion ONE.[40] This study assessed patients who had previous stent implantation for in-stent restenosis.[40]

All included studies were published in 2006 or later.

Eleven[38,39,41–46,48,55,59] of the 21 included studies reported data on difficult-to-image patients as subgroup analyses. Six of these studies[39,41–45] reported sufficient information to allow calculation of the proportion of the total participants who had one or more difficult-to-image criteria; the mean percentage was 41.5% (range 28–51%). *Table 1* shows the details of included studies and the specific difficult-to-image patient groups for which each publication reported data. Further details of the characteristics of study participants and the technical details of the conduct of the index test (NGCCT) and reference standard and their interpretation are reported in the data extraction tables presented in *Appendix 4*.

Accuracy of new-generation cardiac computed tomography for the detection of coronary artery disease in obese patients

One study[42] assessed the performance of NGCCT for the detection of significant stenosis (defined as ≥ 50% vessel narrowing) in obese patients with suspected CAD or suspected progression of known CAD; obese patients were defined as those with a BMI of ≥ 30 kg/m^2. This study reported high sensitivity and specificity values; however, data were only reported per arterial segment; 543 data points (segments) were derived from 44 patients; data of this type are potentially problematic in that they assume independence of data sets derived from the same patient, which is unlikely to be true in practice, and may thus result in underestimation of variance. Some patients with additional characteristics which may contribute to difficulty in imaging [13 patients who had previous bypass graft(s) were excluded from this study, but it was not clear how many, if any, of these patients were also obese]. Therefore, the potential for biased accuracy assessments due to inappropriate exclusions could not be judged. Eleven (2%) of the arterial segments assessed in this study were classified as non-diagnostic and, although these segments appear to have been included in the analysis, it was unclear how they were classified. *Table 2* summarises the QUADAS-2 assessment and the results of this study are summarised in *Table 3*.

Accuracy of new-generation cardiac computed tomography for detection of coronary artery disease in patients with high calcium score

For the purpose of this assessment, levels of coronary calcium likely to result in a patient being difficult to image were classified as a high calcium score (HCS) > 400. Four studies[46,48,55,59] reported 10 data sets describing the accuracy of NGCCT for the detection of CAD in patients with HCS. Three[46,48,55] of the four studies reported only per-segment or per-artery accuracy data; data of this type are potentially problematic in that they assume independence of data sets derived from the same patient, which is unlikely to be true in practice, and may thus result in underestimation of variance. All studies excluded some patients with additional characteristics which may contribute to difficulty in imaging [e.g. previous bypass surgery (four studies[46,48,55,59]), previous stent implantation (three studies[48,55,59])]. However, no study reported the numbers of excluded patients who also had HCS. Therefore, the potential for biased accuracy assessments due to inappropriate exclusions could not be judged. One study[48] excluded non-diagnostic segments from its analysis; however, even if all of these segments were in the HCS patient group considered in this section, they would represent a maximum of 7% of the segments analysed; the effect of their exclusion on the reported accuracy estimates is, therefore, likely to be minimal. *Table 4* summarises the QUADAS-2 assessments for these studies and *Table 5* summarises individual study results.

All four studies reported per-segment data, using a threshold of ≥ 50% or > 50% vessel narrowing to define significant stenosis. The pooled estimates of sensitivity and specificity, derived from

TABLE 2 QUADAS-2 results for studies of the accuracy of NGCCT for the detection of CAD in obese patients

Study ID	Patient selection	Index test	Reference standard	Flow and timing
	Risk of bias	Risk of bias	Risk of bias	Risk of bias
Brodoefel 2008[42]	?	↑	→	→

↑, High risk of bias; ↓, low risk of bias; ?, unclear risk of bias.

TABLE 3 Accuracy of NGCCT for the detection of CAD in obese patients

Study ID	Obesity definition	Patient or segment data (n)	Index test	Reference standard	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean ± SD)
Brodoefel 2008[42]	≥30 kg/m²	Segment (543)	Somatom Definition (+ve test ≥1 stenosis ≥50%)[b]	ICA (+ve test ≥1 stenosis ≥50%)	113	12	33	385	90.4 (95% CI 83.8 to 94.9)[a]	92.1 (95% CI 89.1 to 94.5)[a]	Segment 11 (2.0%)	NR

+ve, positive; ND, non-diagnostic; NR, not reported; SD, standard deviation.
a Calculated values.
b Unclear how non-diagnostic segments were classified.

these data using a bivariate model, were 92.7% (95% CI 88.3% to 95.6%) and 90.6% (95% CI 80.6% to 95.8%), respectively. The I^2-statistic indicated moderate between-study heterogeneity in the estimates of sensitivity ($I^2 = 54.2\%$) and high between-study heterogeneity in the estimates of specificity ($I^2 = 92.2\%$). *Figure 2* shows the associated SROC curve for per-segment data in patients with HCS; the open circles, representing individual study results, are scaled to indicate relative sample size. In contradiction with the I^2-values, this plot indicates a lack of between-study heterogeneity, with individual study results 'clustered' in the upper left quadrant; this contradiction is indicative of the limited utility of statistic tests for heterogeneity in very small sample sizes.

Two studies[48,59] also reported accuracy data on a per-artery basis; these results are summarised in *Table 5*.

Only one study reported per-patient estimates of accuracy and these were of limited value as all 12 included patients were classified as TP using ≥ 50% vessel narrowing as the threshold to define significant stenosis.[59] This same study[59] also reported data for all three units of analysis (patient, artery and segment) using a threshold of > 75% vessel narrowing to define significant stenosis;

TABLE 4 QUADAS-2 results for studies of the accuracy of NGCCT for the detection of CAD in patients with HCS

Study ID	Risk of bias			
	Patient selection	Index test	Reference standard	Flow and timing
Brodoefel 2008[46]	?	↑	↓	↓
Meng 2009[48]	?	↑	↓	?
Scheffel 2006[55]	?	↑	↓	↓
Zhang 2010[59]	?	↓	↓	?

↑, High risk of bias; ↓, low risk of bias; ?, unclear risk of bias.
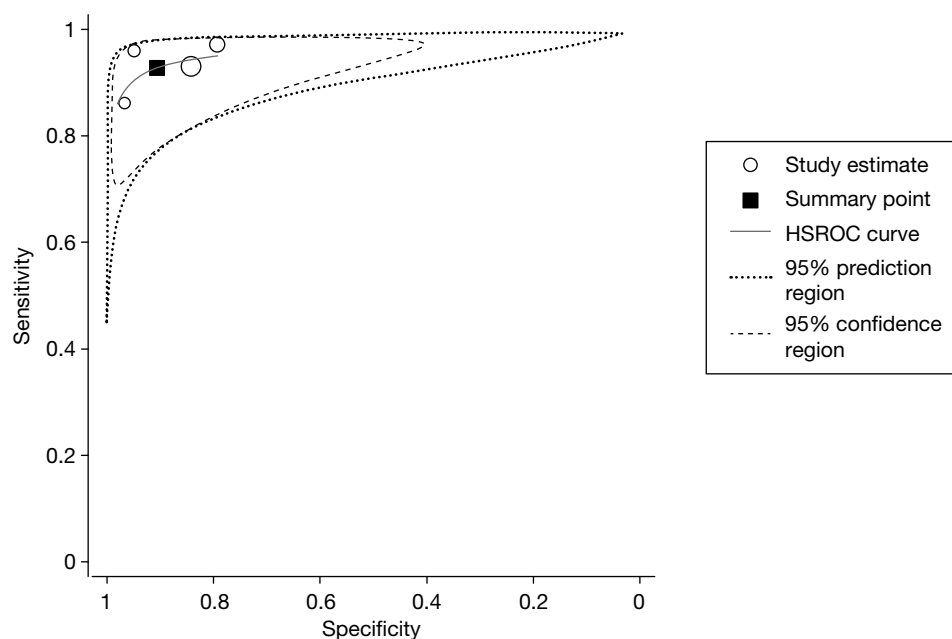
FIGURE 2 Summary receiver operating characteristic curve for per-segment data in studies of patients with HCS. HSROC, hierarchical summary receiver operating characteristic.

TABLE 5 Accuracy of NGCCT for the detection of CAD in patients with HCS

Study ID	HCS threshold	Patient or segment data (n)	Index test	Reference standard	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean ± SD)
Brodoefel 2008[46]	Calcium score >400	Segment (576)	Somatom Definition (+ve stenosis ≥50%)[a]	ICA (+ve test ≥1 stenosis ≥50%)[a]	187	14	59	316	93.0 (95% CI 88.6 to 96.1)[b]	84.3 (95% CI 80.2 to 87.8)[b]	92 (16.0%)	NR
Meng 2009[48]	Calcium score >400	Artery (135)	Somatom Definition (+ve test ≥1 stenosis >50%)	ICA (+ve test ≥1 stenosis >50%)	43	1	19	72	97.7 (95% CI 88.0 to 99.9)[b]	79.1 (95% CI 69.3 to 86.9)[b]	NR	For total population, CT dose index 30–42 mGy
		Segment (342)	Somatom Definition (+ve test ≥1 stenosis >50%)[c]		69	2	56	215	97.2 (95% CI 90.2 to 99.7)[b]	79.3 (95% CI 74.0 to 84.0)[b]	Total population 25/1558 (NR for the HCS group)	
Scheffel 2006[55]	≥400	Segment (206)	Somatom Definition (+ve test >50%)[a]	ICA (+ve test ≥1 stenosis >50%)	49	2	8	147	96.1 (95% CI 86.5 to 99.5)	94.8 (95% CI 90.1 to 97.8)	None[d]	NR
Zhang 2010[59]	>400	Patients (12)	Somatom Definition (+ve test ≥1 stenosis ≥50%)	ICA (+ve test ≥1 stenosis ≥50%)	12	0	0	0	100	–	NR	Total (all patients in study)
		Artery (36)			29	0	0	7	100 (95% CI 88.1 to 100)[b]	100 (95% CI 59.0 to 100)[b]	NR	61.38 ± 11.64 mGy, 16.51 ± 3.75 mSv
		Segment (180)			50	8	4	118	86.2 (95% CI 74.6 to 93.9)[b]	96.7 (95% CI 91.8 to 99.1)[b]	Total (all patients) 134/1661 (8.1%)	
		Patients (12)	(+ve test ≥1 stenosis >75%)	(+ve test ≥1 stenosis >75%)	10	1	0	1	90.9 (95% CI 58.7 to 99.8)[b]	100 (95% CI 25.0 to 100)[b]	NR	
		Artery (36)			17	3	1	15	85.0 (95% CI 62.1 to 96.8)[b]	93.8 (95% CI 69.8 to 99.8)[b]	NR	
		Segment (180)			28	10	6	136	73.7 (95% CI 56.9 to 86.6)[b]	95.8 (95% CI 91.0 to 98.4)[b]	Total (all patients) 193/1661 (11.6%)	

+ve, positive; HCS, high calcium score; ND, non-diagnostic; NR, not reported; SD, standard deviation.
a Unclear how non-diagnostic segments were classified.
b Calculated values.
c Non-diagnostic segments excluded.
d Tabulated results report no non-diagnostic segments for this population but text suggests that one patient had non-diagnostic segments.

sensitivity and specificity estimates were broadly similar to those obtained using the ≥ 50% vessel narrowing threshold and are reported in *Table 5.* However, using the higher threshold, estimates of per-patient accuracy could be calculated, sensitivity 90.9% (95% CI 58.7% to 99.8%) and specificity 100% (95% CI 25.0% to 100%); the wide CIs reflect the very small number of patients included in the analysis.

Accuracy of new-generation cardiac computed tomography for detection of coronary artery disease in patients with arrhythmias

Five studies[35,47,49,54,56] reported 10 data sets describing the accuracy of NGCCT for the detection of CAD in patients with arrhythmias. Three[35,49,54] of the five studies reported using no additional (extra to the patient's normal medication) beta-blockers prior to scanning, and beta-blocker use was unclear in a fourth study.[56] The fifth study[47] used beta-blockers prior to scanning in 40% of patients, and excluded 14% of otherwise eligible patients because they were unresponsive to beta-blockers and had rapid AF (> 100 b.p.m.) at the time of scanning; this study was judged to be at high risk of bias with respect to participant selection. In one study,[54] only 31% of eligible patients received the reference standard and were included in the analysis; this study was judged to be at high risk of bias, with respect to the flow of patients through the study, in this case due to partial verification bias. *Table 6* summarises the QUADAS-2 assessments for these studies and *Table 7* summarises individual study results. All but one of these studies were conducted in patients with AF; the fifth study included patients who were 'without stable sinus rhythm during scanning'.

All four studies[35,47,49,54,56] of patients with AF reported per-patient data. The pooled estimates of sensitivity and specificity (derived from these data using a DerSimonian–Laird random-effects model, in which 0.5 was added to all cells to allow for zero values) were 97.7% (95% CI 88.0% to 99.9%) and 81.7% (95% CI 71.6% to 89.4%), respectively. Between-study heterogeneity was low: the I^2-values were 1.4% for sensitivity and zero for specificity. No SROC curve was fitted as study results were too similar. *Figure 3* illustrates the per-patient sensitivity and specificity values for each study, with pooled estimates. The filled circles, representing individual studies, are scaled to indicate relative sample sizes and the wide CIs reflect the generally small sample sizes involved. One study reported the proportion of patients with AF who had non-diagnostic images (5%).[47]

One study also reported per-artery data and these results are described in *Table 7*.[47]

Four studies[35,49,54,56] reported per-segment data. These data were more heterogeneous than was the case for the per-patient data: the I^2-values were 79.6% for sensitivity and 89.5% for specificity. The pooled estimates of sensitivity and specificity, derived from these data using a bivariate model, were 87.4% (95% CI 68.3% to 95.7%) and 96.0% (95% CI 91.2% to 98.2%), respectively. *Figure 4* shows the associated SROC curve for per-segment data in patients with arrhythmias, with the open circles, representing individual study results, being scaled to indicate relative sample size.

TABLE 6 QUADAS-2 results for studies of the accuracy of NGCCT for the detection of CAD in patients with arrhythmias

Study ID	Risk of bias			
	Patient selection	Index test	Reference standard	Flow and timing
Marwan 2010[47]	↑	?	?	↓
Oncel 2007[49]	↓	↓	↓	↓
Rist 2009[54]	?	↓	↓	↑
Rixe 2009[35]	↓	?	?	?
Tsiflikas 2010[56] and Drosch 2008[57]	?	↑	↓	?

↑, High risk of bias; ↓, low risk of bias; ?, unclear risk of bias.
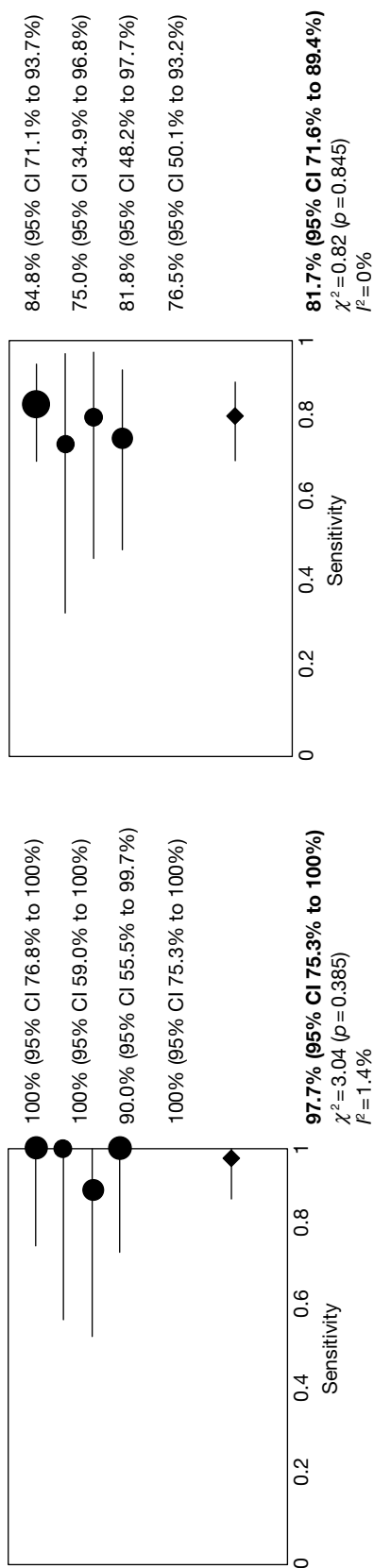
FIGURE 3 Forest plot of per-patient sensitivity and specificity of NGCCT for the detection of CAD in patients with AF.
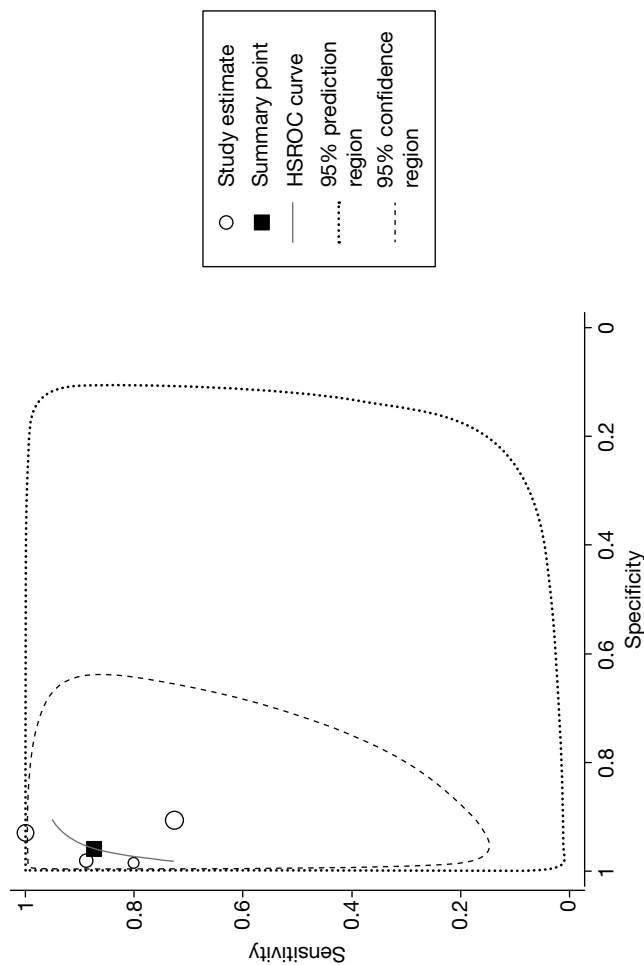
FIGURE 4 Summary receiver operating characteristic (SROC) curve for per-segment data in studies of patients with arrhythmias. HSROC, hierarchical summary receiver operating characteristic.

TABLE 7 Accuracy of NGCCT for the detection of CAD in patients with arrhythmias

Study ID	Arrhythmia definition	Patient or segment data (n)	Index test	Reference standard	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean ± SD)
Marwan 2010[47]	All patients in AF at scan (39 permanent, 21 persistent)	Patient (60)	Somatom Definition (+ve test ≥ 1 stenosis ≥50)[a]	ICA (+ve test ≥1 stenosis >50%)	14	0	7	39	100 (95% CI 76.8 to 100)[b]	84.8 (95% CI 71.1 to 93.7)[b]	3 patients (5%)	Mean DLP 1186 ±375 mGy-cm (range 630–2038 mGy-cm). Using a conversion factor of 0.014 for chest CT in adults, mean effective dose 16±5 mSv
		Artery (240)			21	1	14	204	95.5 (95% CI 77.2 to 100)[b]	93.6 (95% CI 89.5 to 96.4)[b]	3 vessels (1.3%)	
Oncel 2007[49]	Patients with AF. All patients had irregular heart rates during scanning	Patient (15)	Somatom Definition (+ve test ≥ 1 stenosis >50%)[c]	ICA (+ve test ≥1 stenosis >50%)	7	0	2	6	100 (95% CI 59.0 to 100)[b]	75.0 (95% CI 34.9 to 96.8)[b]	NR	13.8 ±1.37 mSv
		Artery (60)			12	3	2	43	80.0 (95% CI 51.9 to 95.7)[b]	95.6 (95% CI 84.9 to 99.5)[b]	NR	
		Segment (212)			12	3	3	194	80.0 (95% CI 51.9 to 95.7)[b]	98.5 (95% CI 95.6 to 99.7)[b]	13 (5.8%)	
Rist 2009[54]	All patients had chronic AF and irregular HR during scan	Patient (21)	Somatom Definition (+ve test ≥ 1 stenosis ≥50%)[c]	ICA (+ve test ≥1 stenosis ≥50%)	9	1	2	9	90.0 (95% CI 55.5 to 99.7)[b]	81.8 (95% CI 48.2 to 97.7)[b]	Total population 4/68 (5.9%)	For all 68 participants, mean DLP 942.9 ± 442 mGy-cm, mean effective dose 13.28 mSv
		Segment (283)			16	2	5	260	88.9 (95% CI 65.3 to 98.6)[b]	98.1 (95% CI 95.7 to 99.4)[b]	Total population 81/979 (8.3%)[d]	
Rixe 2009[35]	AF (no further details)	Patient (30)	Somatom Definition (+ve test ≥ 1 stenosis >50%)[a]	ICA (+ve test ≥1 stenosis ≥50%)	13	0	4	13	100 (95% CI 75.3 to 100)[b]	76.5 (95% CI 50.1 to 93.2)[b]	NR	13.5±4.2 mSv
		Segment (459)			24	0	30	405	100 (95% CI 85.8 to 100)[b]	93.1 (95% CI 90.3 to 95.3)[b]	32 (7.0%)	
Tsiflikas 2010[56] and Drosch 2008[57]	Patients without stable sinus rhythm during CT scan	Segment (572)[e]	Somatom Definition (+ve test ≥ 1 stenosis ≥50%)[f]	ICA (+ve test ≥1 stenosis ≥50%)	69	26	41	400	72.6 (95% CI 62.5 to 81.3)[b]	90.7 (95% CI 87.6 to 93.2)[b]	28 (5%)	NR

+ve, positive; DLP, dose–length product; ND, non-diagnostic; NR, not reported; SD, standard deviation.
a Non-diagnostic segments were classified as positive.
b Calculated values.
c Non-diagnostic segments were excluded.
d Found in 19 patients.
e Total segments reported in text inconsistent with number of segments for which results are reported.
f Unclear how non-diagnostic segments were classified.

Accuracy of new-generation cardiac computed tomography for detection of coronary artery disease in patients with high heart rate

Eight studies[39,41,44–46,48,55,59] reported 24 data sets describing the accuracy of NGCCT for the detection of CAD in patients with HHRs. The five studies[39,41,44,45,55] that reported the heart rates observed in patients classified as HHR reported mean heart rates of between 76 ± 9 and 88.8 ± 8.4 b.p.m. Three studies[46,48,55] reported only per-segment or per-artery accuracy data. Data of this type are potentially problematic in that they assume independence of data sets derived from the same patient; this is unlikely to be true in practice, and may thus result in underestimation of variance. With the exception of one study,[60] all studies in this group excluded patients with previous revascularisations (previous stent implantation and/or previous bypass graft); one study[44] was a retrospective analysis of selected patients who had undergone both CT and ICA and was judged to be at high risk of bias. Two studies[39,45] also excluded patients with AF. The first of these[39] excluded > 10% of otherwise eligible participants and was, therefore, judged to be at high risk of bias with respect to participant selection. In the second of these studies[45] only 48% of patients received the reference standard and were included in the analysis; this study was therefore also judged to be at high risk of bias with respect to the flow of patients through the study, owing to partial verification bias. *Table 8* summarises the QUADAS-2 assessments for these studies and *Table 9* summarises individual study results. Studies in this group defined HHR as ≥ 66, ≥ 65 or ≥ 70 b.p.m.; for the purposes of meta-analysis, these studies were treated as a single group assessing the accuracy of NGCCT in patients with a HR of ≥ 65 b.p.m. The baseline use of beta-blockers by study participants varied (see *Appendix 4*, *Inclusion/exclusion criteria and participant characteristics of included studies*), but all studies in this section reported that no additional beta-blockers were given prior to CT scanning.

Five studies[39,41,44,45,59] reported per-patient data, using a threshold of $\geq 50\%$ or $> 50\%$ vessel narrowing to define significant stenosis. The pooled estimates of sensitivity and specificity, derived from these data using a bivariate model, were 97.7% (95% CI 93.2% to 99.3%) and 86.3% (95% CI 80.2% to 90.7%), respectively; there was moderate between-study heterogeneity in both the estimates of sensitivity ($I^2 = 39.0\%$) and the estimates of specificity ($I^2 = 49.8\%$). *Figure 5* shows the SROC curve for per-patient data in patients with HHR. One study[45] reported per-patient accuracy data for multiple definitions of HHR; these results are summarised in *Table 9*. One study[39] reported the proportion of patients with HHR who had non-diagnostic images (6.8%).

Four studies[39,44,48,59] reported per-artery data, using a threshold of $\geq 50\%$ or $> 50\%$ vessel narrowing to define significant stenosis. The pooled estimates of sensitivity and specificity, derived from these data using a bivariate model, were 93.7% (95% CI 87.8% to 96.9%) and 92.4% (95% CI 83.3% to 96.8%), respectively; between-study heterogeneity was low (zero) for the estimates of sensitivity, but high for estimates of specificity ($I^2 = 83.7\%$). *Figure 6* shows the SROC curve for per-artery data in patients with HHR.

All eight studies reported accuracy data by arterial segment, using a threshold of $\geq 50\%$ or $> 50\%$ vessel narrowing to define significant stenosis. The pooled estimates of sensitivity and specificity, derived from these data using a bivariate model, were 92.7% (95% CI 89.3% to 95.1%) and 95.7% (95% CI 92.8% to 97.4%), respectively; there was high between-study heterogeneity in both the estimates of sensitivity ($I^2 = 67.1\%$) and the estimates of specificity ($I^2 = 92.8\%$). *Figure 7* shows the SROC curve for per-segment data in patients with HHR. One study[45] reported per-segment accuracy data for multiple definitions of HHR; these results are summarised in *Table 9*.

One study[59] reported additional data for all three units of analysis (patient, artery and segment) using a threshold of > 75% vessel narrowing to define significant stenosis; sensitivity and specificity estimates were broadly similar to those obtained using the $\geq 50\%$ vessel narrowing threshold and are reported in *Table 9*.

TABLE 8 QUADAS-2 results for studies of the accuracy of NGCCT for the detection of CAD in patients with HHR

| Study ID | Risk of bias | | | |
	Patient selection	Index test	Reference standard	Flow and timing
Alkadhi 2008[41]	↓	↓	↓	↓
Brodoefel 2008[46]	?	↑	↓	↓
Lin 2010[44]	↑	?	↓	↓
Meng 2009[48]	?	↑	↓	?
Ropers 2007[39]	?	↓	?	↓
Scheffel 2006[55]	?	↑	↓	↓
Weustink 2009[45]	↑	↓	↓	↑
Zhang 2010[59]	?	↓	↓	?

↑, High risk of bias; ↓, low risk of bias; ?, unclear risk of bias.
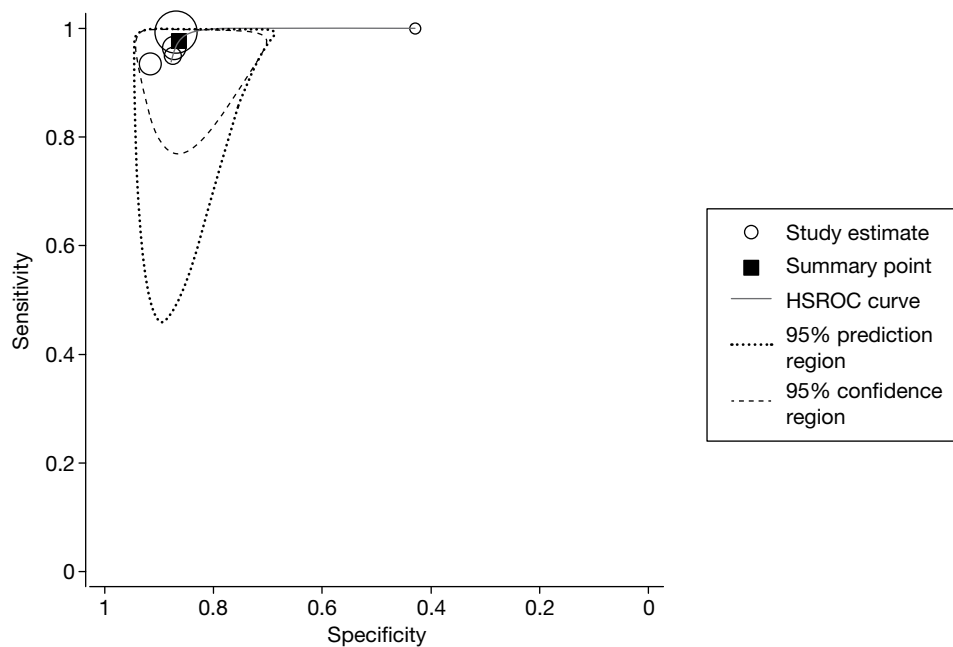
FIGURE 5 Summary receiver operating characteristic curve for per-patient data in studies of patients with HHR. HSROC, hierarchical summary receiver operating characteristic.
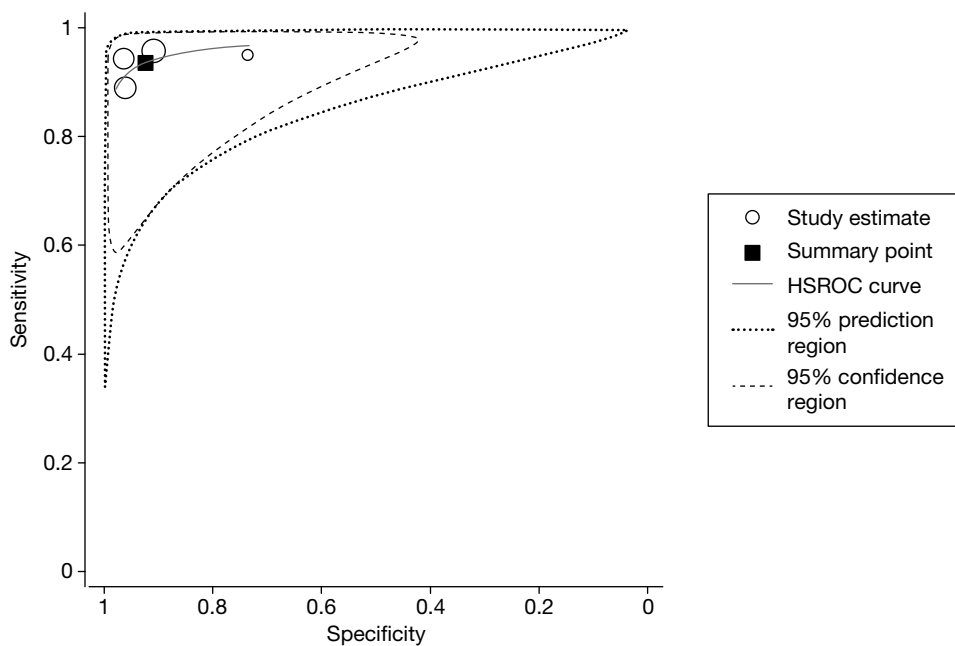
FIGURE 6 Summary receiver operating characteristic curve for per-artery data in studies of patients with HHR. HSROC, hierarchical summary receiver operating characteristic.
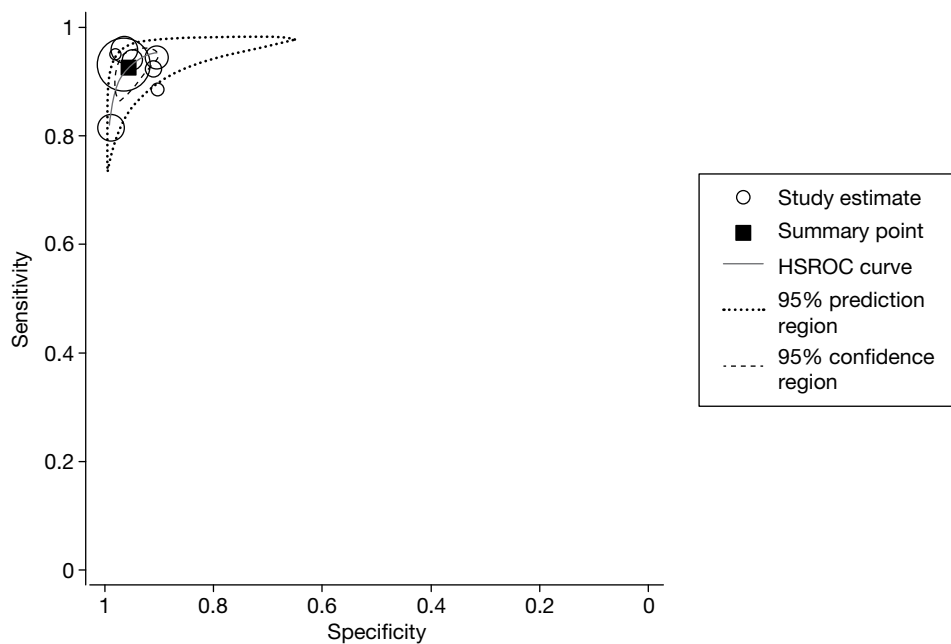
FIGURE 7 Summary receiver operating characteristic curve for per-segment data in studies of patients with HHR. HSROC, hierarchical summary receiver operating characteristic.

TABLE 9 Accuracy of NGCCT for the detection of CAD in patients with HHRs

Study ID	HR	Patient or segment data (n)	Index test	Reference standard	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean ± SD)
Alkadhi 2010[41]	>66 b.p.m.	Patient (75)	Somatom Definition (+ve test ≥1 stenosis >50%)	ICA (+ve test ≥1 stenosis >50%)	27	1	6	41	96.4 (95% CI 81.7 to 99.9)	87.2 (95% CI 74.5 to 95.2)	NR	7–9 mSv?
		Segment (1018)	Somatom Definition (+ve test ≥1 stenosis >50%)[a]		118	5	32	863	95.9 (95% CI 90.8 to 98.7)	96.4 (95% CI 95.0 to 97.5)	Segment 22 (2.2%)	
Brodoefel 2008[46]	>70 b.p.m.	Segment (370)	Somatom Definition (+ve test ≥1 stenosis ≥50%)[b]	ICA (+ve test ≥1 stenosis ≥50%)[b]	73	6	26	265	92.4 (95% CI 84.2 to 97.2)[c]	91.1 (95% CI 87.2 to 94.1)[c]	7 (1.9%)	NR
Lin 2010[44]	≥70 b.p.m.	Patient (18)	Somatom Definition (+ve test ≥1 stenosis >50%)	ICA (+ve test ≥1 stenosis >50%)	11	0	4	3	100 (95% CI 71.5 to 100)[c]	42.9 (95% CI 9.9 to 81.6)[c]	NR	NR
		Artery (54)			19	1	9	25	95 (95% CI 75.1 to 99.9)[c]	73.5 (95% CI 55.6 to 87.1)[c]	NR	
		Segment (223)			31	4	18	170	88.6 (95% CI 73.3 to 96.8)[c]	90.4 (95% CI 85.3 to 94.2)[c]	NR	
Meng 2009[48]	≥70 b.p.m.	Artery (225)	Somatom Definition (+ve test ≥1 stenosis >50%)[d]	ICA (+ve test ≥1 stenosis >50%)	68	3	14	140	95.8 (95% CI 88.1 to 99.1)[c]	90.9 (95% CI 85.2 to 94.9)[c]	NR	For total population, CT dose index 30–42 mGy
		Segment (756)			103	6	62	585	94.5 (95% CI 88.4 to 98.0)[c]	90.4 (95% CI 87.9 to 92.6)[c]	Total population 25/1558 (NR for the HHR group)	
Ropers 2007[39]	≥65 b.p.m.	Patient (44)	Somatom Definition (+ve test ≥1 stenosis >50%)[a]	ICA (+ve test ≥1 stenosis >50%)	19	1	3	21	95 (95% CI 75.1 to 99.9)[c]	87.5 (95% CI 67.6 to 97.3)[c]	3 (6.8%)	Mean effective dose 15.9 ± 3.11 mSv
		Artery (176)			33	2	5	136	94.3 (95% CI 80.8 to 99.3)[c]	96.5 (95% CI 91.9 to 98.8)[c]	9 (5.1%)	
		Segment (616)			62	4	27	523	93.9 (95% CI 85.2 to 98.3)[c]	95.1 (95% CI 92.9 to 96.7)[c]	50 (8.1%)	
Scheffel 2006[55]	≥70 b.p.m.	Segment (175)	Somatom Definition (+ve test ≥1 stenosis >50%)[b]	ICA (+ve test ≥1 stenosis >50%)	19	1	3	152	95.0 (95% CI 75.1 to 99.9)[c]	98.1 (95% CI 94.4 to 99.6)[c]	4/175 (2.2%)	NR
Weustink 2009[45]	66–79 b.p.m.	Patients (333, 170 underwent ICA and were included in the analysis)	Somatom Definition (+ve test ≥1 stenosis ≥50%)[b]	ICA (+ve test ≥1 stenosis ≥50%)	116	1	7	46	99.1 (95% CI 95.3 to 100)[c]	86.8 (95% CI 74.7 to 94.5)[c]	NR	Optimal ECG pulsing: Pitch: 0.25 ± 0.03 $CTDI_{vol}$ (mGy): 56.1 ± 14 $CTDI_{w}$ (mGy): 16.6 ± 3.5

Study ID	HR	Patient or segment data (n)	Index test	Reference standard	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean ± SD)
	≥80 b.p.m.	Patients (171, 85 underwent ICA and were included in the analysis)			47	0	5	33	100 (95% CI 92.5 to 100)[c]	86.8 (95% CI 71.9 to 95.6)[c]	NR	Optimal ECG pulsing: Pitch: 0.3 ± 0.04 $CTDI_{vol}$ (mGy): 42.7 ± 16.9 $CTDI_{w}$ (mGy): 14.9 ± 1
	≥66 b.p.m.	Patients (504, 255 underwent ICA and were included in the analysis)			163	1	12	79	99.4 (95% CI 96.6 to 100)[c]	86.8 (95% CI 78.1 to 93.0)[c]	NR	NR
	66–79 b.p.m.	Segment (2613)			240	21	71	2281	92.0 (95% CI 88.0 to 95.0)[c]	97.0 (95% CI 96.2 to 97.6)[c]	NR	NA
	≥80 b.p.m.	Segment (1327)			102	4	49	1172	96.2 (95% CI 90.6 to 99.0)[c]	96.0 (95% CI 94.7 to 97.0)[c]	NR	NA
	≥66 b.p.m.	Segment (3940)			342	25	120	3453	93.2 (95% CI 90.1 to 95.5)[c]	96.6 (95% CI 96.0 to 97.2)[c]	NR	NA
Zhang 2010[59]	>70 b.p.m.	Patients (70)	Somatom Definition (+ve test ≥1 stenosis ≥50%)	ICA (+ve test ≥1 stenosis >50%)	43	3	2	22	93.5 (95% CI 82.1 to 98.6)[c]	91.7 (95% CI 73.0 to 99.0)[c]	Total (all patients) 134/1661 (8.1%)	Total (all patients in study) 61.38 ± 11.64 mGy, 16.51 ± 3.75 mSv
		Artery (209)			72	9	5	123	88.9 (95% CI 80.0 to 94.8)[c]	96.1 (95% CI 91.1 to 98.7)[c]		
		Segment (1035)			110	25	10	890	81.5 (95% CI 73.9 to 87.6)[c]	98.9 (95% CI 98.0 to 99.5)[c]		
		Patients (70)	(+ve test ≥1 stenosis >75%)	(+ve test ≥1 stenosis >75%)	32	4	1	33	88.9 (95% CI 73.9 to 96.9)[c]	97.1 (95% CI 84.7 to 99.9)[c]		
		Artery (209)			41	8	4	156	83.7 (95% CI 70.3 to 92.7)[c]	97.5 (95% CI 93.7 to 99.3)[c]		
		Segment (1035)			59	16	8	952	78.7 (95% CI 67.7 to 87.3)[c]	99.2 (95% CI 98.4 to 99.6)[c]		

+ve, positive; $CTDI_{vol}$, computed tomography dose index, volume; $CTDI_{w}$, computed tomography dose index, weight; ND, non-diagnostic; NR, not reported; SD, standard deviation.
a　Non-diagnostic segments were classified as positive.
b　Unclear how non-diagnostic segments were classified.
c　Calculated values.
d　Non-diagnostic segments were excluded.

Accuracy of new-generation cardiac computed tomography for detection of coronary artery disease in beta-blocker intolerance

No studies of the accuracy of NGCCT for the detection of CAD in patients who were intolerant to beta-blockers were identified.

Accuracy of new-generation cardiac computed tomography for detection of coronary artery disease in stented patients

Seven studies[34,36,38,40,50–52] reported 10 data sets describing the accuracy of NGCCT for the detection of CAD in patients with previous stent(s) implantation. Three studies[34,38,52] reported only per-stent or stented-lesion accuracy data; data of this type are potentially problematic in that they assume independence of data sets derived from the same patient, which is unlikely to be true in practice, and may thus result in underestimation of variance. Four studies excluded some patients with additional characteristics that may contribute to difficulty in imaging. These included HHR and intolerance to beta-blockers,[40] previous bypass graft[36] and irregular heart rhythm/AF.[51,52] The last of these studies[51] also excluded patients with stents in bypass grafts, resulting in the exclusion of > 10% of otherwise eligible participants and a classification of high risk of bias with respect to participant selection. This same study[51] excluded non-diagnostic stents from its analyses; however, as the distribution of these stents between patients was not reported, their potential effect on per-patient accuracy estimates could not be assessed. *Table 10* summarises the QUADAS-2 assessments for these studies and *Table 11* summarises individual study results. Six[34,38,40,50–52] of the seven studies considered only in-stent restenosis and the seventh[36] considered both in-stent restenosis and stenosis of native vessels.

Four studies[36,40,50,51] reported per-patient data, using a threshold of ≥ 50% or > 50% vessel narrowing to define significant stenosis. The pooled estimates of sensitivity and specificity, derived from these data using a DerSimonian and Laird random-effects model, where 0.5 was added to all cells to allow for zero values, were 96.0% (95% CI 88.8% to 99.2%) and 81.6% (95% CI 74.7% to 87.3%), respectively. Between-study heterogeneity was low: the I^2-values were 19% for sensitivity and zero for specificity. No SROC curve was fitted as study results were too similar. *Figure 8* illustrates the per-patient sensitivity and specificity values for each study, with pooled estimates. One study[40] reported the proportion of patients with previous stent implantation who had non-diagnostic images (9%).

Six studies[34,38,40,50–52] reported accuracy data by stent or stented lesion. The pooled estimates of sensitivity and specificity, derived from these data using a bivariate model, were 93.6% (95% CI 86.1% to 97.2%) and 91.0% (95% CI 87.3% to 93.7%), respectively; between-study heterogeneity

TABLE 10 QUADAS-2 results for studies of the accuracy of NGCCT for the detection of CAD in patients with previous stent(s)

Study ID	Risk of bias			
	Patient selection	Index test	Reference standard	Flow and timing
De Graaf 2010[40]	?	↓	↓	↓
LaBounty 2010[38]	?	↑	↓	?
Oncel 2008[50]	?	↓	↓	↓
Pflederer 2009[51]	↑	?	↓	?
Pflederer 2010[34]	?	↑	?	?
Pugliese 2008[52] and 2007[53]	?	↑	↓	?
Van Mieghem 2007[36]	?	?	?	?

↑, High risk of bias, ↓, low risk of bias; ?, unclear risk of bias.

was low (zero) for the estimates of sensitivity, and moderate for estimates of specificity ($I^2 = 35.1\%$). *Figure 9* shows the SROC curve for per-stent/stented-lesion data in patients with previous stent(s). One study[38] reported additional data, using a threshold of ≥ 70% narrowing to define significant in-stent restenosis; sensitivity and specificity estimates were broadly similar to those obtained using the ≥ 50% narrowing threshold and are reported in *Table 11*.

Accuracy of new-generation cardiac computed tomography for detection of coronary artery disease in patients with coronary artery bypass graft

Three studies[34,37,58] reported six data sets describing the accuracy of NGCCT for the detection of CAD in patients with previous bypass graft(s). Two[34,37] of the three studies included in this section were published only as conference abstracts. In these cases, the minimal methodological information reported made it difficult to assess the risk of bias; this is reflected in the high proportion of unclear (?) judgements. The study that was reported as a full paper[58] reported only accuracy results per segment. *Table 12* summarises the QUADAS-2 assessments for these studies. A variety of different units of analysis were used, including bypass grafts, segments of bypass grafts, segments of native vessels and/or distal run-off, and patients; results are summarised in *Table 13*. Only one study[37] assessed the per-patient accuracy of NGCCT for the detection of any significant stenosis (≥ 50% narrowing) in a bypass graft, distal run-off, or native vessel. The per-patient sensitivity estimated from this study was 96.4% (95% CI 87.5% to 99.6%) and the per-patient specificity was 87.0% (95% CI 66.4% to 97.2%).

Accuracy of new-generation cardiac computed tomography for detection of coronary artery disease (multiple criteria)

Three studies reported the accuracy of NGCCT in patients with different combinations of difficult-to-image criteria.[42,52,58] Two studies[52,58] only reported per segment or per lesion accuracy data. The only study[58] to report per-patient data excluded non-diagnostic segments and, as it was unclear how these were distributed between patients, it was not possible to assess how their exclusion may have affected per-patient results. *Table 14* summarises the QUADAS-2 assessments for these studies and *Table 15* summarises individual study results. Units of analysis differed between studies and only one study[43] reported per-patient data. The per-patient sensitivity estimated from this study was 91.7% (95% CI 61.5% to 99.8%) and the per-patient specificity was 88.2% (95% CI 72.5% to 96.7%), for patients with HR of > 65 b.p.m. and/or AF.
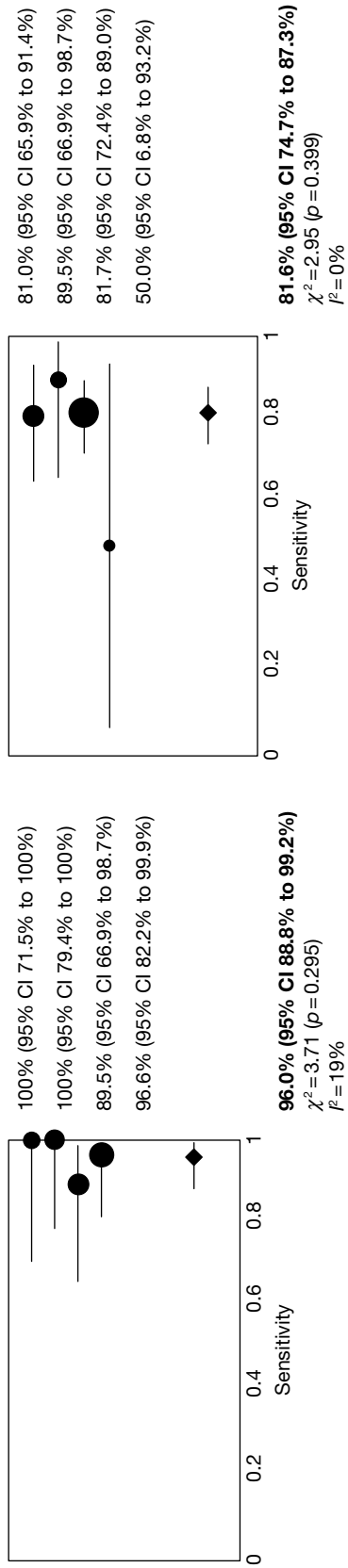
FIGURE 8 Forest plot of per-patient sensitivity and specificity of NGCCT for the detection of CAD in patients with previous stent(s).
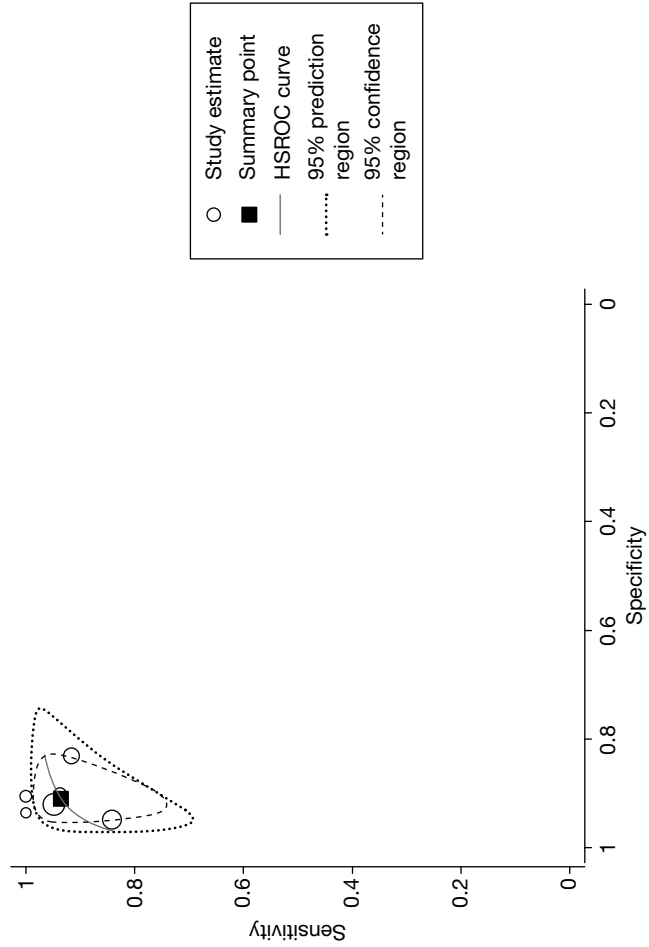
FIGURE 9 Summary receiver operating characteristic curve for per stent/stented-lesion data in studies of patients with previous stent(s). HSROC, hierarchical summary receiver operating characteristic.

TABLE 11 Accuracy of NGCCT for the detection of CAD in patients with previous stent(s)

Study ID	Patient or segment data (n)	Index test	Reference standard	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean ± SD)
De Graaf 2010[40]	Patient (53)[a]	Aquilion ONE (+ve test ≥1 stenosis ≥50%)[b]	ICA (+ve test ≥1 stenosis ≥50%)	11	0	8	34	100 (95% CI 71.5 to 100)[c]	81.0 (95% CI 65.9 to 91.4)[c]	Patients 5 (9%)	Unclear, reported for different imaging protocols. Mean dose ranged from 3.2±1.1 to 16.7±6.3mSv
	Stent (89, overlapping stents treated as a single stent)			11	1	13	64	91.7 (95% CI 61.5 to 99.8)[c]	83.1 (95% CI 72.9 to 90.7)[c]	Stents 7 (7.9%)	
LaBounty 2010[38]	Stent (54)	Unspecified 128-slice, dual source (+ve test stenosis ≥50%)	ICA (+ve test stenosis ≥50%)	1	0	5	48	100 (95% CI 2.5 to 100)[c]	90.6 (95% CI 79.3 to 96.9)[c]	NR	For total population, median=3.9mSv (IQR 1.9 to 9.1), NR for stented patients
		(+ve test stenosis ≥70%)	(+ve test stenosis ≥70%)	1	0	2	51	100 (95% CI 2.5 to 100)[c]	96.2 (95% CI 87.0 to 99.5)[c]		
Oncel 2008[50]	Patient (35)[d]	Somatom Definition (+ve test ≥1 stenosis ≥50%)	ICA (+ve test ≥1 stenosis ≥50%)	16	0	2	17	100 (95% CI 79.4 to 100)[c]	89.5 (95% CI 66.9 to 97.8)[c]	None	CT: 12.3±1.52 mSv, ICA: 5.3±2.76 mSv
	Stent (48)			17	0	2	29	100 (95% CI 80.5 to 100)[c]	93.5 (95% CI 78.6 to 99.2)[c]		
Pflederer 2009[51]	Patient (112)[a,d]	Somatom Definition (+ve test ≥1 stenosis ≥50%)	ICA (+ve test ≥1 stenosis ≥50%)	17	2	17	76	89.5 (95% CI 66.9 to 98.7)[c]	81.7 (95% CI 72.4 to 89.0)[c]	NR	14.8±4.8mSv
	Stent (135)	Somatom Definition (+ve test ≥1 stenosis ≥50%)[b]		16	3	6	110	84.2 (95% CI 60.4 to 96.6)[c]	94.8 (95% CI 89.1 to 98.1)[c]	15 (11%)	
Pflederer 2010[34]	Stent (78)	Somatom Definition (+ve test ≥1 stenosis >50%)	ICA (+ve test stenosis >50%)	15	1	6	56	93.8 (95% CI 69.8 to 99.8)[c]	90.3 (95% CI 80.1 to 96.4)[c]	NR	NR
Pugliese 2008[52] and 2007[53]	Stented lesions (178)[e]	Somatom Definition (+ve test ≥1 stenosis >50%)[b]	ICA (+ve test ≥1 stenosis >50%)	37	2	11	128	94.9 (95% CI 82.7 to 99.4)[c]	86.5 (95% CI 79.9 to 91.5)[c]	9 (5.1%)	NR
Van Mieghem 2007[36]	Patient (33)[f]	DSCT (unspecified) (+ve test >50% stenosis)	ICA (+ve test >50% stenosis)	28	1	2	2	96.6 (95% CI 82.2 to 99.9)[c]	50.0 (95% CI 6.8 to 93.2)[c]	NR	NR

+ve, positive; DSCT, dual-source computed tomography; IQR, interquartile range; ND, non-diagnostic; SD, standard deviation.
a In-stent restenosis only.
b Non-diagnostic stents/lesions were classified as positive.
c Calculated values.
d Non-diagnostic stents/lesions were excluded.
e Multiple stents per lesion were treated as a single unit.
f In-stent restenosis and stenosis of native vessels.

TABLE 12 QUADAS-2 results for studies of the accuracy of NGCCT for the detection of CAD in patients with previous bypass graft(s)

Study ID	Patient selection Risk of bias	Index test Risk of bias	Reference standard Risk of bias	Flow and timing Risk of bias
Pflederer 2010[34]	?	↑	?	?
Ropers 2008[37]	?	?	?	?
Weustink 2009[58]	↓	↑	↓	↓

↑, High risk of bias; ↓, low risk of bias; ?, unclear risk of bias.

TABLE 13 Accuracy of NGCCT for the detection of CAD in patients with previous bypass graft(s)

Study ID	Patient, vessel or segment data (n)	Index test	Reference standard	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean ± SD)
Pflederer 2010[34]	Bypass graft (42)	Somatom Definition (+ve test ≥ 1 stenosis > 50%)	ICA (+ve test stenosis >50%)	15	0	1	26	100 (95% CI 78.2 to 100)[a]	96 (95% CI 81.0 to 99.9)[a]	NR	NR
Ropers 2008[37]	Bypass graft (195)	Unspecified DSCT (+ve test stenosis ≥50%)	ICA (+ve test stenosis ≥50%)	90	0	5	100	100 (95% CI 96.0 to 100)[a]	95.2 (95% CI 89.2 to 98.4)[a]	None	NR
	Native coronary artery and distal run-off, segment (854)			111	12	103	541	90.2 (95% CI 83.6 to 94.9)[a]	84.0 (95% CI 80.9 to 86.8)[a]	87 (10.2%)	
	Patient (78)	Unspecified DSCT (+ve test ≥ 1 stenosis ≥50%)[b]		53	2	3	20	96.4 (95% CI 87.5 to 99.6)[a]	87.0 (95% CI 66.4 to 97.2)[a]	None	
Weustink 2009[58]	Bypass graft, segment (152)	Somatom Definition (+ve stenosis ≥50%)[c]	ICA (+ve stenosis ≥50%)	29	0	0	123	100 (95% CI 88.1 to100)[a]	100 (95% CI 97.0 to 100)[a]	NR	DLP (mGy-cm) 1.726±596
	Native coronary artery (grafted), segment (289)			170	0	5	112	100 (95% CI 97.9 to100)[a]	95.7 (95% CI 90.3 to 98.6)[a]	NR	Effective dose (mSv) 22.1±2.8
	Native coronary artery (non-grafted), segment (118)			33	1	7	77	97.1 (95% CI 84.7 to 99.9)[a]	91.7 (95% CI 83.6 to 96.6)[a]	NR	
	Distal run-off, segment (142)			19	1	0	122	95.0 (95% CI 75.1 to 99.9)[a]	100 (95% CI 97.0 to 100)[a]	NR	

+ve, positive; DLP, dose–length product; DSCT, dual-source computed tomography; ND, non-diagnostic; SD, standard deviation.
a Calculated values.
b Stenosis in a bypass graft, distal run-off or native vessel.
c Segments distal to an occlusion or with lumen diameter of <1.5mm were excluded from analyses.

TABLE 14 QUADAS-2 results for studies of the accuracy of NGCCT for the detection of CAD in patients with combinations of difficult-to-image criteria

Study ID	Risk of bias			
	Patient selection	Index test	Reference standard	Flow and timing
Leber 2007[43]	↓	?	?	?
Pugliese 2008[52] and 2007[53]	?	↑	↓	?
Weustink 2009[58]	↓	↑	↓	↓

↑, High risk of bias; ↓, low risk of bias; ?, unclear risk of bias.

TABLE 15 Accuracy of NGCCT for the detection of CAD in patients with combinations of difficult-to-image criteria

Study ID	Participants	Patient or segment data (n)	Index test	Reference standard	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean ± SD)
Leber 2007[43]	HR >65 b.p.m. and/or AF	Patient (46)	Somatom Definition (+ve test stenosis >50%)[a]	ICA (+ve test stenosis >50%)	11	1	4	30	91.7 (95% CI 61.5 to 99.8)[b]	88.2 (95% CI 72.5 to 96.7)[b]	One patient	For total population, mean dose 9.6 mSv (range 7.1–12.3 mSv). No separate data reported for HHR/AF participants
		Segment (637)			21	3	5	608	87.5 (95% CI 67.6 to 97.3)[b]	99.2 (95% CI 98.1 to 99.7)[b]	NR	
Pugliese 2008[52] and 2007[53]	Previous stent implantation, and HHR (≥70 b.p.m.)	Lesions (54)	Somatom Definition	CA	9	1	4	40	90.0 (95% CI 55.5 to 99.7)[b]	90.9 (95% CI 78.3 to 97.5)[b]	NR	NR
Weustink 2009[58]	Previous bypass graft and HHR (>65 b.p.m.)	Native coronary arteries (grafted), segment (289)[c]	Somatom Definition (+ve stenosis ≥50%)[d]	ICA (+ve stenosis ≥50%)	90	0	1	63	100 (95% CI 96.0 to 100)[b]	98.4 (95% CI 91.6 to 100)[b]	NR	DLP (mGy-cm): 1.726 ±596 Effective dose (mSv): 22.1 ±2.8

+ve, positive; DLP, dose–length product; ND, non-diagnostic; SD, standard deviation.
a Non-diagnostic segments were excluded.
b Calculated values.
c 154 segments in patients with HR >65 b.p.m. included in analysis.
d Segments distal to an occlusion or with lumen diameter of <1.5mm were excluded.

Summary

All 24 studies (26 publications, see *Table 1*) included in the systematic review were diagnostic test accuracy studies that reported data on the performance of NGCCT in difficult-to-image patients with known or suspected CAD. *Figure 10* provides a summary of the risk of bias assessments for these studies. The majority of studies were judged to be at low risk of bias with respect to the reference standard domain of QUADAS-2; this reflects the specification, in the inclusion criteria of the review, of a single acceptable reference standard (ICA). Unclear ratings for this domain mainly reflected poor reporting of the interpretation of the reference standard and uncertainty whether or not those interpreting ICA were blinded to the index test results. The judgement of risk of bias with respect to patient selection was problematic and this is reflected in the high proportion of unclear ratings. The unclear rating frequently related to uncertainty regarding the potential impact of inappropriate exclusions. Difficult-to-image patient groups were frequently reported as subgroups within larger studies, with those who had one or more additional criteria, which may contribute further to difficulty in imaging, being excluded from the study (e.g. a study reporting data for general CAD patients and a subgroup of patients with HHR may have excluded patients with previous revascularisations). In addition, the numbers/proportion of patients excluded in this way were frequently not reported. Inclusion of multiple measurements per patient (per-arterial segment, per-artery or per-stent data) was a common problem in the index test domain. Where studies excluded non-diagnostic arterial segments from their analyses, the potential impact of these exclusions was frequently unclear because their distribution between patients was not reported. For example, if a positive test for per-patient data is defined as one or more positive segments, exclusion of a non-diagnostic segment which is actually stenosed may result in misclassification of the whole patient as TN (i.e. a reduced estimate of the number of FN patients).

Where per-patient estimates of test accuracy were possible, these were generally high. Pooled estimates of sensitivity and specificity are summarised in *Table 16*. In particular, all per-patient estimates of sensitivity were > 95%, indicating that NGCCT could reliably rule out significant stenosis and thus potentially avoid invasive investigations such as ICA. Furthermore, although there were no data specifically for beta-blocker intolerant patients, it should be noted that no study reporting per-patient data for patients with HHR used additional beta-blockers prior to scanning. It may therefore be inferred that NGCCT could reasonably be used to image patients who are intolerant to beta-blockers who could not otherwise be reliably imaged by 64-slice CT.

TABLE 16 Summary of test accuracy results

Patient group	Unit of analysis	No. of studies	n	Sensitivity (%)	I^2 (%)	Specificity (%)	I^2 (%)
Obesity (BMI ≥ 30 kg/m²)	Segment	1	543	90.4 (95% CI 83.8 to 94.9)	NA	92.1 (95% CI 89.1 to 94.5)	NA
HCS (> 400)	Segment	4	1304	92.7 (95% CI 88.3 to 95.6)	54.2	90.6 (95% CI 80.6 to 95.8)	92.2
Arrhythmias	Patient	4	126	97.7 (95% CI 88.0 to 99.9)	1.4	81.7 (95% CI 71.6 to 89.4)	0
	Segment	4	1526	87.4 (95% CI 68.3 to 95.7)	79.6	96.0 (95% CI 91.2 to 98.2)	89.5
HHR (≥ 65 b.p.m.)	Patient	5	462	97.7 (95% CI 93.2 to 99.3)	39.0	86.3 (95% CI 80.2 to 90.7)	49.8
	Artery	4	664	93.7 (95% CI 87.8 to 96.9)	0	92.4 (95% CI 83.3 to 96.8)	83.7
	Segment	8	8133	92.7 (95% CI 89.3 to 95.1)	67.1	95.7 (95% CI 92.8 to 97.4)	92.8
Previous stent implantation	Patient	4	233	96.0 (95% CI 88.8 to 99.2)	19.0	81.6 (95% CI 74.7 to 87.3)	0
	Stent/stented lesion	6	582	93.6 (95% CI 86.1 to 97.2)	0	91.0 (95% CI 87.3 to 93.7)	35.1

NA, not applicable.

With the exception of one small study, data on the accuracy of NGCCT in patients with high coronary calcium scores, previous bypass grafts, or obesity were limited to per arterial segment or per-artery data. Sensitivity estimates remained high (> 90% in all but one study).

Data on the number of difficult-to-image patients in whom NGCCT was non-diagnostic were sparse; where numbers of non-diagnostic images were reported, these were often for the whole study population, rather than the difficult-to-image subgroup. Three studies did report subgroup-specific non-diagnostic image rates in different populations; these were 5% for patients with arrhythmias,[47] 6.8% for patients with HHR[44] and 9% for patients with previous stent implantation.[40]
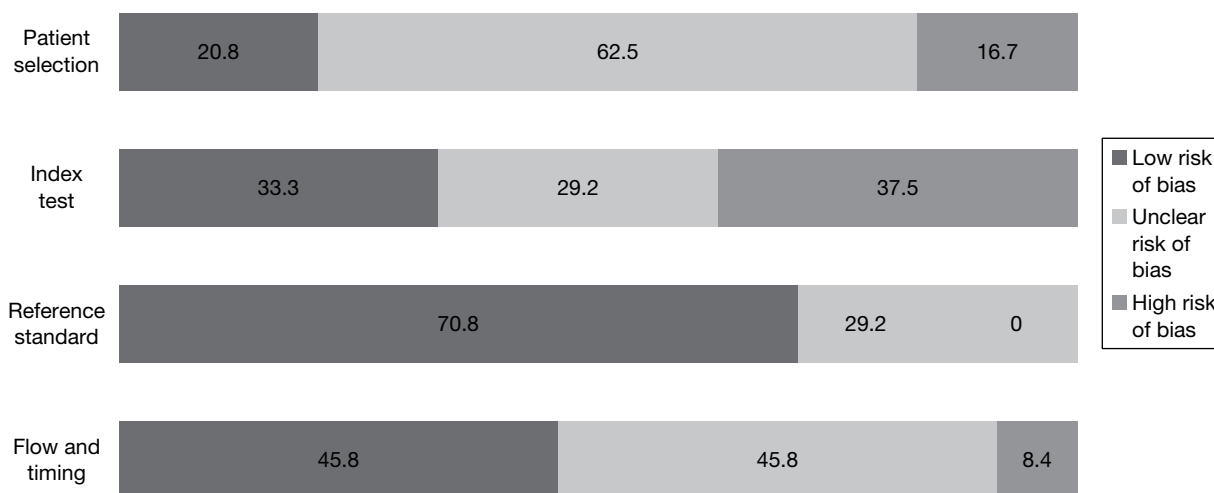
FIGURE 10 Summary of QUADAS-2 assessments.

Chapter 4

Assessment of cost-effectiveness

Search strategy

Searches were undertaken to identify cost-effectiveness studies of NGCCT. As with the clinical effectiveness searching, search strategies were developed specifically for each database and searches took into account generic and other product names for the intervention. No restrictions on language or publication status were applied. Limits were applied to remove animal studies. Full search strategies are reported in *Appendix 1*.

The following databases were searched for relevant studies from 1 January 2000 to 21 March 2011: MEDLINE (2000 to March week 2 2011) (OvidSP)

- MEDLINE In-Process and Other Non-Indexed Citations and Daily Update (2000 to 17 March 2011) (OvidSP)
- EMBASE (2000 to week 11 2011) (OvidSP)
- NHS EED (2000 to 9 March 2011) (CRD website)
- Health Economic Evaluation Database (HEED) (2000 to 9 March 2011) (Wiley) http://onlinelibrary.wiley.com/book/10.1002/9780470510933
- Paediatric Economic Database Evaluation (PEDE) (2000 to 5 March 2011) (internet) http://pede.ccb.sickkids.ca/pede/search.jsp

Supplementary searches on catheter angiography were undertaken on the following resources to identify guidelines and guidance:

- National Guideline Clearinghouse (NGC) (2005 to 16 March 2011) (Internet) www.guideline.gov/
- International Guideline Library (G-I-N) (2005 to 16 March 2011) www.g-i-n.net
- NICE guidance (up to 16 March 2011) (internet) http://guidance.nice.org.uk/
- Turning Rsearch Into Practice (TRIP) database (2005 to 16 March 2011) (internet) www.tripdatabase.com/
- HTA (2005 to 16 March 2011) (CRD website).

Identified references were downloaded in EndNote X4 software for further assessment and handling. References in retrieved articles were checked for additional studies.

Cost-effectiveness of new-generation cardiac computed tomography in coronary artery disease

Model structure and methodology

In order to assess the cost-effectiveness of NGCCT for difficult-to-image patient groups with CAD a model was developed. This model provides a framework for the synthesis of data from the review of clinical effectiveness of NGCCT (see *Chapter 3*, *Results*), which only consisted of accuracy data, and other relevant parameters, such as costs and effects of complications due to procedures, the long-term costs and effects of patients with CAD, and the risk of cancer from radiation exposure, in order to evaluate the potential long-term cost-effectiveness of NGCCT.

The cost-effectiveness of NGCCT for difficult-to-image patient groups is estimated for two CAD populations: the suspected CAD population and the known CAD population. Patients suspected of CAD are patients who have chest pain or other symptoms suggestive of CAD. Patients with known CAD are patients who have previously been diagnosed with CAD and whose symptoms are no longer controlled by drug treatment and/or being considered for revascularisation. The use of NGCCT has different purposes in the two CAD populations: for the suspected CAD population the purpose is to diagnose patients with CAD and for the known CAD population the purpose is to aid decision-making regarding a revascularisation.

The overall decision problem for which we aimed to develop a model can be subdivided into separate components. As for most of these components models were already available, we decided to combine five models to estimate the cost-effectiveness of the NGCCT:

1. a decision tree that models the diagnostic pathway (see below, *Diagnostic model*)
2. an alive–dead Markov model for 'healthy' patients without CAD (see below, *Healthy population Markov model*)
3. a simple stroke model to estimate the impact of test and treatment-related stroke (see below, *Stroke model*)
4. a model for the prognosis of patients with CAD (see below, *EUROPA*)
5. a model constructed by the Centre for Health Economics, University of York to model the impact of imaging due to radiation on cancer morbidity and mortality, hereafter referred to as the York Radiation Model (YRM)[61] (see below, *York Radiation Model*).

The comparator used for the evaluation of suspected or known CAD in difficult-to-image patients was ICA (see *Chapter 3*). Three strategies were evaluated in this assessment. The first strategy (*ICA only*) is a strategy through which patients with suspected or known CAD only undergo an ICA. Although ICA is the reference standard test and is assumed to be 100% sensitive and specific, it is associated with a risk of serious complications, including death, non-fatal MI and stroke. NGCCT does not have a sensitivity and specificity of 100% and thus is less accurate than the ICA. The second strategy (*NGCCT–ICA*) evaluates the combination of cardiac CT using the new-generation technologies and ICA. Cardiac CT is first performed in all patients and patients with a positive CT scan then undergo an ICA.[3] This additional test will reveal any patients with a false-positive CT test result but it also provides other information that a CT currently does not.[3] The third strategy (*NGCCT only*) uses only NGCCT to diagnose patients.

The five models used in the analyses are described, in detail, below. The stochastic analyses are based on cohort simulations. To investigate decision uncertainty, second-order uncertainty microsimulations were run. All costs and effects were discounted by 3.5%. The model incorporated a lifetime horizon to estimate outcomes in terms of quality-adjusted life-years (QALYs) and costs from the perspective of the NHS. Only health effects of patients were included.

Diagnostic model

The diagnostic pathway was modelled using a modified version of the CE-MARC model, developed by Walker (University of York, 2011, personal communication) which is based on the CE-MARC study.[62] The CE-MARC study[62] compared CV MRI with other diagnostic tests. Modification of the original CE-MARC model was necessary because the test strategies considered in this assessment did not correspond with the test strategies used in the original model. Furthermore, they did not include the treatment medication-only option required for our suspected CAD population. Our model identifies patients as TP, TN, FP and FN depending on the diagnostic performance of the test or test strategy and the prior likelihood of the test outcome. Furthermore, it estimates the mortality and morbidity of the tests and the interventions.

Decision trees for this process are shown in *Figures 11–13* for patients with suspected CAD and in *Figures 16–18* for patients with known CAD. Two versions of the diagnostic model were created because the known (two-treatment model) and suspected CAD (three-treatment model) populations are treated differently after a positive test outcome. The disease progression of the survivors of the tests and revascularisation procedures was modelled with the disease progression model (see *EUROPA*, below). We assumed that the tests were performed immediately after each other without any time delay.

Diagnostic model for patients with suspected coronary artery disease

The purpose of testing patients with suspected CAD (based on clinical symptoms) is to diagnose those patients and give, when necessary, appropriate treatment.

The prior likelihood of having CAD in patients with suspected CAD is assumed to be 10–29%, based on the clinical guideline *Chest pain of recent onset*.[63] This prior likelihood is based on some patient characteristics (age, gender, diabetes, smoking and hyperlipidaemia, and either non-anginal chest pain, atypical angina or typical angina). According to the guideline, in these patients, first a CT calcium scoring is performed and the patients referred for 64-slice CT (i.e. our population) have a score of 1–400. Patients with a higher prior likelihood than 10–29% should be referred for ICA. Some difficult-to-image subgroups could have a higher prior likelihood but how much higher is unknown. Therefore, we performed a scenario analysis where the prior likelihood was set at 30% for all subgroups. *Table 17* summarises the prior likelihood of CAD in the known and suspected CAD populations.

The sensitivity and specificity of ICA was assumed to be 100%, as in Mowatt *et al*.[3] The systematic review performed for this assessment provided the estimates of the sensitivity and specificity for the NGCCT. As described in *Chapter 3, Summary,* estimates of sensitivity and specificity differed for the different difficult-to-image patient groups. The sensitivity and specificity of the NGCCT in the beta-blocker-intolerant patient group were assumed to be the same as the sensitivity and specificity in patients with a HHR. As beta-blockers are used to lower the heart rate of the patients, it is not the intolerance itself that makes the patient difficult to scan but rather the fact that such a patient may have a heart rate that is too high during the scan; studies reporting per-patient sensitivity and specificity in patients with a HHR did not use beta-blockers prior to scanning. *Table 18* shows the sensitivity and specificity estimates for the NGCCT in the different difficult-to-image patient groups.

The result of the test and the presence of the disease determine whether a patient is classified as TP, TN, FP or FN (illustrated in *Figure 14*). The three strategies (ICA only, NGCCT only and NGCCT–ICA) all have other properties and therefore test outcomes differ by strategy. The four outcomes were calculated using the following formulae: TP, prior likelihood × sensitivity; TN, (1 – prior likelihood) × specificity; FP, (1 – prior likelihood) × (1 – specificity); FN, prior likelihood × (1 – sensitivity). Possible test outcomes are described by strategy.

Patients with suspected CAD who have a positive test result are thought to have CAD according to the test and need to be treated with medication only or a revascularisation. A negative test result implies that the patient with suspected CAD does not have the disease and does not need to be treated.

- *ICA-only strategy* Patients diagnosed with the reference standard ICA can be defined as only TP or TN because ICA is assumed to be 100% accurate and therefore misdiagnosis is not possible.
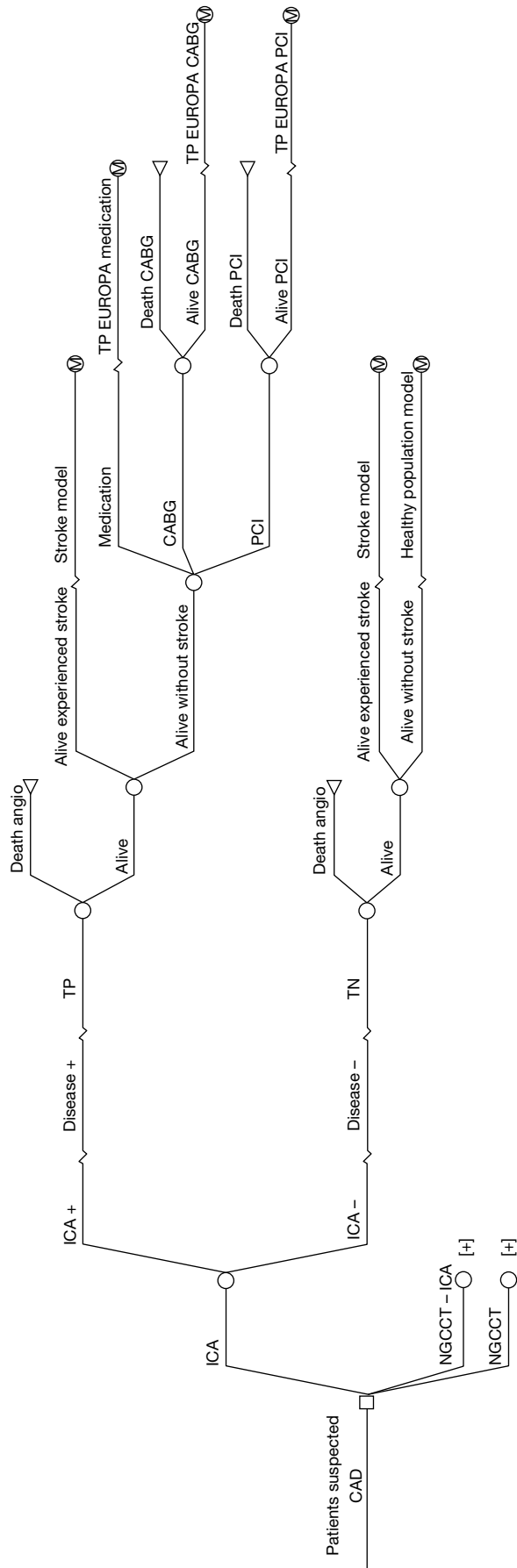
FIGURE 11 Coronary artery disease suspected population: ICA only.
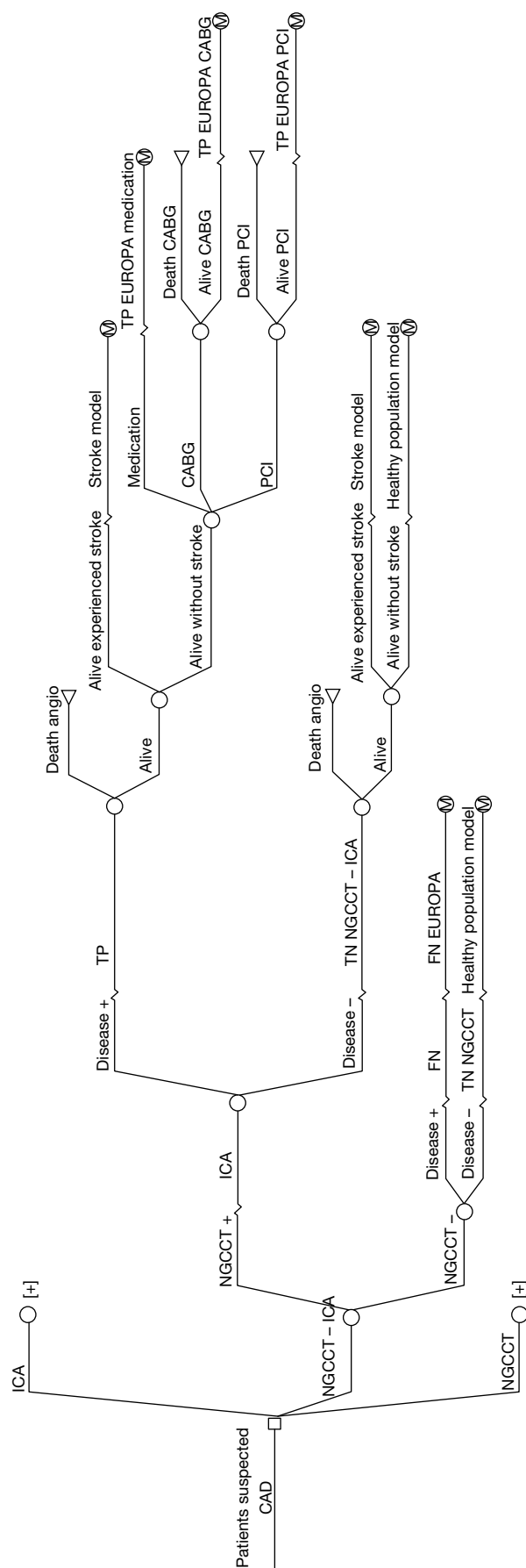
FIGURE 12 Coronary artery disease suspected population: NGCCT–ICA.
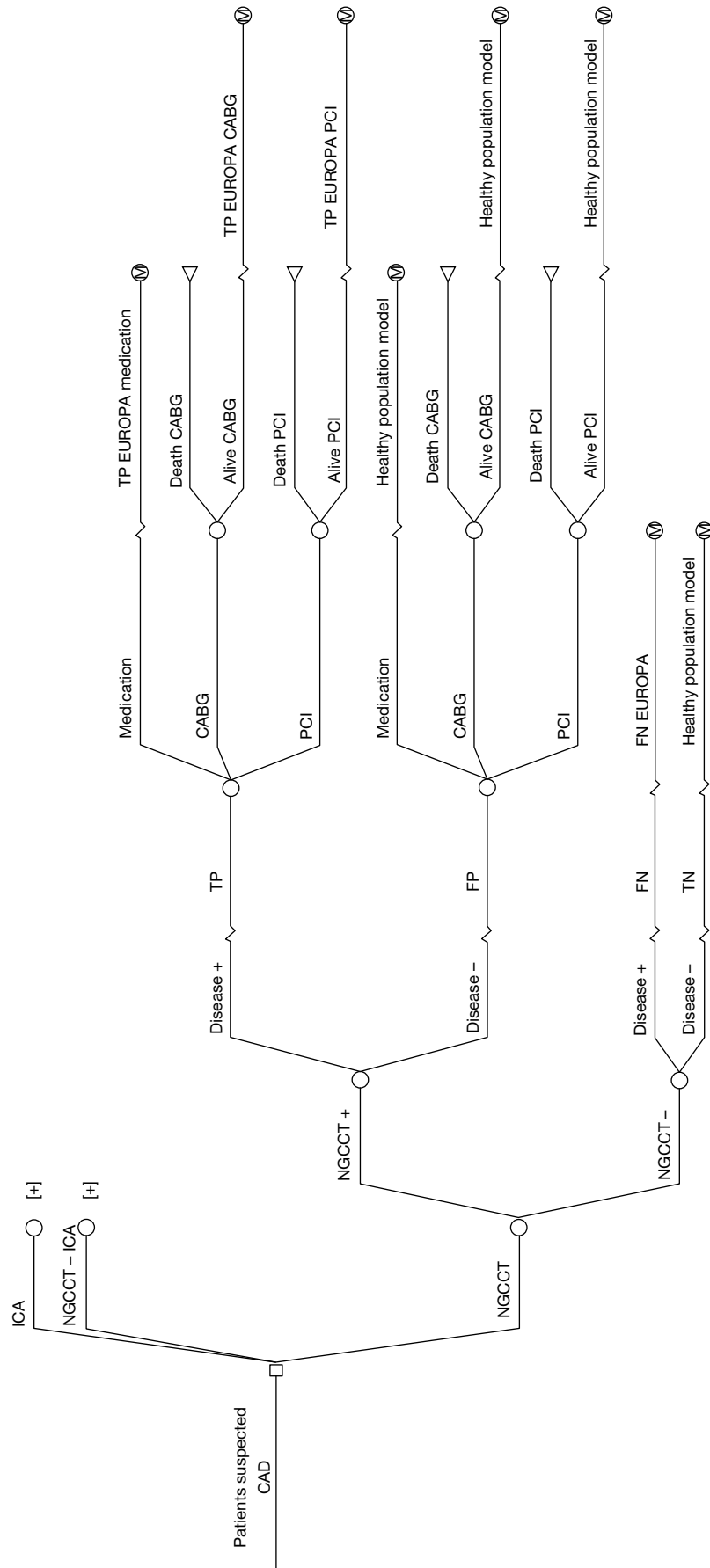
FIGURE 13 Coronary artery disease suspected population: NGCCT.

Test outcome	Disease positive	Disease negative
Test positive	TP	FP
Test negative	FN	TN

FIGURE 14 A 2 × 2 table for patients with suspected CAD.

Test Outcome	Revascularisation needed	Revascularisation not needed
Test positive	TP	FP
Test negative	FN	TN

FIGURE 15 A 2 × 2 table for patients with known CAD.

- *NGCCT-only strategy* The sensitivity and specificity of the NGCCT are not 100%, and the results of these tests can therefore define patients as TP, TN, FP or FN. For the patients who are diagnosed incorrectly the test result will have consequences. A proportion of the FNs will later be identified as TPs because patients may have persistent symptoms. However, in our model, these patients could have experienced an event [e.g. MI or cardiac arrest (CA)] before the correct diagnosis is established. The FPs may receive unnecessary treatment with its attendant consequences.
- *NGCCT–ICA strategy* In this strategy, an ICA is performed to confirm a positive NGCCT scan. Therefore, all patients with a FP result for the NGCCT will subsequently be correctly classified by the ICA as TNs. As a result, these patients will not receive any unnecessary treatment. In the model, all of these patients are subsequently considered as TNs for the NGCCT–ICA strategy since the ICA correctly reclassified them. However, an ICA is not performed in patients with a negative NGCCT result. As the sensitivity of the NGCCT is not 100%, it is possible for FN results to arise from this NGCCT–ICA strategy. As with the FNs from the NGCCT-only strategy, a proportion of these FNs will be identified at a later stage.

Diagnostic model for population with known coronary artery disease

The purpose of testing patients with known CAD (defined as those who have previously been diagnosed with CAD and whose symptoms are no longer controlled by drug treatment and/or are being considered for revascularisation) is to inform revascularisation decisions.

The prior likelihood of performing a revascularisation in patients with known CAD is assumed to be 39.5%, based on the CE-MARC study (see *Table 17*).[64] The CE-MARC study[62] calculated the cost-effectiveness of using CV MRI to determine whether or not a revascularisation is necessary. The purpose of diagnostic testing assessed in the CE-MARC study[62] captures the aim of this economic evaluation for the known CAD population and therefore the prior likelihood of the CE-MARC population can be used in the diagnostic model.

The accuracy of the NGCCT for the known CAD population is assumed to be the same as for the suspected CAD population. This assumption was made because for some difficult-to-image patient groups there were no data or just one article for a known CAD population. Details of the reported inclusion criteria, for all studies included in the systematic review, are provided in *Appendix 4*.
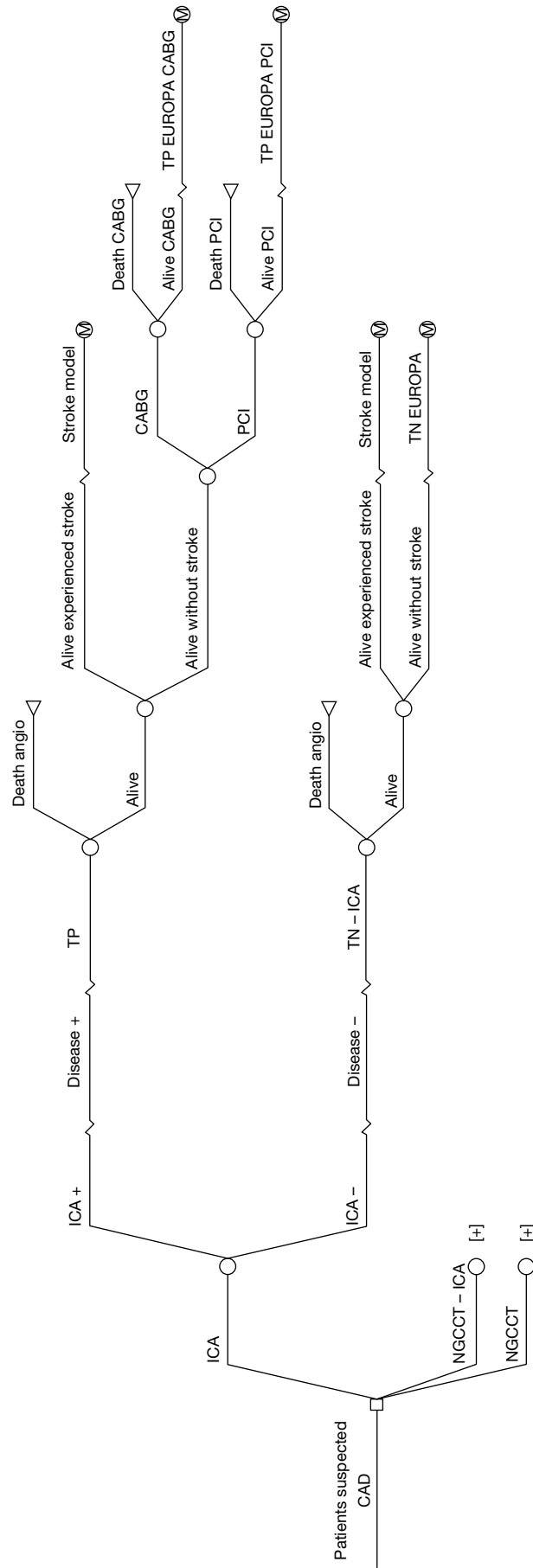
FIGURE 16 Known CAD: ICA only.

FIGURE 17 Known CAD: NGCCT–ICA.
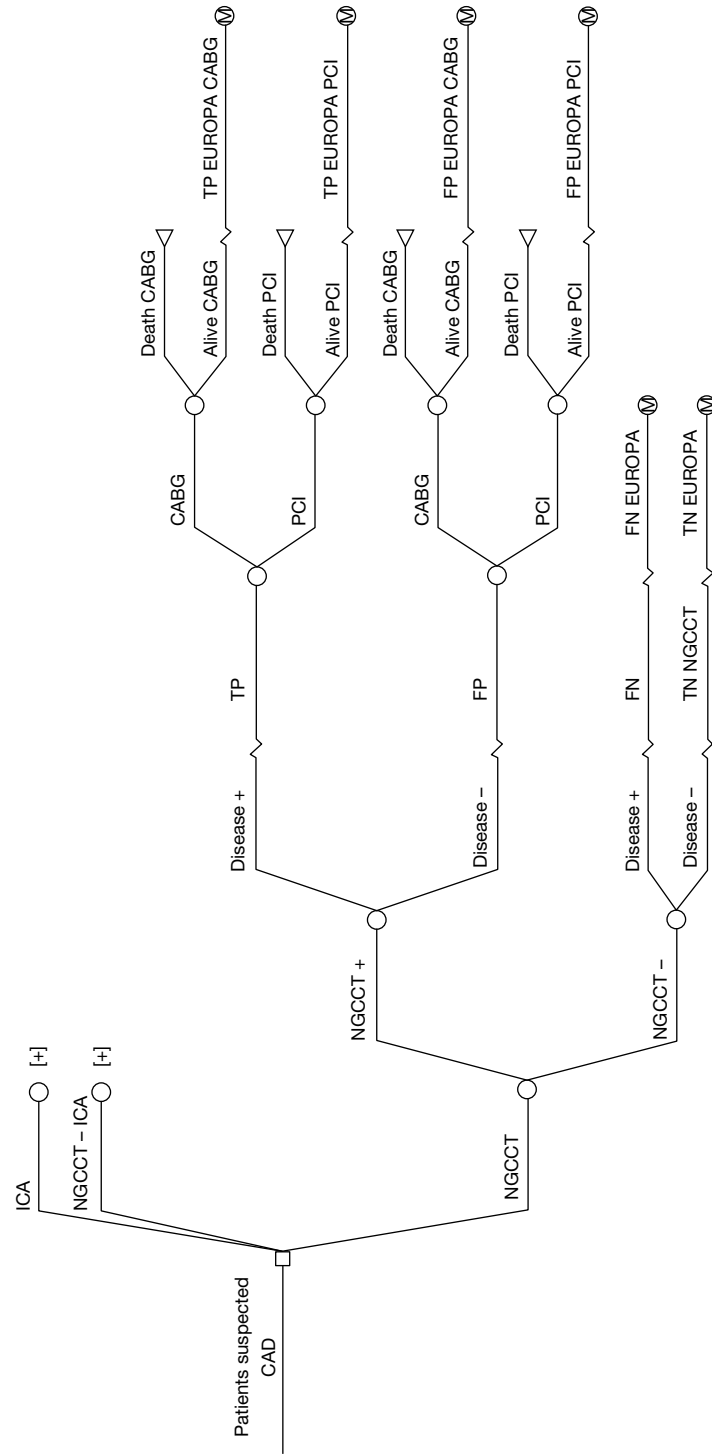
FIGURE 18 Known CAD: NGCCT only.
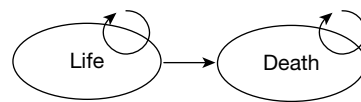
FIGURE 19 Simple alive–dead Markov model.

TABLE 17 Prevalence in CAD populations

Prevalence	Mean	Source
Suspected CAD	0.200	CG95[63]
Known CAD	0.395	Walker 2011[64]

TABLE 18 New-generation cardiac computed tomography accuracy estimates (subgroup specific)

Test and population	Sensitivity (95% CI)	Specificity (95% CI)	Source
ICA: reference standard	1	1	
NGCCT: obesity	0.904 (0.838 to 0.949)	0.921 (0.891 to 0.945)	Review
NGCCT: high coronary calcium score	0.927 (0.883 to 0.956)	0.906 (0.806 to 0.958)	Review
NGCCT: arrhythmias	0.977 (0.881 to 0.999)	0.817 (0.716 to 0.894)	Review
NGCCT: HHR	0.977 (0.932 to 0.993)	0.863 (0.802 to 0.907)	Review
NGCCT: beta-blocker intolerance	0.977 (0.932 to 0.993)	0.863 (0.802 to 0.907)	Assumption
NGCCT: previous stented	0.960 (0.822 to 0.999)	0.816 (0.747 to 0.873)	Review
NGCCT: previous CABG	0.964 (0.875 to 0.996)	0.87 (0.664 to 0.972)	Review

A positive test result for the patient population who have previously been diagnosed with CAD and whose symptoms are no longer controlled by drug treatment and/or who are being considered for revascularisation indicates that the patient will benefit from a revascularisation and should undergo a CABG or a PCI. A negative test result for the same population implies that the patient will not benefit from a revascularisation and drug treatment only should be continued.

The same test outcomes apply to the known CAD population as previously described before for the suspected CAD population (*Figure 15*). Thus the ICA-only strategy will define only TP and TN because ICA is assumed to be 100% accurate. The NGCCT-only strategy gives four possible outcomes: TP, FP, TN and FN. The combined strategy (NGCCT–ICA) defines three outcomes: TP, TN and FN.

Healthy population Markov model
Patients without the disease (TN and FP from the suspected CAD population; see *Table 19*) were modelled with a simple alive–dead Markov model (*Figure 19*) based on UK life tables.[65] Based on UK life tables, patients could either die of all causes (including CV, because a negative test result does not mean that patients will never develop CAD) or stay in the 'alive' state. Only QALYs but no costs were calculated with this model.

Of the patients without the disease, only those with a FP test result may undergo unnecessary medical tests and procedures before the absence of CAD is established. The analyses performed in this study included the costs and health outcomes resulting from these tests and procedures in the diagnostic model. However, beyond this, there was no reason to expect any long-term difference in prognosis between patients with a TN test result and those with a FP test result. Long-term costs were therefore not included in the analyses.

Stroke model

As stated previously, ICA and revascularisations are associated with complications and one of these is stroke. The costs and health expectancy of patients who experienced a stroke due to the initial ICA or revascularisation were modelled using a simple alive–dead stroke model. Life expectancy is based on updated UK life tables, combined with a multiplier for age-specific mortality among stroke patients.[66] Costs and QALYs for stroke patients were calibrated to correspond with the results of an economic evaluation by Sandercock *et al.*,[66] which estimated the cost-effectiveness of thrombolytic treatment for acute ischaemic stroke compared with standard care for the NHS perspective. In particular, we assumed that stroke patients would receive thrombolytic treatment.[67]

EUROPA

The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) trial assessed the ability of the ACE inhibitor perindopril to reduce CV death, MI, and CA in a broad population of patients with stable coronary heart disease and without heart failure or substantial hypertension.[68] Based on the patients in this trial, Briggs *et al.*[69] built a Markov model.

Patients with the disease who have not experienced a stroke due to the initial ICA or initial revascularisation, irrespective of the test outcome enter the EUROPA model. The Markov based EUROPA model predicts changes to life expectancy and QALYs for patients with CAD. These changes are calculated based on risk equations which predict the probability of events [CA, (non-)fatal MI] that patients could suffer and the mortality associated with those events. The time cycle used in the EUROPA model is 3 months.

EUROPA model structure

The EUROPA Markov model (*Figure 20*) consisted of five health states that were defined as absence of primary event in the EUROPA trial: 'trial entry', 'CV death', 'non-fatal primary event in current year', 'history of non-fatal event (NFE)' and 'non-CV death'.[70] The 3-monthly transition
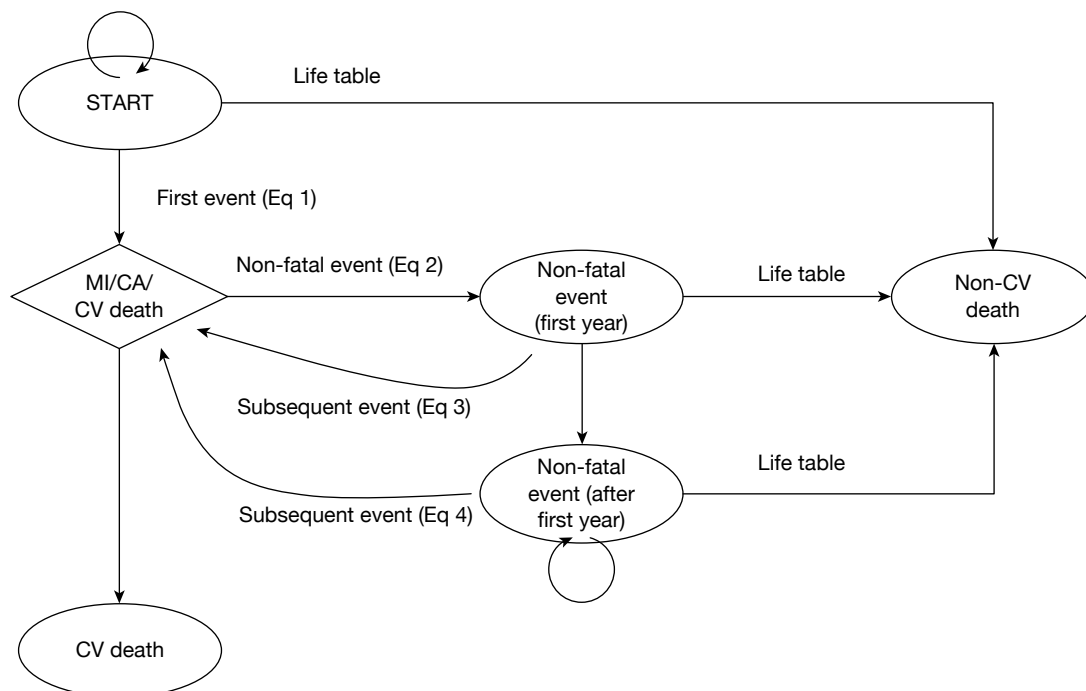
FIGURE 20 EUROPA Markov model. Based on Briggs *et al.*[69] CA, cardiac arrest; Eq, equation.

TABLE 19 EUROPA model entry and healthy population model entry: suspected CAD population

Strategy	Without angiographic and revascularisation mortality				With angiographic and revascularisation mortality							
	TP	FP	TN	FN	TP	FP	TN	FN	Mortality ICA	Morbidity ICA	Mortality revascularisation	Morbidity revascularisation
Obese												
ICA only	0.2000	–	0.8000	–	0.1996	–	0.7994	–	0.0007	0.0006	0.0003	0.000
NGCCT–ICA	0.1808	–	0.8000	0.0192	0.1804	–	0.8000	0.0192	0.0002	0.0002	0.0002	0.000
NGCCT only	0.1808	0.0632	0.7368	0.0192	0.1806	0.0631	0.7368	0.0192	–	–	0.0003	0.001
Arrhythmias												
ICA only	0.2000	–	0.8000	–	0.1996	–	0.7994	–	0.0007	0.0006	0.0003	0.000
NGCCT–ICA	0.1954	–	0.8000	0.0046	0.1950	–	0.7999	0.0046	0.0002	0.0002	0.0003	0.000
NGCCT only	0.1954	0.1464	0.6536	0.0046	0.1951	0.1462	0.6536	0.0046	–	–	0.0005	0.001
High coronary calcium score												
ICA only	0.2000	–	0.8000	–	0.1996	–	0.7994	–	0.0007	0.0006	0.0003	0.000
NGCCT–ICA	0.1854	–	0.8000	0.0146	0.1851	–	0.7999	0.0145	0.0002	0.0002	0.0003	0.000
NGCCT only	0.1854	0.0752	0.7248	0.0146	0.1852	0.0747	0.7252	0.0145	–	–	0.0004	0.001
HHR												
ICA only	0.2000	–	0.8000	–	0.1996	–	0.7994	–	0.0007	0.0006	0.0003	0.000
NGCCT–ICA	0.1954	–	0.8000	0.0046	0.1950	–	0.7999	0.0046	0.0002	0.0002	0.0003	0.000
NGCCT only	0.1954	0.1096	0.6904	0.0046	0.1951	0.1095	0.6904	0.0046	–	–	0.0004	0.001
Intolerance beta-blocker												
ICA only	0.2000	–	0.8000	–	0.1996	–	0.7994	–	0.0007	0.0006	0.0003	0.000
NGCCT–ICA	0.1954	–	0.8000	0.0046	0.1950	–	0.7999	0.0046	0.0002	0.0002	0.0003	0.000
NGCCT only	0.1954	0.1096	0.6904	0.0046	0.1951	0.1095	0.6904	0.0046	–	–	0.0004	0.001

probabilities between the different states were based on risk equations and on UK life tables on non-CV death. The risk equations consisted of several covariates based on baseline characteristics and previous conditions, such as age, gender, previous MI, diabetes mellitus, etc. The prognosis of the patients was partly dependent on the initial test outcome and treatment decision.

All patients with CAD (with the exception of those who experience non-fatal complications from ICA, PCI or CABG) enter the EUROPA model in the 'Start' state. A patient can either stay in this state, die from a non-CV cause (and move to the 'Non-CV death' state), or experience a CV event and move to the 'CV death' state if the event is fatal or to the state 'non-fatal event (first year)' if the event is not fatal. The 'non-CV death' and the 'CV death' states are both mutually absorbing states. Patients can end up in the 'non-fatal event (first year)' state in two different ways: by experiencing a non-fatal MI from the initial ICA or revascularisation or by experiencing a non-fatal event at a later time (modelled in the EUROPA model by the risk equations). When a patient is in the 'non-fatal event (first year)' state he or she can remain in this state for maximum of 1 year without experiencing a subsequent event. After that, a patient can move to the 'non-fatal event (after first year)' state if he or she has stayed in the 'non-fatal event (first year)' state for a year without experiencing a new event. Patients in the 'non-fatal event (first year)' can also move to the 'Non-CV death' state if the patient dies from a non-CV cause; the 'CV death state' if the patient experiences a subsequent event which is fatal ('CV death' state) or stay in the 'non-fatal event (first year)' state if the subsequent event is not fatal. A patient in the 'non-fatal event (after first year)' state can stay there, move to the 'non-fatal event (first year)' state if the patient experiences a non-fatal subsequent event, move to the 'CV death' state if the patient experiences a fatal subsequent event, or move to the 'non-CV death' state if the patient dies from a non-CV cause. The risks of events and the mortality associated with events are predicted by the risk equations. Non-CV mortality was based on UK life tables.

EUROPA model entry for population with suspected coronary artery disease

The proportions of patients classified as TP and FN entering the EUROPA model were based on the calculations using prevalence of the disease, sensitivity and specificity of the tests as defined in the diagnostic model. These proportions can vary between the three strategies. *Table 19* shows intermediate results of the diagnostic model in two ways. The first part shows how the four test outcomes are represented for each strategy, each difficult-to-image patient group. The second part shows the impact of immediate procedure-related mortality and morbidity on the distribution of the test outcomes. As expected the mortality rates differ considerably between the three strategies. Patients suspected of CAD diagnosed with the ICA alone have the highest overall mortality and morbidity rate. The TN proportion is the lowest in the difficult-to-image arrhythmias group due to the low specificity. The disease progression of the TP and the FN (patients with the disease) was modelled with the EUROPA model. These two outcomes were divided into three treatment possibilities: medication, PCI or CABG. The other two test outcomes (FP and TN) were modelled through a simple alive–dead Markov model (healthy population model) based on life tables, as described above (see *Healthy population Markov model*).

EUROPA model entry for population with known coronary artery disease

Table 20 presents the intermediate outcomes of the three strategies for the known CAD population. The first part shows how the test outcomes are distributed in each strategy for each difficult-to-image patient group. The second part incorporates also the mortality and morbidity associated with the ICA and revascularisations. The NGCCT–ICA strategy results in the lowest mortality and morbidity rates. The prognosis of patients in all four outcomes (TP, TN, FP and FN) was modelled using the EUROPA model because all patients have CAD.

TABLE 20 EUROPA entry for patients with known coronary artery disease

Strategy	Without angiographic and revascularisation mortality					With angiographic and revascularisation mortality					Mortality ICA	Morbidity ICA	Mortality revascularisation	Morbidity revascularisation
	TP	FP	TN	FN		TP	FP	TN	FN					
Obese														
ICA only	0.3947	–	0.6053	–		0.3915	–	0.6048	–		0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	0.3568	–	0.6053	0.0379		0.3541	–	0.6052	0.0379		0.0001	0.0003	0.0027	0.0046
NGCCT only	0.3568	0.0478	0.5574	0.0379		0.3542	0.0475	0.5574	0.0379		–	–	0.0030	0.0052
Arrhythmias														
ICA only	0.3947	–	0.6053	–		0.3915	–	0.6048	–		0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	0.3857	–	0.6053	0.0091		0.3827	–	0.6052	0.0091		0.0002	0.0003	0.0029	0.0050
NGCCT only	0.3857	0.1108	0.4945	0.0091		0.3828	0.1099	0.4945	0.0091		–	–	0.0037	0.0064
High coronary calcium score														
ICA only	0.3947	–	0.6053	–		0.3915	–	0.6048	–		0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	0.3659	–	0.6053	0.0288		0.3633	–	0.6052	0.0286		0.0001	0.0003	0.0027	0.0047
NGCCT only	0.3659	0.0569	0.5484	0.0288		0.3634	0.0562	0.5486	0.0286		–	–	0.0032	0.0054
HHR														
ICA only	0.3947	–	0.6053	–		0.3915	–	0.6048	–		0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	0.3857	–	0.6053	0.0091		0.3827	–	0.6052	0.0091		0.0001	0.0003	0.0029	0.0050
NGCCT only	0.3857	0.0829	0.5223	0.0091		0.3828	0.0823	0.5223	0.0091		–	–	0.0035	0.0060
Intolerance beta-blocker														
ICA only	0.3947	–	0.6053	–		0.3915	–	0.6048	–		0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	0.3857	–	0.6053	0.0091		0.3827	–	0.6052	0.0091		0.0001	0.0003	0.0029	0.0050
NGCCT only	0.3857	0.0829	0.5223	0.0091		0.3828	0.0823	0.5223	0.0091		–	–	0.0035	0.0060
Previous stent														
ICA only	0.3947	–	0.6053	–		0.3915	–	0.6048	–		0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	0.3789	–	0.6053	0.0158		0.3760	–	0.6052	0.0158		0.0002	0.0003	0.0028	0.0049
NGCCT only	0.3789	0.1114	0.4939	0.0158		0.3761	0.1105	0.4939	0.0158		–	–	0.0037	0.0063
Previous CABG														
ICA only	0.3947	–	0.6053	–		0.3915	–	0.6048	–		0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	0.3805	–	0.6053	0.0142		0.3776	–	0.6052	0.0142		0.0001	0.0003	0.0028	0.0049
NGCCT only	0.3805	0.0787	0.5266	0.0142		0.3777	0.0781	0.5266	0.0142		–	–	0.0034	0.0059

Every cycle a certain proportion of the FN patients in both populations will be identified as TP based on the Canadian Cardiovascular Society (CCS) angina classification. Identified TPs will be treated and they will have the same prognosis as the TPs who were identified directly by the diagnostic test. The FNs that are still not identified have a higher chance of experiencing an event.

EUROPA model risk equation adjustments

Risk equations to predict the events for patients with CAD were based on the EUROPA trial.[68] Using the EUROPA model for the evaluation of the NGCCT in the two CAD populations (suspected and known), and for the different difficult-to-image patient groups, required some adjustment of the EUROPA model. These adjustments were necessary as the baseline characteristics of the EUROPA population were not completely comparable with the subgroups in the known and suspected CAD populations.

As shown in *Figure 20,* four equations were used to calculate transition probabilities between the states. The first equation based on time-to-event survival analysis estimated the probability of any event that will occur in one cycle of 3 months as a function of the following covariates: age, years older than 65, perindopril usage, smoking, previous MI, existing vascular disease [stroke, transient ischaemic attack (TIA) or peripheral vascular disease], family history of CAD, symptomatic angina or history of heart failure, systolic blood pressure, total cholesterol, obese (BMI of $> 30 \, \text{kg/m}^2$), gender, nitrates usage, calcium channel blockers usage, lipid-lowering treatment, units creatinine clearance below 80 ml/minute and previous revascularisation (PCI or CABG) (*Table 21*). The second equation of the EUROPA model estimates the odds that the event is fatal, based on age, previous MI and total cholesterol. The third equation estimates the risk of a subsequent event in the first year after a first NFE and is based on the presence of symptomatic angina or history of heart failure. The fourth equation, which predicts the risk of a subsequent event after 1 year, is the same as the first equation except that the covariate previous MI is updated by setting the covariate previous MI at '1'.

The risk equations consist of covariates based on the EUROPA trial and therefore baseline characteristics had to be established for the 12 subgroups (seven difficult-to-image patient groups in the known CAD population and five in the suspected CAD population). Means were used in the risk equation, as we used a cohort model. The accuracy of the NGCCT was based on the systematic review reported in *Chapter 3*, and this review was also used as a source to estimate the baseline characteristics of the different subgroups for use in the risk equations; details of the baseline characteristics of study populations included in the review are reported in *Appendix 4*. Only subgroup-specific publications were used, thus studies which determined the accuracy of the NGCCT in two or more difficult-to-image patient groups were not used. The baseline characteristics of the EUROPA population were used when information for a specific subgroup and baseline characteristic was not found; this approach assumes that there were no differences between the EUROPA population and the specific subgroup (see *Table 21*).

Population with suspected coronary artery disease

Baseline characteristics, such as age, gender, family history, diabetes mellitus, obesity, smoking and symptomatic angina, were collected from the articles included in the review that focused on the suspected CAD population. The richness of the information collected from the articles differed between the difficult-to-image patient groups. In all difficult-to-image patient groups except for the 'intolerant to beta-blockers' group, a minimum of gender and age data were found. When population specific information regarding risk-related characteristics was not found in the literature, the assumption was made that the difficult-to-image subgroup did not differ from the EUROPA population and therefore the value of the EUROPA population (see *Table 21*) was taken. 'Perindopril usage' was assumed to be 0.23 for the whole suspected CAD population.[71] We will assume that the effect of perindopril does apply for any ACE inhibitor. The covariates

TABLE 21 Original EUROPA risk equations and mean values: EUROPA population

Covariates	Mean values EUROPA population: mean (SD) or % (95% CI)	*Equation 1*: Risk of first primary event		*Equation 2*: Odds that first event is fatal		*Equation 3*: Risk of subsequent event in first year after initial NFE	
		Coefficient	HR	Coefficient	OR	Coefficient	HR
Perindopril usage	100%	−0.2148	0.8067				
Age (years)	60 (9)			0.0396	1.0403		
Age > 65 years	0	0.0592	1.0610			0.6139	1.8476
Gender	85.4% (84.8% to 86.0%)	0.4349	1.5448				
Smoking	15.2% (14.6% to 15.8%)	0.3959	1.4858				
Previous MI	64.8% (64.0% to 65.6%)	0.3675	1.4441	0.4673	1.5956		
Previous revascularisation	54.9% (54.0% to 55.8%)	−0.1332	0.8753				
Existing vascular disease	9.8% (9.3% to 10.3%)	0.5233	1.6876				
Diabetes mellitus	12.3% (11.7% to 12.9%)	0.4005	1.4926				
Family history	27.2% (26.4% to 28.0%)	0.1873	1.2060				
Symptomatic angina	24.5% (24.2% to 25.8%)	0.2801	1.3232				
Systolic blood pressure	137 (15)	0.0045	1.0045				
Creatinine clearance < 80 ml/minute	6.9 (10.3)	0.0114	1.0115				
Obesity	21.1% (20.3% to 21.7%)	0.3455	1.4127				
Total cholesterol	5.4 (1.0)	0.1248	1.1329	0.1870	1.2056		
Use of nitrates at baseline	44.4% (43.1% to 44.9%)	0.3537	1.4243				
Use calcium channel blockers at baseline	32.4% (31.6% to 33.2%)	0.1815	1.1990				
Use lipid-lowering treatment at baseline	55.9% (55.0% to 56.8%)	−0.1566	0.8551				
Constant (log scale)	1		−12.2737		−4.3725		−6.459
Ancillary parameter							0.7

HR, hazard ratio; OR, odds ratio; SD, standard deviation.

'age', 'age > 65 years', 'men (y/n)', 'smoking (y/n)', 'diabetes mellitus (y/n)', 'positive family history (y/n)', 'obese (y/n)', 'symptomatic angina (y/n)' differed per difficult-to-image subgroup. No subgroup-specific information was collected for the covariates 'systolic blood pressure', 'creatinine clearance', 'total cholesterol' and 'the usage of lipid-lowering treatment at baseline'. The five other covariates depended on the strategy, treatment and test outcomes. *Tables 22* and *23* illustrate how proportions were assigned to the covariates. The proportion that has had an MI was based on the non-fatal complications of ICA and revascularisation. FNs in strategies 2 and 3 have not experienced an MI, revascularisation or vascular disease because they do not undergo an ICA or a revascularisation. The covariate previous revascularisation was set at 1 for the TPs treated with a revascularisation. Nitrates usage was assumed to be '0' for all test outcomes. Usage of calcium channel blockers was assumed to be '1' for TPs who received medical treatment. This is because, although they might actually be prescribed a beta-blocker instead,[71] there was only a covariate in the risk equation for calcium channel blocker and not beta-blocker. This assumption can be justified because the efficacy of calcium channel blockers does not differ from that of beta-blockers.[71]

Population with known coronary artery disease

The procedure described above to establish the baseline characteristics for the suspected CAD population was also used for the known CAD population. No information about gender and age was available for the beta-blocker intolerance and high coronary calcium score groups. For the

TABLE 22 Input for the EUROPA risk equations: suspected CAD population

Explanatory baseline characteristics	Strategy 1: ICA only		Strategy 2: HDCT–ICA			Strategy 3: HDCT only		
	TP revascularisation	TP medication	TP revascularisation	TP medication	FN	TP revascularisation	TP medication	FN
Age, gender, positive family history, smoking, diabetes mellitus, obesity and symptomatic angina	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population
Systolic blood pressure, creatinine clearance, total cholesterol, lipid-lowering treatment usage at baseline	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population
ACE inhibitor usage[a]	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23
Previous MI	MI due to ICA and revascularisation	MI due to ICA	MI due to ICA and revascularisation	MI due to ICA	0	MI due to revascularisation	0	0
Previous revascularisation	1	0	1	0	0	1	0	0
Existing vascular disease[b]	Stroke due to ICA and revascularisation	Stroke due to ICA	Stroke due to ICA and revascularisation	Stroke due to ICA	0	0	0	0
Use of nitrates at baseline	0	0	0	0	0	0	0	0
Use calcium channel blockers at baseline	Proportion EUROPA population	1	Proportion EUROPA population	1	Proportion EUROPA population	Proportion EUROPA population	1	Proportion EUROPA population

a Daly et al.[71]
b Stroke, TIA and peripheral vascular disease.

TABLE 23 Subgroup-specific input for the EUROPA risk equations: suspected CAD population

Explanatory baseline characteristics	Obese	Arrhythmias	Beta-blockers	High coronary calcium	HHR
Age (years)	63	66.11	N/A	63.93	61.91
Gender	0.659	0.69	N/A	0.75	0.68
Positive family history	N/A	0.17	N/A	N/A	0.16
Smoking	0.28	0.08	N/A	N/A	0.37
Diabetes mellitus	0.341	0.27	N/A	N/A	0.19
Obesity	1	0.42	N/A	0.37	0.18
Symptomatic angina	N/A	N/A	N/A	N/A	0.85

N/A: not available – EUROPA proportions are used: *Table 21.*

other groups these data were collected from the accuracy studies included in the systemic review. The covariates 'age', 'age > 65 years', 'men (y/n)', 'smoking (y/n)', 'diabetes mellitus (y/n)', 'positive family history (y/n)' and 'obese (y/n)' differed per difficult-to-image patient group. No subgroup-specific information was available for the covariates 'symptomatic angina', 'systolic blood pressure', 'creatinine clearance', 'total cholesterol' and 'the usage of lipid-lowering treatment at baseline'. Perindopril intake proportion was set at 0.23, based on published data.[70] The proportion of patients experiencing an MI or the proportion where vascular disease is present was based on the EUROPA population. The proportions were not raised with ICA or revascularisation-induced MI. Nitrates usage and calcium channel blockers at baseline were not reported in the studies included in the systematic review and therefore these proportions were based on the EUROPA population (see *Table 21*). The proportion for previous revascularisation was set at '1' for the TPs in all strategies, for the FPs in strategy 3, and for the subgroups' previous PCI and previous CABG this was set at '1' for all test outcomes. The remaining proportions were set as for the EUROPA population (*Tables 25* and *26*).

Difficult-to-image patient group-specific data
In addition to CAD population-specific adjustments of the EUROPA risk equations, adjustments were necessary for each specific difficult-to-image patient group. It is likely that some of the reasons why patients are difficult to scan may also lead to a higher probability of a CV event.

In the obese patient group, the increased risk of events was already captured in the risk equation, as it contains a covariate for obesity. For the obese group, the covariate obesity was set at '1' for all test outcomes, strategies and CAD populations.

For simplicity, we treated the difficult-to-image subgroup with a previous CABG the same as the difficult-to-image subgroup with a previous PCI.[72] The covariate 'previous revascularisation' is present in the first and fourth risk equations of the EUROPA model; thus, the risk of having a primary or subsequent event for these specific patient groups was captured.

For the difficult-to-image groups arrhythmias and high coronary calcium level, a relative risk (*Table 24*), compared with the EUROPA population, was used to adjust the risk of events. For the HCS patient group, data from an unpublished study[73] were used to estimate the relative risk without correcting for other factors of experiencing primary events in patients with a coronary calcium score > 400 compared with patients without a coronary calcium score of > 400. The proportion with a coronary calcium score of > 400 in the EUROPA population was not reported and therefore the study of Shemesh *et al.*[74] was used to estimate a proportion assuming that the populations are comparable. We assumed that this relative risk also applies for the risk of having a subsequent event.

TABLE 24 Relative risks of CV events compared with EUROPA population for arrhythmias and high coronary calcium level subgroups for the known and suspected CAD population

Subgroup	RR female	RR male	Source	Proportion condition stable angina (%)	Source	Adjusted RR female	Adjusted RR male
Arrhythmias	3.06	2.04	Hippisley-Cox *et al.*[75]	19	Banasiak (2007)[76]	2.2	1.7
HCS	4.58	4.58	Joosen *et al.*[73]	49	Shemesh (1998)[74]	1.66	1.66

TABLE 25 Subgroup-specific input for the EUROPA risk equations: known CAD population

Explanatory baseline characteristics	Obese	Arrhythmias	Beta-blockers	High coronary calcium	HHR	Revascularisation
Age (years)	63	68	N/A	N/A	56.2	65.12
Gender	0.659	0.71	N/A	N/A	0.52	0.69
Positive family history	N/A	0.7	N/A	N/A	N/A	0.39
Smoking	0.28	N/A	N/A	N/A	N/A	0.2858
Diabetes mellitus	0.341	0.2	N/A	N/A	N/A	0.3
Obesity	1	0.59	N/A	N/A	N/A	0.264
Symptomatic angina	N/A	N/A	N/A	N/A	N/A	N/A

N/A, not available – EUROPA proportions are used: see *Table 21*.

A relative risk, compared with the EUROPA population, was also used to estimate the risk of experiencing events for the patient group with arrhythmias. The term 'arrhythmias' encompasses several different conditions, with AF being the most common. A relative risk was calculated, controlling for other factors for patients with arrhythmias, based on the relative risk found in the QRISK study, which investigated the relative risk of experiencing events for patients with AF against patients without AF.[75] The proportion of the patients with AF was not reported by the EUROPA study and therefore we assumed that the proportion AF in patients with CAD is 19% based on Banasiak *et al.*[76]

No adjustments to the risk equations were necessary for the intolerant to beta-blockers patient group because it was assumed that intolerance of beta-blockers does not lead to an increased risk of experiencing events; patients undergoing a cardiac CT receive beta-blockers to lower their heart rate in order to produce images of adequate quality, not in order to prevent events. Patients with CAD will often be treated with beta-blockers but these can be replaced with calcium channel blockers and/or ACE inhibitors and therefore intolerance to beta-blockers will probably not affect prognosis.

For the patient group with HHR the risk equations were not adjusted because it was assumed that HHRs affect only the quality of CT imaging. The patient groups with HHR and intolerance to beta-blockers were modelled with the original risk equations based on the EUROPA population.

York Radiation Model
The impact of imaging-associated radiation on cancer rates and outcomes was not estimated with the EUROPA model but was with the YRM.[61] The EUROPA model takes into account only mortality and not the QALYs and costs of treatment of radiation-induced cancer. The YRM is a radiation impact model recently developed by the Technology Assessment Group of the University of York to assess the health impact of a reduction in radiation when using a new X-ray imaging system for diagnostic purposes.[61]

TABLE 26 Input for the EUROPA risk equations: known CAD population

Explanatory baseline characteristics	Strategy 1: ICA only		Strategy 2: HDCT–ICA			Strategy 3: HDCT only			
	TP revascularisation	TN	TP revascularisation	TN	FN	TP revascularisation	TN	FN	FP revascularisation
Age, gender, positive family history, smoking, diabetes mellitus, obesity and symptomatic angina	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population	Subgroup specific, if not available EUROPA population
Systolic blood pressure, creatinine clearance, total cholesterol, lipid-lowering treatment usage at baseline	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population
ACE inhibitor usage[a]	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23
Previous MI	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population
Previous revascularisation	1	Proportion EUROPA population (if subgroup is previous PCI/CABG than 1)	1	Proportion EUROPA population (if subgroup is previous PCI/CABG than 1)	Proportion EUROPA population (if subgroup is previous PCI/CABG than 1)	1	Proportion EUROPA population (if subgroup is previous PCI/CABG than 1)	Proportion EUROPA population (if subgroup is previous PCI/CABG than 1)	1
Existing vascular disease[b]	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population
Use of nitrates at baseline	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population
Use calcium channel blockers at baseline	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population	Proportion EUROPA population

a　Daly et al.[71]
b　Stroke, TIA and peripheral vascular disease.

Biological effects of radiation

The dose of ionised radiation absorbed by a body is measured in grays (Gy). However, the health-relevant (and harmful) energy absorbed depends on the tissue and type of radiation and is expressed in sieverts (Sv). Because of the small doses of imaging radiation, more often millisieverts (mSv) are used (1000 mSv = 1 Sv). Also, 1 Sv = 1 Gy × a weighting factor (e.g. for a breast scan the weighting factor is 0.05).

Exposure to ionised radiation has mainly three biological adverse effects.[77] First, radiation has a harmful effect on developing embryos when the expecting mother is exposed to radiation. This is not relevant in our application. Second, radiation exposure might affect reproductive health, i.e. radiation exposure may lead to adverse congenital health outcomes of later offspring. There is, however, no convincing evidence for this effect in humans, only in animal experiments. The third, most harmful, effect is an increased lifetime risk of cancer incidence. For low doses, sparse clinical evidence exists. A prominent source is a cohort study of Japanese atomic bomb survivors who were exposed to radiation. These data provide strong evidence of an increased cancer mortality risk at equivalent doses of > 100 mSv, good evidence of an increased risk for doses between 50 and 100 mSv, and reasonable evidence for an increased risk for doses between 10 and 50 mSv.[78]

The standard epidemiological risk models use a linear relationship between radiation exposure and lifetime probability of solid cancer without assuming a threshold, i.e. even a minimal exposure is assumed to increase the lifetime risk of cancer incidence. The younger the age at exposure, the higher is the lifetime probability of cancer incidence for a given amount of radiation, partly because children have on average more life-years remaining to develop cancer. The cumulative lifetime risk of an individual for repeated exposure to radiation is calculated by summing the probabilities for lifetime cancer incidence over each exposure.

In a recent report, the Centre for Radiation, Chemical and Environmental Hazards (CRCE), formerly the National Radiological Protection Board (NRPB), of the Health Protection Agency (HPA), has calculated lifetime risks for cancer incidence by age and sex for different levels of radiation.[79] Those calculations are based on a 2007 publication of the International Commission on Radiological Protection (ICRP).[80]

Structure of York Radiation Model

The calculations for health consequences of radiation exposure are based on an adjusted version of the YRM (*Figure 21*). The YRM consists mainly of four elements: a radiation module, a cancer module, a utility module and a main module combining all intermediate calculations.

In the radiation module, the YRM estimates the lifetime probability of an individual, given the timing and the amount of radiation exposure. To translate the cumulative radiation dose into the probability of lifetime cancer incidence the HPA model is used (see *Table 47*).[80]

The cancer module is based on prior research.[61] In the absence of cancer models for all types of cancer, four common cancers are modelled: lung and colorectal cancer for both sexes, breast cancer only for females, and prostate cancer only for males. For each cancer, the module contains the further expected QALYs and disease costs for patients with cancer at the average age at diagnosis (see *Table 46*). For each sex, these values are then combined and weighted according the relative incidence of radiation-induced cancer. For males, the weights are approximately 46% colorectal, 42% lung and 12% prostate, whereas for females the weights are 16% colorectal, 50% lung and 34% breast.
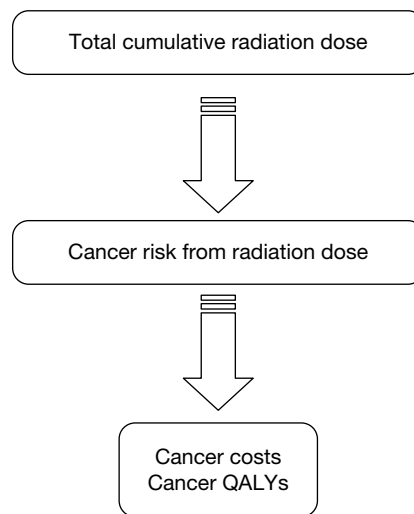
FIGURE 21 Stylised overview of YRM.

The utility module is based on data for the general UK population (see *Table 49*).[61] For patients who do not get cancer, the remaining lifetime QALYs from the age at first radiation exposure are calculated. For patients who do get cancer, the utility module calculates the QALYs until the age at diagnosis of cancer, i.e. the timespan without cancer.

The main module combines the outcome of the three prior modules. So for a given age at first exposure, the share of patients who get radiation-induced cancer during their lifetime is calculated. For those patients, their QALYs until age at cancer diagnosis equal the general UK population and after that the remaining QALYs and the (additional) disease costs owing to cancer are taken from the cancer module. For the rest of the patients, just the remaining QALYs based on the general UK population are calculated. These values are combined and weighted by the sex ratio of the patient population. Both QALYs and disease costs are discounted to the age at first exposure to radiation. The intervention, i.e. the reduction in radiation exposure through the comparator technology, is modelled via the reduction in the probability of lifetime radiation-induced cancer. The YRM allows to conduct a probabilistic sensitivity analysis (PSA) accounting for the uncertainties in age at cancer incidence, cancer costs and QALYs lost due to cancer.

Radiation dose and patient populations

Computer tomography is a relatively high-dose X-ray imaging technique. The effective dose, i.e. absorbed radiation dose by a patient measured in sieverts, depends on a number of factors such as age of patient, the region of the body scanned, tissue type involved, precise type of CT, and scanning protocol for the particular diagnosis in question. Furthermore, CTs are an evolving technology in which the radiation doses vary with CT generation and by manufacturer. Moreover, scanning protocols themselves change over time. In particular, multislice CTs allow for increasingly rapid scans and lower radiation doses. Although 64-slice scanners have increasingly become the standard, earlier-generation CTs are still in use.

The broad range of CT types and CT applications compels studies which aim to quantify the radiation burden attributable to CTs in the general population to measure the radiation dose by scan for a particular body region/diagnosis type, for example head or full chest, roughly differentiating only by CT type (mostly single slice vs multislice). To account for the particular diagnostic needs of the disease assessed, we conducted expert surveys to obtain the relevant dosages by scanning strategy. The results are shown in *Table 52* (for patients with CAD) and *Table 66* (for patients with congenital heart disease).

The results of our expert surveys are in line with the literature that focuses on general chest CTs (*Table 27*). A study by the NRPB for the UK, conducted in 2003, shows slightly higher results than our expert survey, as its results were mostly based on single-slice and four-slice technology,[81] which usually have higher radiation doses than 64-slice technology. More recent studies, such as the UNSCEAR 2008 report, assessing the trends in worldwide radiation exposure,[82] and a review article focusing on children's exposure and based on German data,[83] support the overall lower radiation dose for CT64 indicated by our expert survey. Note that in *Table 27* values are also presented for younger age groups, as those values are required for the analysis presented below (see *Cost-effectiveness of new-generation cardiac computed tomography in congenital heart disease*).

The YRM was used for the two patient populations under assessment, the patients with CAD (this section) and the congenital heart disease patients (see *Cost-effectiveness of new-generation cardiac computed tomography in congenital heart disease*). The adjusted version of the YRM does not model benefits of the different CT strategies, but only the harmful consequences of radiation exposure. Hence, it can be used for both patient populations without further modifications; only the key parameter age at exposure, radiation dose (dependent on type and number of scans) and sex are used. In the case of the patients with CAD, the YRM output was used for further analysis. For an overview of the radiation doses in the patient populations for the different strategies under assessment see *Tables 52* and *69*.

Overview of the models used

Table 28 provides an overview of which models were used for each difficult-to-image patient group within each CAD population (suspected or known). The diagnostic model was used for each subgroup and modelled separately for 100% of the patients. To estimate the extra costs and QALY loss due to radiation, the YRM was used for each subgroup for the entire population. The healthy population model was used only for the suspected CAD population to model the patients who do not have CAD (TN and FP). The known and suspected CAD populations with CAD were modelled separately using two versions of the EUROPA model. The suspected CAD population had three treatment options (PCI, CABG and medication), whereas the known CAD population could undergo only a CABG or a PCI. The difficult-to-image patient groups 'previous CABG' and 'previous stent implantation' were treated as one subgroup in the EUROPA model because Deckers *et al.*[72] and Briggs *et al.*[69] use only one coefficient in the risk equation, namely previous revascularisation.[69,72] Cost and QALYs for patients who have experienced a stroke due to the initial ICA or initial revascularisation are based on a previously conducted study by Sandercock *et al.*[66] Subgroup-specific costs and QALYs obtained in the stroke model were calculated by using the subgroups 'specific age' and 'proportion men'.

Model parameters

This section describes the parameters used in the diagnostic model, the EUROPA model, the healthy population model, the YRM and the stroke model. Distributions of the parameters are presented in *Table 61* and described below (see *Results*, *Sensitivity analyses*). The last section

TABLE 27 Comparative radiation dose by age at exposure from diagnostic examination of 'chest' with a CT (in millisieverts)

Source	Age			
	1 year	5 years	10 years	Adult
UNSCEAR report[82] (lowest and highest reported values)	1.8–6.3	2.1–3.6	3.0–3.9	3.5–12.9
NRPB report[81] [mean (25th/75th percentile)]	6.3 [2.9–7.9]	3.6 [2.1–4.1]	3.9 [2.3–4.8]	5.8 [3.9–6.9]
Linet (2009)[83]	2.2	2.5	3.0	5.9

TABLE 28 Overview model runs for subpopulations

| | | | | EUROPA model | | |
| | | | | Two-treatment | Three-treatment | |
Subgroups	Diagnostic model	YRM	Healthy population model	model	model	Stroke
Suspected CAD population						
Obese	✗	✗	✗		✗	✗
Arrhythmias	✗	✗	✗		✗	✗
High coronary calcium level	✗	✗	✗		✗	✗
HHR	✗	✗	✗		✗	✗
Beta-blocker intolerant	✗	✗	✗		✗	✗
Known CAD population						
Obese	✗	✗		✗		✗
Arrhythmias	✗	✗		✗		✗
High coronary calcium level	✗	✗		✗		✗
HHR	✗	✗		✗		✗
Beta-blocker intolerant	✗	✗		✗		✗
Previous stent implantation	✗	✗		✗		✗
Previous CABG	✗	✗		✗		✗

describes how the difficult-to-image patient groups were combined to get overall incremental cost-effectiveness ratio (ICER) estimates for each CAD population (suspected and known).

Diagnostic model

The diagnostic model estimates the initial costs of diagnosis and initial treatment. Mortality and morbidity associated with the treatments and the diagnostic tests were also modelled and have an impact on the effectiveness of the three strategies. The events occur at one moment in time; the diagnostic model is time independent.

Costs

The costs included in the diagnostic model were the costs for the diagnostic tests and the costs of the two revascularisation procedures (*Table 31*). Medication-induced costs were modelled as part of the background costs in the disease progression model. The average cost prices for the revascularisation procedures and the ICA were calculated based on the NHS reference prices 2010–11.[84] An average cost price is calculated by multiplying the number of admissions with the costs for each different specific procedure. An ICA was estimated as costing on average £1003. A CABG would cost £8280 per procedure, and £9242 in combination with a ICA. A PCI in combination with an ICA would cost £4196, and a PCI without an ICA would cost £3633 per procedure.

Given that the cost of ICA (invasive CA) was estimated using the NICE reference cost, for comparability a reference cost would have been useful for each of the different types of scan – both standard 64-slice and the NGCT. However, the only data available were for any CT, i.e. not specifically for CTCA (*Table 29*).

Therefore, a bottom-up costing was performed, which attempted to use the categories that the reference cost would be composed of, which are shown below (*Table 30*).

The final costs of 64-slice and NGCCT are calculated to be £132.62 and £169.26, respectively. The estimated costs of 64-slice CT are higher than the reference costs. However, this is plausible

TABLE 29 Costs for any CT

Currency code	Currency description	Activity	National average unit cost (£)	Lower quartile unit cost (£)	Upper quartile unit cost (£)	No. of data submissions
RA08Z	CT scan, one area, no contrast	535,388	101	69	108	159
RA09Z	CT scan, one area with post contrast only	200,500	116	88	126	144
RA10Z	CT scan, one area, pre- and post contrast	48,604	112	73	128	102

TABLE 30 Estimated costs for any cardiac CT

Category	64-slice	NGCCT	Source
Capital, £	500,000	1,000,000	The ImPACT Group, 2009[85]
Maintenance per year, £	73,624	137,941	Expert opinion
Scanner life, years	10	10	National Audit Office, 2011[86]
Capital per year plus maintenance per year, £	123,624	237,941	Calculated
No. of scans per year	3120	3120	Calculated[a]
Scanner cost (capital plus maintenance) per scan, £	59.43	114.39	Calculated
Radiographer time, hours	0.5	0.5	Expert opinion
Radiologist time, hours	0.5	0.5	Expert opinion
Radiographer cost per hour (includes overheads), £	40	40	PSSRU, 2010[87]
Radiologist cost per hour (includes overheads), £	146	146	PSSRU, 2010[87]
Radiographer cost per scan, £	20	20	Calculated
Radiologist cost per scan, £	73	73	Calculated
Total staff cost per scan, £	93	93	Calculated
Total cost (scanner plus staff) per scan, £	132.62	169.26	Calculated

PSSRU, Personal Social Services Research Unit.

a   Assuming a maximum of 12 scans per day (expert opinion: Simon Padley, Chelsea and Westminster Hospital and Royal Brompton Hospital, 9 July 2011, personal communication; see *Appendix 7*), 5 days per week and 52 weeks per year.

TABLE 31 Costs of diagnostic tests and treatment

Diagnostic test	HDCT model	
	Cost per diagnostic test (£)	Source
Coronary angiography	1003	NHS reference costs
NGCCT	169	Calculated (see *Table 30*)
CABG	8280	NHS reference costs
PCI	3633	NHS reference costs
CABG + ICA	9242	NHS reference costs
PCI + ICA	4196	NHS reference costs

given that much of the capital cost of existing scanners is probably not included in the reference costs. This is because many scanners are actually purchased using non-NHS money, i.e. by private donations (Valerie Fone, Trust Imaging Services Manager, Royal Brompton and Harefield NHS Foundation Trust, personal communication; see *Appendix 7*). Also, the staff costs for CTCA are higher given the considerable use of consultant as opposed to more junior or no radiologist time. Scenario analyses will be performed for 4160 scans per year (cost price NGCCT: £150) and 2080 scans per year (cost price NGCCT: £207).

Prior likelihood

The prior likelihood for the suspected and known CAD populations is presented above (see *Model structure and methodology*, *Diagnostic model*).

Initial treatment decision

Diagnostic tests, using the NGCCT, are performed to determine if treatment is necessary for a difficult-to-image patient. The cost-effectiveness of the NGCCT was estimated for two CAD populations which are treated differently. For the assumptions concerning the treatment options for the suspected CAD population expert opinion was used.

Suspected coronary artery disease population

Patients with suspected CAD and a positive cardiac CT or ICA test result can be treated with drug therapy alone, a CABG or a PCI. The proportions undergoing either revascularisation (18.1%) or medication (81.9%) after a positive test result were based on expert opinion (Hofstra, 2011, personal communication; which was based on an unpublished study conducted in the Netherlands[73]). The proportion of PCI compared with CABG in patients requiring revascularisation was based on UK procedure figures, which showed a 70% : 30% proportion for PCI compared with CABG.[88]

Patients treated with medication only are treated with beta-blockers or calcium channel blockers.[12] When the symptoms are not controlled with one of the two drugs, then a combination can be given or a nitrate can be prescribed. A revascularisation is then considered if symptoms of patients are still uncontrolled by drug treatment alone. The proportions undergoing revascularisation or medication treatment is comparable with a previously published article based on the Euro Heart Survey, which reported a revascularisation rate of 13%.[70] Furthermore, expert opinion indicated that the results of this study were also appropriate for the difficult-to-image patient groups considered in this assessment.

Population with known coronary artery disease

Given a positive CT or ICA test for patients with known CAD, two treatment options are considered: either PCI or CABG. The proportions undergoing PCI or CABG in patients with known CAD were also assumed to be 70% : 30%, based on the same expert opinion used for the suspected CAD population.

Procedure-related mortality and morbidity

Invasive coronary angiography and revascularisation are accompanied by a risk of serious complications, including stroke, non-fatal MI and death (*Table 32*). The mortality rates are important for the impact on QALYs of the three strategies. The strategy in which all patients will undergo an ICA has the highest test-related mortality rate and this mortality rate influences the cost-effectiveness ratio by lowering the expected QALYs.

The complication rate used in this model is based on published data.[89] A literature search for UK guidelines for performing coronary angiography was conducted to identify a study that provided primary data on complications caused by diagnostic ICA. Seventeen UK guidelines were found and these were checked for studies presenting primary data; 17 potentially relevant studies were found. A further four primary studies[89–92] were identified after checking the references of the initial 17 studies and performing a citation search. Two studies[90,91] did not present a complication rate based on the UK population but were conducted in Turkey and Canada, respectively. One study[92] reported a complication rate for a UK population but was based on a single centre. A multicentre study[89] on diagnostic angiography in the UK (and the most recently performed study) was considered to be the most appropriate study to inform the model. This study reported a complication rate of 7.4 (95% CI 7.0 to 7.7) and a mortality rate of 0.7 (95% CI 0.6 to 0.9) per

TABLE 32 Complications of ICA and revascularisations

Complications	Batyraliev et al.[90]	Chandrasekar et al.[91]	West et al.[89]	Smith et al.[92]
ICA				
Total complication rate	0.0205	0.0460	0.0074	
Mortality rate	0.0008	0.0043	0.0007	0.0007
Cerebrovascular accident rate	0.0006	0.0024	0.0006	0.0014
MI rate	0.0008	0.0010	0.00003	
Other complications	0.0182	0.0383	0.0060	
PCI				
Mortality rate	0.0029	Rajani (2011)[96]		
Cerebrovascular accident rate	0.0005	Rajani (2011)[96]		
MI rate	0.0005	Rajani (2011)[96]		
CABG				
Mortality rate	0.018	Bridgewater (2007)[93]		
Cerebrovascular accident rate	0.016	Tarakji (2011)[94]		
MI rate	0.024	Serruys (2001)[95] and Tarakji (2011)[94]		

1000 patients, based on 219,227 procedures undertaken between 1991 and 1999. The mortality rate and the cerebrovascular accident rate presented in this study were comparable with data from another of the identified studies.[90] The overall complication rate and the MI rate presented were considerably lower than those presented in the other studies. We assumed that the complication rate of coronary angiography presented by the selected study is applicable regardless of the underlying risk of CV events particularly in difficult-to-image patient groups.

Both revascularisation procedures, CABG and PCI, are associated with complications including stroke, non-fatal MI and death. These complications are included in the diagnostic model. The mortality rate (0.018) of a CABG is based on Bridgewater et al.[93] CABG-related stroke was taken from the study.[93] As there were no studies that reported CABG-related MI, we used the study by Serruys et al.[95] to give an estimate of CABG-related MI. A survival curve (patients without MI and stroke) presented in the Serruys study[95] was used: at 30 days, the survival was 96%; thus, 4% experienced a stroke or a MI. As we found a stroke rate of 1.6%[94] related to the procedure we used 2.4% as an estimate for CABG-related MI assuming that within 30 days after the procedure it is still related to the procedure. This could lead to an overestimation of the MI rate, because the 4% reported by Serruys et al.[95] is not related to the procedure per se.

The complication rates induced by PCI were based on the study of Rajani et al.;[96] mortality due to a PCI is 0.0029, to a MI 0.0005 and stroke due to PCI 0.0005.

Finally, it has also been suggested that the intravenous contrast used in ICA, PCI and the NGCCT may carry a small risk of contrast-induced renal failure, dialysis and mortality.[97] However, a paper reviewing this risk in CT scans showed a negligible risk. In a total of six studies in patients receiving contrast fluid for a CT, no patients needed dialysis or died out of 1175 patients.[98] Thus, we have added no complications for the NGCCT. Contrast-related mortality may be assumed to be part of overall mortality due to ICA and PCI discussed earlier. Thus, the only remaining issue is a potential underestimation of the complications of these invasive procedures. As the complication rate can be greatly influenced by taking prophylactic measures in patients who are more at risk, this additional risk is here considered to be negligible.[99]

Healthy population model

The healthy population model applies only for the suspected CAD population because all patients with known CAD have a different prognosis than patients without CAD; this was modelled using the EUROPA model. The TN and the FP patients in the suspected CAD population do not have CAD and therefore modelling their 'future' with the EUROPA model is not appropriate. Life tables were used to predict mortality for those groups of patients assuming that these patients do not differ from the average UK population. Costs are not assigned to this Markov model.

Survival

Three-monthly, age-dependent transition probabilities were used to model mortality for TN and FP patients in the suspected CAD population. The transition probabilities were based on UK life tables for all-cause mortality (*Table 33*).[65] All-cause mortality life tables were used, as these patients can still develop and die from CAD in the future.

Utility for patients without coronary artery disease

Patients from the suspected CAD population with a TN or FP test outcome are patients without CAD and it is therefore assumed that the health-related quality of life (HRQoL) for these patients would be equal to the population norms by gender and age (*Table 34*).[100] Of course, when patients presented they must have had similar symptoms to those who actually have CAD. However, we have assumed that these symptoms resolve over time, either through spontaneous improvement or through appropriate treatment. Additionally, it should be realised that the general population utility already is based on the presence of some illness, which implies that the difference between the utility of suspected CAD population who do not have CAD and the general population may be expected to be small. QALYs are discounted with 3.5%.[97]

TABLE 33 Quarterly mortality rates (all causes)[65]

Age (years)	All causes	
	Male	Female
0–4	0.000344	0.00027018
5–9	2.43E-05	2.1251E-05
10–14	3.54E-05	2.6616E-05
15–19	0.000104	5.4024E-05
20–24	0.000159	6.7097E-05
25–29	0.00018	8.4161E-05
30–34	0.000229	0.00011491
35–39	0.00031	0.00016842
40–44	0.000445	0.00028385
45–49	0.000706	0.00046288
50–54	0.001107	0.00073712
55–59	0.001708	0.00112255
60–64	0.00288	0.00175231
65–69	0.00457	0.00292024
70–74	0.007701	0.00485634
75–79	0.013048	0.00881416
80–84	0.022073	0.01569499
85–89	0.034578	0.02697076
90+	0.059551	0.05399661

EUROPA model

The EUROPA model models the progression of stable CAD by predicting CV events and mortality. Health-care costs were evaluated by Briggs et al.[69] from resource items collected as part of the EUROPA study[68] and these are grouped, for our analysis, into three categories: background costs, NFE costs and fatal event costs. More details can be found in the technical appendix of Briggs et al.[69] During the EUROPA trial a cost data set was constructed by recording, for each patient, the costs for each year in the trial. Covariates were then defined that related to the states of the model. A linear regression model (controlling for clustering by individual) was then used to estimate the cost associated with each of the model states, together with the potential effects of other covariates.[69] Table 35 shows the results of the cost regression.

The original cost prices of the EUROPA trial 2003–4 were updated with a price correction based on the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2010 (PSSRU 2010). Inflation correction is 1.2077402 and costs are discounted at an annual rate of 3.5%.[101]

Background costs

Background costs are costs which are applied to the trial entry state and the NFE states. The background costs are based on age, the existence of vascular diseases or diabetes mellitus, medication usage, creatinine clearance and symptomatic disease. For each combination of difficult-to-image patient group, strategy, treatment decision, test outcome and known or suspected CAD population background costs (Tables 37 and 38) were estimated with the linear regression presented in Table 35. The costs of medication for patients who are treated with

TABLE 34 Population norm by European Quality of Life-5 Dimensions (EQ-5D) (Kind et al.[100])

Age (years)	Males		Females	
	Mean	SE	Mean	SE
55–64	0.78	0.02	0.81	0.02
65–74	0.78	0.02	0.78	0.02
75+	0.75	0.03	0.71	0.02

TABLE 35 EUROPA costs

Covariate	Coefficient (£)
Proportion of the year remaining following death/censoring	−1224
NFE	11,805
Non-fatal event history	986
CV fatal event	3641
Non-CV fatal event	12,421
Age	13
Existing vascular diseases	392
Diabetes mellitus	253
Symptomatic disease	283
Creatinine clearance below 80 ml/minute	8
Using nitrates at baseline	273
On calcium channel blockers at baseline	189
On lipid-lowering treatment at baseline	121
UK resource use	−107
Constant	−21

medication only were included in this background cost. An example is presented below for a patient from the known CAD population who is obese and defined TP in the ICA-only strategy.

The average age of an obese patient with known CAD and a TP test outcome is 63 years; 34% have diabetes mellitus and 25% are symptomatic. Creatinine clearance below 80 ml/minute is on average 6.9 ml/minute, nitrates usage at baseline 44%, the presence of existing vascular disease is 10.1%, calcium channel blocker usage at baseline 32% and lipid-lowering therapy at baseline 55.9%. So, in total, £298.05 is assigned per cycle of 3 months as a background cost (*Table 36*).

TABLE 36 Example background cost calculation

Covariate	Coefficient	Mean	Annual	Quarterly
Age	13	63	819	204.8
Existing vascular disease	392	0.10	40.3	10.1
Diabetes mellitus	253	0.34	86.3	21.6
Symptomatic angina	283	0.25	69.3	17.3
Creatinine clearance of < 80 ml/minute	8	6.9	55.2	13.8
Nitrates usage	273	0.44	121.2	30.3
Calcium channel blocker usage	189	0.32	61.2	15.3
Lipid-lowering drugs usage	121	0.56	67.6	16.9
UK	−107	1	−107	−26.8
Constant	−21	1	−21	−5.3
Total background costs (£)			1192.2	298.05

TABLE 37 Monthly background costs EUROPA: suspected CAD population (£)

Strategy	Test outcome	Treatment	Obese	HHC	HHR	Intolerance beta-blocker	Arrhythmias
ICA only	TP	Revascularisation	298.0	287	328.2	288.3	303.6
	TP	Medication	329.6	319	359.8	319.8	335.1
NGCCT–ICA	TP	Revascularisation	298.0	287	328.2	274.6	303.6
	TP	Medication	329.6	319	359.8	319.8	335.1
	FN		0	0	0	0	0
NGCCT only	TP	Revascularisation	298.0	287.3	328.2	288.3	303.6
	TP	Medication	329.5	318.8	359.7	319.8	335.1
	FN		0	0	0	0	0

TABLE 38 Monthly background costs EUROPA: known CAD population (£)

Strategy	Test outcome	Obese	HHC	HHR	Intolerance beta-blocker	Arrhythmias	Revascularisation
ICA only	TP	298.0	274.6	262.2	274.6	305.4	302.6
	TN	297.6	274.1	261.8	274.1	304.9	302.1
NGCCT–ICA	TP	298.0	274.6	262.2	274.6	305.4	302.6
	TN	297.5	274.0	261.7	274.0	304.8	302.1
	FN	297.5	274.0	261.7	274.0	304.8	302.1
NGCCT only	TP	298.0	274.5	262.2	274.5	305.3	302.6
	TN	297.5	274.0	261.7	274.0	304.8	302.1
	FN	297.5	274.0	261.7	274.0	304.8	302.1
	FP	298.0	274.5	262.2	274.5	305.3	302.6

Non-fatal event costs

For the year in which a NFE occurs, £11,805 was added to the background cost. For subsequent years, the additional cost was estimated as £986. In the year that a fatal CV event occurs, the additional cost was estimated as £3641. When a fatal non-CV event occurred, an additional cost of £12,421 was added.

Utilities for patients with coronary artery disease

Health-related quality-of-life estimates were assigned to the states in the Markov model based on age, gender, baseline CCS classification and whether or not the patient had undergone treatment. Patients modelled through the disease progression model are assumed to have a CCS class (Campeau[102]) of 2. The HRQoL estimates were based on three sources: population norm for the EQ-5D,[100] EQ-5D scores per CCS class[103] and treatment effect on quality of life (QoL) based on the Randomized Intervention Treatment of Angina (RITA-2) trial.[64]

Baseline EQ-5D – untreated patients with CAD Combining the population norm values with the EQ-5D scores per CCS class (0–4) (*Tables 39* and *40*) generates relative HRQoL by CCS class and gender. Longworth's scores[103] were based on a median age of 61 years and these were divided by population norms for the age group 55–64 years. To obtain HRQoL by CCS class and age, the HRQoL by CCS class was multiplied by the age-specific HRQoL scores from Kind *et al.*,[100] assuming that the relative HRQoL by CCS class compared with the general population would hold across all ages. This multiplication was taken for the patients with CAD at baseline (without treatment).

Treatment EQ-5D – patients with coronary artery disease, treated The RITA-2 trial provided data on the initial CCS class and the CCS class following revascularisation to estimate the HRQoL for a patient who is treated. The long-term effects of PCI and medical treatment in patients with CAD are compared in the RITA-2 trial. The baseline EQ5D score was combined with the RITA 2 trial to generate HRQoL scores by baseline CCS (i.e. CCS before treatment), age and gender following revascularisation (*Tables 41* and *42*). Improvement in HRQoL (a better CCS class) was estimated by combining the changes in CCS after treatment with association seen between baseline CCS and baseline HRQoL. A new HRQoL was calculated from the shifts to the other CCS classes. For example, 20% of the patients will have a better CCS class after treatment, 10% will have a worse CCS class after treatment and 70% will stay in the same CCS class. The product of the proportion and the HRQoL in each specific CCS class after treatment provided an updated HRQoL for a patient by baseline CCS class. The assumption was made that the effect of revascularisation on HRQoL continues. The same HRQoL values were used for patients treated with medication only.

A 3-monthly disutility of 0.010225[104] was assigned to the non-fatal event states because an event has occurred. We assumed that the disutility owing to a MI is the same as for a cardiac arrest. Of the NFEs only 2.5% will be a cardiac arrest; thus, the impact of changes in the disutility of a cardiac arrest will be minimal.

Population with known coronary artery disease

For the suspected CAD population, the baseline HRQoL applies for the patients with CAD, but not treated with a revascularisation or medication (FNs). In the EUROPA model, after a while a FN patient with CAD could be identified and would be treated; for this identified patient the HRQoL following treatment applies. The TPs from the suspected CAD population have CAD and will be treated with a revascularisation or medication and therefore the HRQoL following treatment applies (*Table 43*).

TABLE 39 Baseline HRQoL: male

Age (years)	CCS class				
	0	1	2	3	4
55–64	0.81	0.75	0.60	0.41	0.36
65–74	0.81	0.75	0.60	0.41	0.36
75+	0.78	0.72	0.58	0.39	0.35

TABLE 40 Baseline HRQoL: female

Age (years)	CCS class				
	0	1	2	3	4
55–64	0.8	0.75	0.60	0.41	0.36
65–74	0.8	0.72	0.58	0.39	0.35
75+	0.7	0.66	0.53	0.36	0.32

TABLE 41 Health-related quality of life following treatment: male

Age (years)	Before-treatment CCS class				
	0	1	2	3	4
55–64	0.79	0.74	0.75	0.69	0.72
65–74	0.79	0.74	0.75	0.69	0.72
75+	0.76	0.72	0.72	0.66	0.69

TABLE 42 Health-related quality of life following treatment: female

Age (years)	Before-treatment CCS class				
	0	1	2	3	4
55–64	0.79	0.74	0.75	0.69	0.72
65–74	0.76	0.72	0.72	0.66	0.69
75+	0.69	0.65	0.65	0.60	0.63

TABLE 43 Health-related quality of life per population and test outcome

Population	Test outcome	HRQoL
Suspected	TP	HRQoL following treatment
	FN	Baseline HRQoL – without treatment
Known	TP	HRQoL following treatment
	FN	Baseline HRQoL – without treatment
	FP	HRQoL following treatment
	TN	HRQoL following treatment

Population with known coronary artery disease

Patients from the known CAD population all have CAD irrespective of their test outcome. Therefore, they are already identified and the TPs who are treated will have the HRQoL following treatment. The TNs do not need a revascularisation; therefore they have a HRQoL of being treated because we assume that these patients are in such a good state that a revascularisation is not necessary and therefore they have the highest HRQoL, namely that of treated patients. The FPs are treated with a revascularisation although this was not necessary. Therefore, we assumed that patients being FP and who are treated have the highest HRQoL, namely that of patients who are treated. The FNs need a revascularisation so the HRQoL of patients who are not treated applies for these patients (see *Table 43*).

Transition probabilities

Tables 44 and *45* present the 3-monthly transition probabilities for the suspected and known CAD populations for each subgroup. These transition probabilities were based on the risk equations which are explained in *Model structure and methodology, EUROPA*.

Stroke model

The costs and effects of the patients who experience a stroke due to the initial ICA or revascularisation are modelled with a relatively simple alive–dead model based on estimates by Sandercock *et al.*[66] for thrombolytic therapy of stroke.

Survival

Mortality rates were based on UK life tables[65] and a relative risk of 2.5 to reflect the increased risk of mortality following a stroke.[105] Survival for each subgroup modelled in this study was therefore not simply dependent on stroke but also on the average age in that subgroup.

Costs

Sandercock *et al.*[66] estimated a cost of approximately £6260 in the first year after a stroke. As Sandercock *et al.*[66] presented both 12-month and lifetime costs, we estimated the average annual costs of treating stroke patients after the first year to be approximately £3400. These costs were then inflated to reflect costs for 2009–10 and then discounted at a rate of 3.5%.

Quality-adjusted life-year

Calibration of the model to fit with the results by Sandercock *et al.*[66] resulted in an average health utility of 0.37. This value was combined with survival and the resulting QALYs were discounted using at a rate of 3.5%.

York Radiation Model

The following tables show the key parameters for the base-case scenario for the YRM when modelling the effect of radiation on CAD patients. *Table 46* shows the mean parameter values (costs and QALY loss due to cancer) for the cancer module of the YRM. If the age at first exposure to radiation is < 40 years, the average age of incidence for breast cancer is assumed to be 40 years; for higher ages the average is assumed to be 60 years. In the CAD patient population all patients are aged > 40 years. This can be seen clearly in *Table 51,* with demographic characteristics of the patient population. The lifetime risk of cancer incidence by age and sex for a one-time exposure to 10 mSv, based on the HPA model, is shown in *Table 47*. *Table 49* shows the age-specific utilities used to calculate the QALYs for non-cancer patients. *Table 50* shows the life expectancy for the general population, i.e. patients who do not get cancer, based on the 2007 England and Wales life table. Note that in various tables values are presented for younger age groups, as those values are required for the analysis presented below (see *Cost-effectiveness of new-generation cardiac computed tomography in congenital heart disease*).

TABLE 44 Transition probabilities: CAD suspected population

Transition probabilities	Obese	Arrhythmias	HCC	HHR	Beta-blocker
Probability first trial event, TP revascularisation, strategy 1, 3-monthly	0.0078	0.0113	0.0095	0.0067	0.0056
Probability first trial event, TP revascularisation, strategy 2, 3-monthly	0.0078	0.0113	0.0095	0.0067	0.0056
Probability first trial event, TP revascularisation, strategy 3, 3-monthly	0.0078	0.0113	0.0095	0.0067	0.0056
Probability first trial event, TP medication, strategy 1, 3-monthly	0.0100	0.0145	0.0121	0.0087	0.0073
Probability first trial event, TP medication, strategy 2, 3-monthly	0.0100	0.0145	0.0121	0.0087	0.0073
Probability first trial event, TP medication, strategy 3, 3-monthly	0.0100	0.0145	0.0121	0.0087	0.0073
Probability first trial event, FN strategy 2, 3-monthly	0.0089	0.0129	0.0107	0.0077	0.0064
Probability first trial event, FN strategy 3, 3-monthly	0.0089	0.0129	0.0107	0.0077	0.0064
Probability event is fatal, TP strategy 1, medication	0.2951	0.3212	0.3028	0.2861	0.2710
Probability subsequent event is fatal, TP strategy 1, medication	0.4004	0.4303	0.4093	0.3901	0.3723
Probability event is fatal, TP strategy 2, medication	0.2951	0.3212	0.3028	0.2861	0.2710
Probability subsequent event is fatal, TP strategy 2, medication	0.4004	0.4303	0.4093	0.3901	0.3723
Probability event is fatal, TP strategy 3, medication	0.2951	0.3212	0.3028	0.2861	0.2710
Probability subsequent event is fatal, TP strategy 3, medication	0.4004	0.4303	0.4093	0.3901	0.3723
Probability event is fatal, TP strategy 1, revascularisation	0.2958	0.3220	0.3035	0.2869	0.2750
Probability subsequent event is fatal, TP strategy 1, revascularisation	0.4004	0.4303	0.4093	0.3901	0.3723
Probability event is fatal, TP strategy 2, revascularisation	0.2958	0.3220	0.3035	0.2869	0.2750
Probability subsequent event is fatal, TP strategy 2, revascularisation	0.4004	0.4303	0.4093	0.3901	0.3723
Probability event is fatal, TP strategy 3, revascularisation	0.2958	0.3220	0.3035	0.2869	0.2750
Probability subsequent event is fatal, TP strategy 3, revascularisation	0.4004	0.4303	0.4093	0.3901	0.3723
Probability event is fatal, FN strategy 2	0.2951	0.3212	0.3028	0.2861	0.2710
Probability event is fatal, FN strategy 3	0.2951	0.3212	0.3028	0.2861	0.2710
Probability of subsequent event within first year post event, 3 monthly	0.0272	0.0272	0.0272	0.0272	0.0272
Probability of subsequent event within first year post event, annually	0.1046	0.1046	0.1046	0.1046	0.1046
Probability subsequent event after first year, TP strategy 1, medication, 3-monthly	0.0144	0.0210	0.0175	0.0125	0.0105
Probability subsequent event after first year, TP strategy 1, revascularisation, 3-monthly	0.0112	0.0163	0.0136	0.0097	0.0081
Probability subsequent event after first year, TP strategy 2, medication, 3-monthly	0.0144	0.0210	0.0175	0.0125	0.0105
Probability subsequent event after first year, TP strategy 2, revascularisation, 3-monthly	0.0112	0.0163	0.0136	0.0097	0.0081
Probability subsequent event after first year, TP strategy 3, medication, 3-monthly	0.0144	0.0210	0.0175	0.0125	0.0105
Probability subsequent event after first year, TP strategy 3, revascularisation, 3-monthly	0.0112	0.0163	0.0136	0.0097	0.0081
Probability subsequent event after first year, FN strategy 2, 3-monthly	0.0128	0.0185	0.0155	0.0110	0.0092
Probability subsequent event after first year, FN strategy 3, 3-monthly	0.0128	0.0185	0.0155	0.0110	0.0092
Quarterly probability of a FN patient being identified as TP	0.1930	0.1930	0.1930	0.1930	0.1930

Table 52 presents the radiation doses for each of the analysed scanning strategies for patients with CAD. The value for NGCCT is based on an expert survey (response: $n = 2$) for this particular patient group, whereas the average radiation doses for ICA and PCI are taken from literature.[61]

For all of the scanning strategies, the uncertainty in the costs (*Table 48*) and remaining QALYs of the cancer module in the YRM are modelled via a PSA. The values for the input are shown in *Table 46*.

TABLE 45 Transition probabilities: known CAD population

Transition probabilities	Obese	Arrhythmias	HCC	HHR	Beta-blocker	Revascularisation
Probability first trial event, TP strategy 1 known, 3-monthly	0.01212	0.0231	0.0145	0.0076	0.0088	0.0097
Probability first trial event, TN strategy 1 known, 3-monthly	0.01286	0.0245	0.0154	0.0080	0.0093	0.0097
Probability first trial event, TP strategy 2 known, 3-monthly	0.01212	0.0231	0.0145	0.0076	0.0088	0.0097
Probability first trial event, TN strategy 2 known, 3-monthly	0.01286	0.0245	0.0154	0.0080	0.0093	0.0097
Probability first trial event, FN strategy 2 known, 3-monthly	0.01286	0.0245	0.0154	0.0080	0.0093	0.0097
Probability first trial event, FP strategy 2 known, 3-monthly	0.01286	0.0245	0.0154	0.0080	0.0093	0.0097
Probability first trial event, TP strategy 3 known, 3-monthly	0.01212	0.0231	0.0145	0.0076	0.0088	0.0097
Probability first trial event, TN strategy 3 known, 3-monthly	0.01286	0.0245	0.0154	0.0080	0.0093	0.0097
Probability first trial event, FN strategy 3 known, 3-monthly	0.01286	0.0245	0.0154	0.0080	0.0093	0.0097
Probability first trial event, FP strategy 3 known, 3-monthly	0.01212	0.0231	0.0145	0.0076	0.0088	0.0097
Probability event is fatal, TP strategy 1	0.36165	0.4084	0.3347	0.3021	0.3347	0.3820
Probability subsequent event is fatal, TP strategy 1 known	0.40043	0.4487	0.3723	0.3379	0.3723	0.4216
Probability event is fatal, TN strategy 1	0.36165	0.4084	0.3347	0.3021	0.3347	0.3820
Probability subsequent event is fatal, TN strategy 1 known	0.40043	0.4487	0.3723	0.3379	0.3723	0.4216
Probability event is fatal, TP strategy 2	0.36165	0.4084	0.3347	0.3021	0.3347	0.3820
Probability subsequent event is fatal, TP strategy 2 known	0.40043	0.4487	0.3723	0.3379	0.3723	0.4216
Probability event is fatal, TN strategy 2	0.36165	0.4084	0.3347	0.3021	0.3347	0.3820
Probability subsequent event is fatal, TN strategy 2 known	0.40043	0.4487	0.3723	0.3379	0.3723	0.4216
Probability event is fatal, FN strategy 2 known	0.29506	0.3212	0.3028	0.2861	0.2710	0.0335
Probability event is fatal, TP strategy 3	0.36165	0.4084	0.3347	0.3021	0.3347	0.3820
Probability subsequent event is fatal, TP strategy 3 known	0.40043	0.4487	0.3723	0.3379	0.3723	0.4216
Probability event is fatal, TN strategy 3	0.36165	0.4084	0.3347	0.3021	0.3347	0.3820
Probability subsequent event is fatal, TN strategy 3 known	0.40043	0.4487	0.3723	0.3379	0.3723	0.4216
Probability event is fatal, FP strategy 3	0.36165	0.4084	0.3347	0.3021	0.3347	0.3820
Probability subsequent event is fatal, FP strategy 3 known	0.40043	0.4487	0.0524	0.3379	0.3723	0.4216
Probability event is fatal, FN strategy 3 known	0.36165	0.4084	0.3347	0.3021	0.3347	0.3820
Probability of subsequent event within first year post event, 3-monthly	0.0272	0.0272	0.0272	0.0272	0.0272	0.0272
Probability of subsequent event within first year post event, annually	0.1046	0.1046	0.1046	0.1046	0.1046	0.1046
Probability subsequent event after first year, TP strategy 1, 3-monthly	0.01378	0.0262	0.0165	0.0086	0.0100	0.0110
Probability subsequent event after first year, TN strategy 1, 3-monthly	0.01463	0.0278	0.0176	0.0091	0.0106	0.0110
Probability subsequent event after first year, TP strategy 2, 3-monthly	0.01378	0.0262	0.0165	0.0086	0.0100	0.0110
Probability subsequent event after first year, TN strategy 2, 3-monthly	0.01463	0.0278	0.0176	0.0091	0.0106	0.0110
Probability subsequent event after first year, FN strategy 2, 3-monthly	0.01463	0.0278	0.0176	0.0091	0.0106	0.0110
Probability subsequent event after first year, FP strategy 2, 3-monthly	0.01463	0.0278	0.0176	0.0091	0.0106	0.0110
Probability subsequent event after first year, TP strategy 3, 3-monthly	0.01378	0.0262	0.0165	0.0086	0.0100	0.0110
Probability subsequent event after first year, TN strategy 3, 3-monthly	0.01463	0.0278	0.0176	0.0091	0.0106	0.0110
Probability subsequent event after first year, FN strategy 3, 3-monthly	0.01463	0.0278	0.0176	0.0091	0.0106	0.0110
Probability subsequent event after first year, FP strategy 3, 3-monthly	0.01378	0.0262	0.0165	0.0086	0.0100	0.0110
Quarterly probability of a FN patient being identified as TP	0.1930	0.1930	0.1930	0.1930	0.1930	0.1930

TABLE 46　Total costs and QALYs lost due to cancer, discounted at 3.5% per annum to age at cancer diagnosis[61] (SD in parentheses)

Cancer	Age at diagnosis (years)	Costs of cancer (£)	QALYs lost due to cancer
Breast	40 (0)	14,990 (940)	5.6988 (0.4533)
Breast	60 (0)	13,927 (848.11)	3.4219 (0.311)
Lung	72.2684 (0.0395)	22,712 (440,60)	6.8011 (0.056)
Colorectal	73.72 (0.139)	14,075 (356.00)	3.4493 (0.1386)
Prostate	74 (NA)	12,389 (NA)	4.6226 (NA)

NA, not applicable; SD, standard deviation.

TABLE 47　Lifetime risks of cancer incidence for all cancers by age and sex at exposure based on HPA data[61]

Age at exposure (years)	Risk of all cancers (for exposure to 10 mSv)	
	Males	Females
0–9	0.000999	0.00127
10–19	0.0008	0.000994
20–29	0.000623	0.000795
30–39	0.000512	0.000646
40–49	0.000422	0.000562
50–59	0.000327	0.000441
60–69	0.000223	0.00032
70–79	0.000132	0.000194
80–89	0.000055	0.000075
90–99	0.000004	0.000002

TABLE 48　Cost per scan for CT64 and NGGCT (base case)

Strategy	Cost per scan (£)
CT64	132.62
NGCCT	169.26

TABLE 49　Age-specific utilities based on underlying health of the general UK population

Age (years)	Mean utility	SD
<25	0.94	0.12
25–34	0.93	0.15
35–44	0.91	0.16
45–54	0.85	0.25
55–64	0.80	0.26
65–74	0.78	0.26
75+	0.73	0.27

SD, standard deviation.

TABLE 50 Overview of age-specific remaining life expectancy

Age (years)	Males	Females	Combined (50% male)
0	77.98	82.09	80.04
10	68.50	72.53	70.52
20	58.67	62.63	60.65
30	49.04	52.80	50.92
40	39.55	43.07	41.31
50	30.32	33.61	31.97
60	21.71	24.63	23.17
70	14.09	16.35	15.22
80	7.98	9.36	8.67
90	4.15	4.59	4.37
100	2.13	2.22	2.18

TABLE 51 Demographic characteristics of the CAD patient population

	Known		Suspected	
Subgroup	Mean age (years)	% Male	Mean age (years)	% Male
Obese	63	0.659	63	0.659
Arrhythmias	68	0.71	66.11	0.69
Intolerance beta-blockers	60	0.854	60	0.854
Previous stents	65	0.66	✗	✗
Previous CABG	66	0.788	✗	✗
HHR	61.91	0.52	56.2	0.68
High coronary calcium score	63.93	0.854	60	0.7503

TABLE 52 Radiation dose (in millisieverts) of scanning strategies for CAD patients based on a disease-specific expert survey

Scanning strategy	Radiation dose (mSv)
ICA	7
NGCCT	4.5
ICA–NGCCT	11.5
ICA–PCI	22
NGCCT–PCI	19.5
ICA-NGCCT–PCI	26.5

Proportions of patients in difficult-to-image subgroups

Difficult-to-image patient group-specific costs and QALYs were calculated. The aim was to calculate an overall ICER for the three strategies and for the two populations (suspected and known CAD). Expert opinion was used to gather information on the relative proportions of patients in the different difficult-to-image groups in a known or suspected CAD population. Primary data collection from patient records was considered, but due to time constraints a questionnaire distributed to experts in the field was used to derive a reasonable estimate of the relative proportions. Multiplying the relative proportions with the subgroup-specific costs and effects produced an overall ICER for the suspected CAD population and an overall ICER for the known CAD population.

The questionnaire was distributed to six experts, four of whom completed and returned it. Means are calculated from the proportions that the experts filled in. See *Appendix 7* for details on the experts. *Table 53* shows the relative proportions for each population. According to the experts it is impossible to have a revascularisation before the test is performed in a population with suspected CAD.

Assumptions

Using five models that were each designed for another purpose lead to some unavoidable assumptions. Assumptions made are summarised in *Table 54*.

Results

Initially the costs of using the NGCCT instead of an ICA are lower but what is the influence of the lower sensitivity and specificity on the effectiveness side and the costs side? The cost-effectiveness of the three strategies is described below. First intermediate results are given for the three strategies for each subgroup.

Intermediate outcomes

In addition to the cost-effectiveness of the NGCCT, intermediate outcomes in terms of mortality, morbidity and the percentages of correct diagnostic classification (TP, FP, TN and FN) are also important. *Tables 55* and *56* show, for both CAD populations and for each difficult-to-image group, these three intermediate outcomes.

Population with suspected coronary artery disease

As expected, the ICA had 100% correct diagnostic classification due to the assumption of 100% sensitivity and 100% specificity. Unfortunately, this comes with higher mortality and morbidity rates due to the complications of the test itself. The strategy where each patient will undergo an ICA had the highest test-induced mortality and morbidity rate, and the strategy that uses only the NGCCT to diagnose patients has test-induced mortality and morbidity rates of zero. Conversely, revascularisation-induced mortality and morbidity rates were highest in

TABLE 53 Mean proportion difficult-to-image subgroups, per expert and overall

| Subgroups | Mean proportion (%) | | | | |
	1	2	3	4	Average
Suspected CAD population					
Obese	26	15	14	10	16.25
High-level coronary calcium	12	10	48	40	27.50
Arrhythmias	12	10	10	15	11.75
HHR	38	50	9	20	29.25
Intolerance beta-blocker	12	15	19	15	15.25
	100	100	100	100	100
Known CAD population					
Obese	20	5		5	10.00
High-level coronary calcium	12	20		45	25.67
Arrhythmias	12	5		5	7.33
HHR	32	40		10	27.33
Intolerance beta-blocker	8	10		10	9.33
Previous PCI	8	15		10	11.00
Previous CABG	8	5		15	9.33
	100	100	100	100	100

TABLE 54 Assumptions

Assumptions	Reference
General assumptions	
A mean BMI is transformed to obesity percentage assuming a normal distribution	
The suspected CAD group cannot have had a previous revascularisation	Questionnaire
Proportion PCI–CABG is 70–30%	
Diagnostic model general	
An ICA is performed only after a positive HDCT test outcome in the strategy HDCT–ICA	
ICA is the gold standard with a 100% sensitivity and 100% specificity	
When a PCI is performed after an ICA, the mortality of PCI only is used. Assumption is that a PCI is performed at the same time as ICA	
All diagnostic tests are performed immediately after each other without any time delay	
The most relevant complications of an ICA and PCI/CABG are mortality, non-fatal MI or cerebrovascular accident	
The sensitivity and specificity of the HDCT in patients intolerant of beta-blockers is assumed to be the same as for the subgroup with a HHR	
Accuracy estimates are the same for the suspected and known population	
Complication rates of revascularisation and ICA are assumed to be the same in all difficult-to-image subgroups	
Patients treated with a revascularisation are treated with a CABG or a PCI. The proportion is 30% and 70%, respectively	
Diagnostic model suspected population	
Patients suspected with CAD with the disease and with a positive test outcome have three treatment options: CABG/PCI or medication. A revascularisation is performed in 15% of the patients and 85% of the patients receive medication	Hofstra (personal communication)
Prior likelihood of patients suspected of CAD is 10–29%	NICE CG95[63]
Diagnostic model known population	
Patients with known CAD with a positive test outcome have two treatment options: CABG/PCI	
Prior likelihood that a known patient would benefit from a revascularisation is 0.395	CE-MARC[64]
EUROPA model	
The difficult-to-image indications CABG and PCI are treated as one indication in the EUROPA model. The covariate 'previous revascularisation' captures the impact of an previous revascularisation on the risk of experiencing an event	
The covariates of the risk equation of the EUROPA study are appropriate for the known and suspected CAD population	
Primary events predicted with the EUROPA model are cardiac arrest, non-fatal MI and death	
The input values for the risk equations were based on the systematic review if available, otherwise they were based on the EUROPA population	
Relative risks are used to update the risk equations of the EUROPA model for the subgroups: high coronary calcium, HHR and arrhythmias	
Patients intolerant for beta-blockers do not have an increased risk of experiencing events. Beta-blockers are provided to make interpretable images and not to prevent events. Patients intolerant for beta-blockers can also receive calcium channel blockers to reduce events as an alternative	
The risk of experiencing a non-fatal MI, cardiac arrest or mortality is for the subgroup obesity captured in the risk equation by the covariate obese	
A relative risk based on Hofstra *et al.* is used to update the risk equation for the difficult-to-image subgroup high coronary calcium level	
Proportion HCC in the EUROPA trial is assumed to be the same as in the study …	
A relative risk based on the QRISK study is used to update the risk equation for the difficult-to-image subgroup 'arrhythmias'	
AF is taken as an proxy for the difficult-to-image subgroup arrhythmias because AF is the most common type of arrhythmia	British Heart Foundation[1]
Proportion AF in EUROPA population is assumed to be the same as in study …	
It is assumed that the conditions of the subgroups HHR and beta-blockers intolerant do not have an impact on the transition probabilities	

TABLE 54 Assumptions (*continued*)

Assumptions	Reference
Age- and CCS-specific HRQoL values based on Longworth *et al.* 2005,[102] Kind *et al.* 1999[100] and the RITA-2 trial give good estimates for (un)treated patients with CAD	
Disutility for experiencing a cardiac arrest is assumed to be the same as for a non-fatal MI	
Patients with a positive test outcome who will be treated with medication will be treated with a calcium channel blocker. Calcium channel blocker usage is a covariate in the risk equation. Normally patients with CAD will receive a calcium channel blocker or a beta-blocker. The clinical effectiveness of these two drugs is comparable and therefore we assume that the HR is the same. Even when a combination of both drugs is given the HR will probably the same because we assume that a second drug will only be given when the first was not (fully) effective	
EUROPA suspected CAD	
The input values for the risk equations for the suspected group are based on the accuracy studies performed on the suspected population. If suspected specific input values are not available then studies which combine suspected and known CAD are used. If combined studies are not available the input values will be based on the EUROPA population	
Proportion MI in the risk equation is based on the non-fatal complications due to the initial revascularisation or ICA	
Patients are not treated with nitrates at baseline	
ACE inhibitor usage at baseline 23%	
EUROPA known CAD	
The input values for the risk equations for the known group are based on the accuracy studies performed based on known CAD population. If known specific input values are not available then the input values will be based on the EUROPA population	
All patients with known CAD are modelled with the EUROPA model irrespective of the test outcome	
ACE inhibitor usage at baseline 23%	Daly (2005)[70]
Proportion MI in risk equation is based on the EUROPA population; the proportion is not raised with the ICA and initial revascularisation-induced MI	
A HRQoL value following treatment is assigned to patients with the test outcomes FPs and TNs	
Alive–dead model	
TN and FP modelled with the life death model with all-cause mortality probabilities	
Stroke model	
Patients are treated with thrombolytic agents	

the NGCCT-only strategy due to the FPs who undergo unnecessary revascularisations with the associated complications. The NGCCT–ICA strategy had the lowest revascularisation-induced mortality and morbidity rates because only TPs are treated and the FNs who are not correctly diagnosed will not receive a revascularisation where they should have. The NGCCT-only strategy has the lowest overall mortality rate in the suspected population. The NGCCT-only strategy, as expected, had the lowest correct classification proportion.

Population with known coronary artery disease

The same results apply for the known CAD population; the ICA classifies 100% of patients correctly, the ICA strategy has the highest test mortality and morbidity rates and the NGCCT-only strategy has the highest revascularisation mortality and morbidity. However, in the known population the overall mortality and morbidity is lowest in the NGCCT–ICA strategy. ICA only has the highest overall mortality and morbidity rate.

TABLE 55 Intermediate outcomes: suspected CAD population

Strategy	Proportion correct classification	Misclassification		Mortality tests	Morbidity tests	Mortality revascularisation	Morbidity revascularisation
		FPs	FNs				
Obese							
ICA only	100.0	–	–	0.0007	0.0006	0.0003	0.0005
NGCCT–ICA	98.1	–	1.9	0.0002	0.0002	0.0002	0.0004
NGCCT only	91.8	6.3	1.9	–	–	0.0003	0.0006
Arrhythmias							
ICA only	100.0	–	–	0.0007	0.0006	0.0003	0.0005
NGCCT–ICA	99.5	–	0.5	0.0002	0.0002	0.0003	0.0005
NGCCT only	84.9	14.6	0.5	–	–	0.0005	0.0008
High coronary calcium score							
ICA only	100.0	–	–	0.0007	0.0006	0.0003	0.0005
NGCCT–ICA	98.5	–	1.5	0.0002	0.0002	0.0003	0.0004
NGCCT only	91.0	7.5	1.5	–	–	0.0004	0.0006
HHR							
ICA only	100.0	–	–	0.0007	0.0006	0.0003	0.0005
NGCCT–ICA	99.5	–	0.5	0.0002	0.0002	0.0003	0.0005
NGCCT only	88.6	11.0	0.5	–	–	0.0004	0.0007
Intolerance beta-blocker							
ICA only	100.0	–	–	0.0007	0.0006	0.0003	0.0005
NGCCT–ICA	99.5	–	0.5	0.0002	0.0002	0.0003	0.0005
NGCCT only	88.6	11.0	0.5	–	–	0.0004	0.0007

Costs per model

Table 57 shows the costs assigned to the patients in the diagnostic model, the EUROPA model, the YRM and costs from the stroke model per subgroup. The presented costs are after including the probabilities; adding the cost per model gives the total costs.

Population with suspected coronary artery disease

Most of the costs in the EUROPA model do not differ significantly between the three strategies. The difference in costs between the strategies is mainly due to the difference in the costs in the diagnostic model. The ICA-only strategy has the highest costs in the diagnostic model because the test itself is much more expensive than NGCCT. The impact of treating FPs unnecessary with a revascularisation in the NGCCT-only strategy is marginal because the proportion that receives a revascularisation is just 18%. The incremental cost induced due to radiation is lowest in the NGCCT-only strategy because the radiation dose is lowest in the NGCCT-only strategy. Also, not surprisingly, the costs in the stroke model are the highest for the ICA-only strategy due to the largest proportion having non-fatal complications of the initial ICA and revascularisations.

Population with known coronary artery disease

In the known population, the costs in the diagnostic model are still the highest for the ICA-only strategy. However, the NGCCT–ICA strategy instead of the NGCCT-only strategy has the lowest cost in the diagnostic model. This is different from the suspected CAD population because the treatment decision differs between the two models. The known FPs of the NGCCT-only strategy are always treated with a revascularisation with accompanying extra costs. In the suspected CAD

TABLE 56 Intermediate outcomes: known CAD population

Strategy	Proportion correct classification (%)	Misclassification (%)		Mortality tests	Morbidity tests	Mortality revascularisation	Morbidity revascularisation
		FPs	FNs				
Obese							
ICA only	100.0	–	–	0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	96.2	–	3.8	0.0001	0.0003	0.0027	0.0046
NGCCT only	91.4	4.8	3.8	–	–	0.0030	0.0052
Arrhythmias							
ICA only	100.0	–	–	0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	99.1	–	0.9	0.0002	0.0003	0.0029	0.0050
NGCCT only	88.0	11.1	0.9	–	–	0.0037	0.0064
High coronary calcium score							
ICA only	100.0	–	–	0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	97.1	–	2.9	0.0001	0.0003	0.0027	0.0047
NGCCT only	91.4	5.7	2.9	–	–	0.0032	0.0054
HHR							
ICA only	100.0	–	–	0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	99.1	–	0.9	0.0001	0.0003	0.0029	0.0050
NGCCT only	90.8	8.3	0.9	–	–	0.0035	0.0060
Intolerance to beta-blocker							
ICA only	100.0	–	–	0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	99.1	–	0.9	0.0001	0.0003	0.0029	0.0050
NGCCT only	90.8	8.3	0.9	–	–	0.0035	0.0060
Previous stent							
ICA only	100.0	–	–	0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	98.4	–	1.6	0.0002	0.0003	0.0028	0.0049
NGCCT only	87.3	11.1	1.6	–	–	0.0037	0.0063
Previous CABG							
ICA only	100.0	–	–	0.0007	0.0006	0.0030	0.0051
NGCCT–ICA	98.6	–	1.4	0.0001	0.0003	0.0028	0.0049
NGCCT only	90.7	7.9	1.4	–	–	0.0034	0.0059

population, only 18% of FPs receive a revascularisation and, as medication costs are modelled in the EUROPA model, it will lead to fewer costs for the FPs.

The same applies for the stroke model because the non-fatal complication rate of the NGGCT-only strategy in the known group is higher than that of the NGCCT–ICA strategy and in the suspected population the NGGCT-ICA has a higher non-fatal complication rate. The proportion of the suspected CAD population that receives a revascularisation after a positive test is 18%, and corresponding proportion in the known population is 100%, therefore the proportion that experience a stroke due to the revascularisation is higher in the known population.

Quality-adjusted life-years per model

Table 58 shows an overall QALY estimate and a separate QALY estimate per model for every strategy, subgroup and population. The presented QALYs are after including the probabilities;

TABLE 57 Costs per model (£)

Strategy	Diagnostic model		EUROPA model		YRM[a]		Stroke model		Total	
	Suspected	Known	Suspected	Known	Suspected	Known	Suspected	Known	Suspected	Known
Obese										
ICA only	1174	2867	5747	26,676	2.6	3.9	44	147	6968	29,694
NGCCT–ICA	568	2252	5709	26,806	2.3	3.8	18	116	6297	29,177
NGCCT only	405	2360	5686	26,776	1.7	3.0	13	116	6106	29,254
Arrhythmias										
ICA only	1175	2869	5569	24,436	2.8	4.4	39	119	6785	27,428
NGCCT–ICA	675	2450	5530	24,529	2.7	4.7	19	101	6227	27,084
NGCCT only	536	3115	5524	24,493	1.9	3.8	16	114	6077	27,726
HHR										
ICA only	1172	2866	6111	27,405	2.8	4.0	56	159	7342	30,434
NGCCT–ICA	640	2455	6089	27,484	2.7	4.3	26	136	6758	30,080
NGCCT only	484	2864	6089	27,463	1.9	3.4	20	146	6595	30,477
High coronary calcium score										
ICA only	1172	2867	5577	28,126	2.2	3.5	49	148	6801	31,145
NGCCT–ICA	591	2321	5528	28,216	2.0	3.6	21	120	6142	30,661
NGCCT only	430	2525	5515	28,188	1.5	2.8	15	123	5962	30,839
Intolerance to beta-blockers										
ICA only	1173	2869	5791	26,303	2.0	3.1	49	164	7016	29,339
NGCCT–ICA	643	2457	5763	26,371	1.9	3.3	23	141	6430	28,972
NGCCT only	485	2862	5775	26,339	1.4	2.6	18	150	6279	29,354
Previous stents										
ICA only	–	2868	–	25,443	–	4.1	–	136	–	28,450
NGCCT–ICA	–	2378	–	25,562	–	4.3	–	112	–	28,056
NGCCT only	–	3020	–	25,522	–	3.5	–	127	–	28,672
Previous CABG										
ICA only	–	2867	–	25,465	–	4.0	–	130	–	28,466
NGCCT–ICA	–	2405	–	25,570	–	4.1	–	109	–	28,088
NGCCT only	–	2892	–	25,540	–	3.3	–	118	–	28,554

a   Incremental costs compared with no exposure to radiation.

adding up the QALYs of the different models leads to the total QALYs per strategy. The YRM provides disutilities, as it induces QALY loss due to radiation.

Population with suspected coronary artery disease

In the EUROPA model the ICA-only strategy obtains, in every difficult-to-image patient group, the highest number of QALYs. This is because of the lower HRQoL FNs experienced in the NGCCT-only strategy and in the NGCCT–ICA strategy owing to lower sensitivity and specificity of the NGCCT. FNs do not occur in the ICA-only strategy; they will all be classified as TP with a higher HRQoL. The QALYs in the healthy population model are the lowest in the ICA-only population because the proportion of TNs is the lowest for this strategy. The NGCCT–ICA and NGCCT-only strategies have larger proportion in the TNs because less ICA-related mortality

TABLE 58 Quality-adjusted life-years per model

Strategy	EUROPA model		Healthy population model	YRM[a]		Stroke model		Total	
	Suspected	Known	Suspected	Suspected	Known	Suspected	Known	Suspected	Known
Obese									
ICA only	1.89	8.85	8.62	−0.0007	−0.0011	0.0025	0.0082	10.519	8.857
NGCCT–ICA	1.87	8.87	8.63	−0.0007	−0.0011	0.0010	0.0065	10.508	8.872
NGCCT only	1.87	8.86	8.63	−0.0005	−0.0009	0.0007	0.0065	10.508	8.869
Arrhythmias									
ICA only	1.67	6.54	7.78	−0.0008	−0.0013	0.0022	0.0068	9.448	6.545
NGCCT–ICA	1.63	6.58	7.79	−0.0008	−0.0014	0.0011	0.0058	9.419	6.588
NGCCT only	1.63	6.59	7.79	−0.0006	−0.0011	0.0009	0.0065	9.420	6.595
HHR									
ICA only	1.98	11.21	8.99	−0.0008	−0.0012	0.0030	0.0088	10.969	11.223
NGCCT–ICA	1.97	11.24	9.00	−0.0008	−0.0012	0.0014	0.0075	10.968	11.242
NGCCT only	1.97	11.23	9.00	−0.0006	−0.0010	0.0011	0.0080	10.967	11.233
High coronary calcium score									
ICA only	1.79	9.26	8.42	−0.0010	−0.0010	0.0027	0.0083	10.210	9.271
NGCCT–ICA	1.78	9.30	8.43	−0.0010	−0.0010	0.0011	0.0067	10.202	9.306
NGCCT only	1.78	9.30	8.43	−0.0008	−0.0008	0.0008	0.0069	10.201	9.301
Intolerance to beta-blockers									
ICA only	2.11	10.01	9.43	−0.0006	−0.0009	0.0027	0.0090	11.541	10.016
NGCCT–ICA	2.10	10.04	9.44	−0.0006	−0.0009	0.0012	0.0077	11.540	10.042
NGCCT only	2.10	10.03	9.44	−0.0004	−0.0007	0.0010	0.0083	11.542	10.039
Previous stents									
ICA only	–	8.72	–	–	−0.0012	–	0.0077	–	8.724
NGCCT–ICA	–	8.73	–	–	−0.0012	–	0.0063	–	8.737
NGCCT only	–	8.74	–	–	−0.0010	–	0.0072	–	8.744
Previous CABG									
ICA only	–	8.71	–	–	−0.0011	–	0.0074	–	8.719
NGCCT–ICA	–	8.72	–	–	−0.0012	–	0.0062	–	8.725
NGCCT only	–	8.72	–	–	−0.0010	–	0.0067	–	8.725

a　Incremental QALYs compared with no exposure to radiation.

occurs. *Table 19* shows the four test outcomes; the proportion that is modelled with the healthy population model is the sum of the proportions classified as TN and FP. The QALYs from the stroke model are highest in the ICA-only strategy because in this strategy the largest proportion of patients is modelled with this model due to the highest morbidity induced by the initial treatment and initial ICA.

Population with known coronary artery disease
In the known population there is little difference between the three strategies, as all test outcomes are modelled with the EUROPA model. In the known population, every patient has CAD and therefore the healthy population model is not used for this population. In all cases, the ICA only

has the lowest QALYs in the EUROPA model. This could be because ICA only has the largest overall mortality rate and therefore fewer people are modelled with the EUROPA model. The morbidity rate was the highest for the ICA-only strategy and therefore it accumulates the highest number of QALYs in the stroke model. The NGCCT–ICA strategy has the lowest morbidity rate and therefore it obtains fewer QALYs than the other strategies in the stroke model. More QALYs obtained in the stroke model can lead to less QALY gain in the EUROPA model; as the HRQoL in the stroke model is lower than in the EUROPA model, the higher complication rate of ICA is not favourable for the ICA-only strategy. The disutilities associated with the YRM are the largest (*Table 58* shows no difference between the first two strategies but this is due to rounding) for the ICA-only strategy owing to the higher radiation dose of the ICA compared with the NGCCT.

Cost-effectiveness

The aim of this assessment was to estimate the cost-effectiveness of the NGCCT in difficult-to-image patients for a suspected and for a known CAD population. ICERs are presented below for the suspected CAD population (see *Table 59*) and for the known CAD population (see *Table 60*). The cost-effectiveness is based on probabilistic modelling as the models are non-linear. After running the subgroup-specific probabilistic sensitivity analyses we combined them into one population by using each subgroup-specific costs and effects (mean and SE), the correlations between the costs and effects, and the relative frequencies of the subgroups. The uncertainty regarding these relative frequencies was included in the probabilistic analyses. The relative proportions were based on expert opinion, as described above (see *Proportions of patients in difficult-to-image subgroups* and *Table 53*).

Population with suspected coronary artery disease

Table 59 presents very small differences in QALYs; however, the ICA-only strategy is in general more effective than the other two strategies. In most subgroups, the NGCCT–ICA strategy achieves fewer QALYs than the other strategies. The ICA-only strategy is the most expensive strategy; the NGCCT-only strategy is cost saving compared with the other strategies. The negative incremental costs of the NGCCT-only strategy are due to the lower costs in the diagnostic model. The lower costs in the diagnostic model are the result of the large difference between the cost prices of the NGCCT and the ICA. After combining the results of the subgroups, we see that the NGCCT-only strategy might be considered the most attractive. The ICER of NGCCT–ICA compared with NGCCT only is so high (£71,000) that, given conventional willingness-to-pay threshold of £20,000–30,000, it is unlikely that commissioners of health care would consider this a cost-effective use of NHS resources.

Population with known coronary artery disease

In the known CAD population the cost-effectiveness differed by subgroup (*Table 60*). The NGCCT–ICA and the NGCCT-only strategies are, in all subgroups, more effective than the ICA-only strategy. In the subgroups obese, HCS, HHR, and beta-blocker intolerance, the NGCCT–ICA strategy dominated the other strategies, being more effective and of lower cost than the other two strategies. In all subgroups, the NGCCT–ICA strategy was less expensive than the other strategies. When results of the subgroups are combined, the most attractive strategy would be to perform a NGCCT with ICA; this scenario yields the highest cost saving, and dominates ICA only. The ICER of NGCCT only compared with NGCCT–ICA is so high (£726,230) that it is unlikely to be considered cost-effective, given conventional willingness-to-pay threshold of £20,000 to £30,000.

Sensitivity analyses

Probabilistic sensitivity analyses were performed to explore the robustness of the outcomes. The NGCCT accuracy parameters, the prior likelihood of CAD for both populations, treatment decisions, complication and mortality rates, cost of events, cost of radiation, disutilities due

TABLE 59 Cost-effectiveness: suspected CAD population (sorted by QALYs)

Strategy	Costs (£)		QALYs		iCosts	iQALYs	ICER
	Mean	SE	Mean	SE			
Obese							
NGCCT–ICA	6297	1237	10.508	0.167			
NGCCT only	6106	1202	10.508	0.167	−191	0.000	Dominates NGCCT–ICA
ICA only	6968	1217	10.519	0.163	862	0.011	81,318
Arrhythmias							
NGCCT–ICA	6227	1190	9.419	0.171			
NGCCT only	6077	1161	9.420	0.171	−150	0.000	Dominates NGCCT–ICA
ICA only	6785	1205	9.448	0.166	708	0.029	24,645
HHR							
NGCCT only	6595	1256	10.967	0.156			
NGCCT–ICA	6758	1289	10.968	0.157	162	0.001	312,047
ICA only	7342	1263	10.969	0.155	584	0.001	440,057
HCC							
NGCCT only	5962	1168	10.201	0.169			
NGCCT–ICA	6142	1248	10.202	0.169	180	0.001	205,536
ICA only	6801	1189	10.210	0.167	659	0.008	80,446
Intolerance to beta-blockers							
NGCCT–ICA	6430	1320	11.540	0.151			
ICA only	7016	1242	11.541	0.148	586	0.001	972,803
NGCCT only	6279	1240	11.542	0.151	−736	0.001	Dominant
Suspected overall							
NGCCT only	5808	573	10.588	0.109			
NGCCT–ICA	5950	589	10.590	0.109	142	0.002	71,000
ICA only	6534	572	10.597	0.107	584	0.007	83,429

to radiation, the QoL and transition rates in the disease progression model are varied in the sensitivity analysis. The test accuracy parameters of the ICA were not varied in the sensitivity analysis. Cost-effectiveness acceptability curves are presented in this section per population after combining the difficult-to-image subgroups into one population group. *Table 61* presents the distributions of the parameters. Subgroup-specific parameters such as sensitivity, specificity, etc., are presented for only the obese subgroup of the suspected CAD population.

The acceptability curves in *Figures 22* and *23* are in line with the base-case results presented in *Tables 59* and *60*. In the suspected population, in the range of thresholds of < £30,000, the NGCCT-only strategy has the highest probability of being cost-effective. Once thresholds are > £70,000, the three different strategies are equivalent. For the known CAD patients, the NGCCT–ICA strategy has the highest probability of being cost-effective, over the whole range of thresholds, while the ICA-only strategy has always the smallest probability of being cost-effective.

TABLE 60 Cost-effectiveness: known CAD population (sorted by QALYs)

Strategy	Costs (£)		QALYs		iCosts	iQALYs	ICER
	Mean	SE	Mean	SE			
Obese							
ICA only	29,694	928	8.857	0.464			
NGCCT only	29,254	924	8.869	0.477	−439	0.012	Dominates ICA only
NGCCT–ICA	29,177	920	8.872	0.460	−77	0.003	Dominant
Arrhythmias							
ICA only	27,428	908	6.545	0.504			
NGCCT–ICA	27,084	916	6.588	0.503	−344	0.043	Dominates ICA only
NGCCT only	27,726	971	6.595	0.499	642	0.007	90,683
HHR							
ICA only	30,434	1169	11.223	0.381			
NGCCT only	30,477	1190	11.233	0.377	43	0.011	4021
NGCCT–ICA	30,080	1184	11.242	0.378	−397	0.009	Dominant
HCS							
ICA only	31,145	1079	9.271	0.538			
NGCCT only	30,839	1103	9.301	0.533	−306	0.030	Dominates ICA only
NGCCT–ICA	30,661	1075	9.306	0.539	−178	0.005	Dominant
Intolerance to beta-blockers							
ICA only	29,339	986	10.016	0.392			
NGCCT only	29,354	1004	10.039	0.392	14	0.024	610
NGCCT–ICA	28,972	988	10.042	0.394	−381	0.003	Dominant
Previous stents							
ICA only	28,450	842	8.724	0.364			
NGCCT–ICA	28,056	855	8.737	0.358	−394	0.013	Dominates ICA only
NGCCT only	28,672	888	8.744	0.354	617	0.007	93,526
Previous CABG							
ICA only	28,466	844	8.719	0.363			
NGCCT–ICA	28,088	859	8.725	0.360	−378	0.006	Dominates ICA only
NGCCT only	28,554	1028	8.725	0.359	466	0.000	2,943,850
Known overall							
ICA only	28,234	502	9.516	0.288			
NGCCT–ICA	27,785	531	9.537	0.283	−449	0.022	Dominates ICA only
NGCCT only	28,228	498	9.538	0.286	443	0.001	726,230

Scenario analyses

Scenario analyses based on a probabilistic analysis were performed to estimate the influence of the cost price of the NGCCT, the prior likelihood of the CAD suspected population, and the influence of the complication rates on the cost-effectiveness. In the first two scenarios, the cost price of the NGCCT is fixed at £150 and at £207, respectively. All other parameters are varied as in the PSA. *Tables 62* and *63* show the results for the lower cost price of the NGCCT in both CAD populations for each subgroup. *Tables 64* and *65* present the results of the higher cost price.

The prior likelihood of the suspected population was increased to 0.3. *Table 66* presents the results of this scenario analysis.

TABLE 61 Parameters distributions

Parameter	Distribution	Mean	SE	Alpha	Beta
Logit of sensitivity (obese 0,904)	Normal	2.24	0.33		
Logit of specificity (obese 0,921)	Normal	2.46	0.19		
Prior likelihood of suspected CAD	Beta	0.2		20	80
Prior likelihood of known CAD	Beta	0.395		296	454
Proportion of patients receiving revascularisation (CAD-suspected population)	Beta	0.181		50	227
ICA mortality	Beta	0.0007		155	211,490
PCI mortality	Beta	0.0029		11	3849
CABG mortality	Beta	0.018		47	2552
ICA non-fatal complications	Beta	0.00064		136	211,509
PCI non-fatal complications	Beta	0.001		4	3856
CABG non-fatal complications	Beta	0.04		24	581
Proportion MI of non-fatal complications ICA	Beta	0.052		7	129
Proportion MI of non-fatal complications PCI	Beta	0.5		50	50
Proportion MI of non-fatal complications CABG	Beta	0.6		60	40
Transition probabilities (TP ICA-only suspected, obese)					
Risk equation 1: risk of first primary event	Logistic regression: Cholesky decomposition	0.0078			
Risk equation 2: odds that first event is fatal	Logit: Cholesky decomposition	0.2950			
Risk equation 3: risk of subsequent event in first year after initial NFE	Weibull regression: Cholesky decomposition	0.0272			
Risk equation 4: subsequent event after 1 year	Logit: Cholesky decomposition	0.0112			
Background costs	Regression: Cholesky decomposition				
YRM incremental costs (obese 26.5 mSv vs 0 mSv)	Normal	9.194	0.1305		
YRM incremental effects (obese 26.5 mSv vs 0 mSv)	Normal	−0.0026	0.000029		
Annual disutility due to MI or cardiac arrest	Normal	0.0409	0.0002		
Cost of events					
NFE	Ordinary least squares regression	11,805			
NFE history	Ordinary least squares regression	986			
CV fatal event	Ordinary least squares regression	3641			
Non-CV fatal event	Ordinary least squares regression	12,421			
QALYs disease progression model					
Population norms (male, 65–74 years)	Beta			388	109
After treatment QoL	Dirichlet				
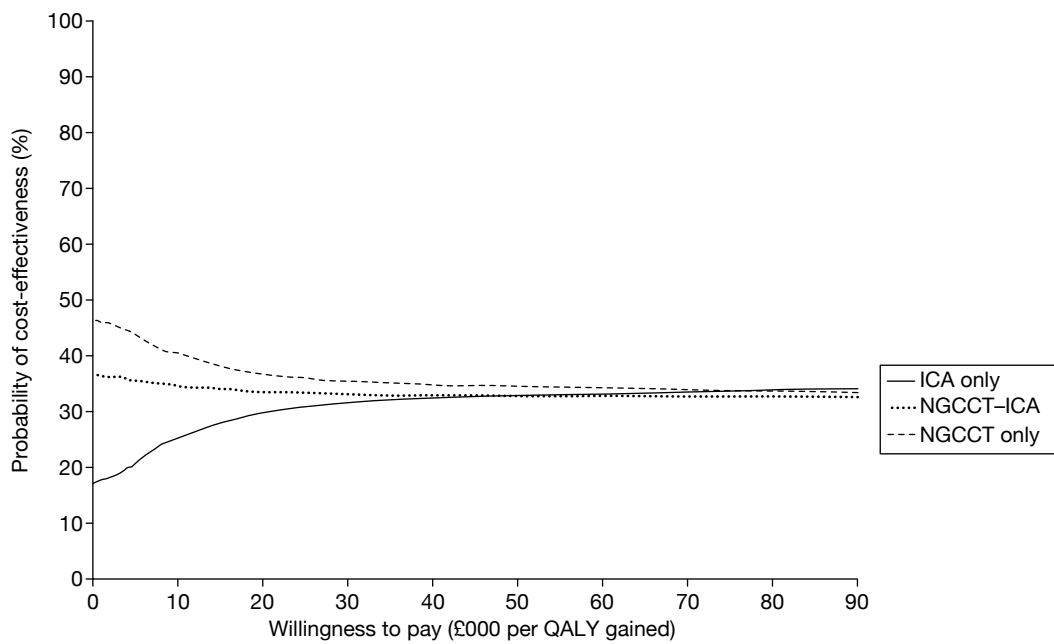
FIGURE 22 Suspected CAD population: CEAC.
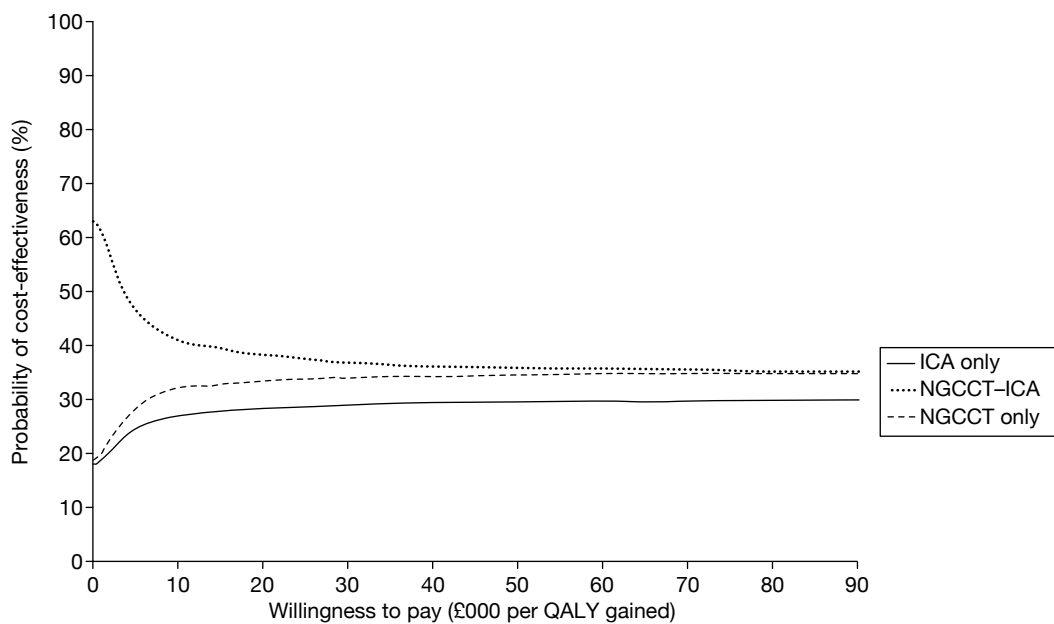
FIGURE 23 Known CAD population: CEAC.

Worst-case and best-case scenario analyses were performed to show the influence of the revascularisation and test complications on the cost-effectiveness. The influence of the rates on the cost-effectiveness in the suspected CAD population is shown below; see *Tables 67* and *68*.

Scenario analysis: new-generation cardiac computed tomography £150, coronary artery disease
A lower cost price means that the NGCCT–ICA and the NGCCT-only strategies become less expensive. The overall results do not change.

TABLE 62 Scenario analysis: NGCCT £150, CAD-suspected population

Strategy	Costs (£)		QALYs		iCosts	iQALYs	ICER
	Mean	SE	Mean	SE			
Obese							
NGCCT–ICA	6295	1191	10.507	0.165			
NGCCT only	6102	1157	10.510	0.166	−193	0.003	Dominates NGCCT–ICA
ICA only	6988	1169	10.516	0.160	886	0.006	145,092
Arrhythmias							
NGCCT only	6023	1160	9.421	0.172			
NGCCT–ICA	6172	1189	9.423	0.172	148	0.001	144,492
ICA only	6741	1205	9.449	0.168	569	0.027	21,258
HHR							
NGCCT–ICA	6771	1286	10.961	0.157			
NGCCT only	6604	1255	10.964	0.156	−167	0.003	Dominates NGCCT–ICA
ICA only	7372	1257	10.964	0.152	768	0.000	5,182,062
HCS							
NGCCT–ICA	6167	1220	10.199	0.170			
NGCCT only	5978	1156	10.199	0.170	−189	0.000	Dominates NGCCT–ICA
ICA only	6837	1172	10.206	0.169	859	0.007	123,267
Intolerance beta-blockers							
ICA only	6997	1203	11.544	0.150			
NGCCT–ICA	6374	1282	11.545	0.153	−624	0.001	Dominates ICA only
NGCCT only	6243	1191	11.545	0.151	−131	0.001	Dominant
Suspected overall							
NGCCT–ICA	5980	580	10.59	0.11			
NGCCT only	5819	559	10.59	0.11	−161	0.002	Dominates NGCCT–ICA
ICA only	6572	567	10.60	0.11	753	0.006	125,500

Scenario analysis: new-generation cardiac computed tomography £207, coronary artery disease

This scenario shows the impact of a higher NGCCT cost price on the cost-effectiveness. There is little change in the incremental costs, even when the cost of the NGCCT increases. In the suspected population the ICA-only strategy is still the most expensive strategy and NGCCT only the least expensive strategy. The higher price of the NGCCT led to a change in cost rank in the known CAD population. In the base case ICA only was the most expensive strategy but when the price is increased the NGCCT-only strategy is the most expensive strategy. Based on the ICER, for the suspected population NGCCT only remains the most favourable strategy, whereas for the known population the most favourable strategy remains NGCCT–ICA.

Scenario: prior likelihood, suspected population 0.3

'ICA only' is still the most expensive strategy and it gains the most QALYs. However, a higher prior likelihood leads to an increase in costs and a decrease in QALYs for all strategies. A higher prior likelihood means that more patients will have CAD and therefore more patients must be treated, which leads to higher costs. Furthermore, fewer patients will be modelled with the healthy population model resulting in a decrease in QALYs and more costs in the EUROPA model. With regards to the ICER, the NGCCT-only strategy remains the most favourable.

TABLE 63 Scenario analysis: NGCCT £150, known CAD population

Strategy	Costs (£)		QALYs		iCosts	iQALYs	ICER
	Mean	SE	Mean	SE			
Obese							
ICA only	29,705	930	8.853	0.463			
NGCCT–ICA	29,163	918	8.871	0.463	−542	0.019	Dominates ICA only
NGCCT only	29,241	920	8.877	0.459	78	0.006	13,597
Arrhythmias							
ICA only	27,453	888	6.560	0.505			
NGCCT only	27,085	899	6.591	0.507	−368	0.031	Dominates ICA only
NGCCT–ICA	27,729	947	6.603	0.488	644	0.012	52,655
HHR							
ICA only	30,458	1194	11.229	0.383			
NGCCT only	30,451	1181	11.251	0.372	−6	0.022	Dominates ICA only
NGCCT–ICA	30,056	1175	11.262	0.379	−395	0.010	Dominant
HCS							
ICA only	31,133	1073	9.276	0.531			
NGCCT–ICA	30,629	1074	9.308	0.539	−504	0.032	Dominates ICA only
NGCCT only	30,809	1081	9.314	0.530	179	0.006	29,531
Intolerance to beta-blockers							
ICA only	29,333	981	10.025	0.390			
NGCCT only	29,347	998	10.033	0.394	14	0.008	1640
NGCCT–ICA	28,972	982	10.034	0.394	−375	0.001	Dominant
Previous stent							
ICA only	28,454	843	8.725	0.364			
NGCCT only	28,664	875	8.727	0.361	210	0.001	147,862
NGCCT–ICA	28,043	845	8.729	0.357	−620	0.002	Dominant
Previous CABG							
ICA only	28,452	839	8.722	0.365			
NGCCT–ICA	28,051	847	8.733	0.361	−401	0.010	Dominates ICA only
NGCCT only	28,518	1030	8.735	0.374	468	0.003	166,672
Known overall							
ICA only	28,121	501	9.52	0.29			
NGCCT only	28,302	500	9.54	0.29	181	0.021	8748
NGCCT–ICA	27,818	499	9.55	0.29	−484	0.004	Dominant

Scenario analysis complication rates

In the best-case scenario (*Table 67*) for the NGCCT, the complication rates are set at the upper limit of the 95% CI. ICA only is still the most effective strategy. However, the incremental QALYs gained by the ICA-only strategy have become smaller in comparison with the base-case analysis. As the ICA induces more complications than the NGCCT, this scenario analysis can be seen as the best-case scenario for the NGCCT strategies.

TABLE 64 Scenario analysis: new-generation cardiac computed tomography £207, CAD-suspected population

Strategy	Costs (£)		QALYs		iCosts	iQALYs	ICER
	Mean	SE	Mean	SE			
Obese							
NGCCT only	6132	1195	10.509	0.171			
NGCCT–ICA	6319	1228	10.511	0.167	187	0.002	88,132
ICA only	6960	1209	10.516	0.165	641	0.005	129,189
Arrhythmias							
NGCCT only	6071	1178	9.418	0.175			
NGCCT–ICA	6221	1207	9.419	0.173	149	0.001	171,745
ICA only	6737	1216	9.445	0.168	517	0.026	19,545
HHR							
NGCCT–ICA	6828	1320	10.966	0.158			
ICA only	7372	1293	10.967	0.155	544	0.001	481,876
NGCCT only	6660	1286	10.968	0.157	–711	0.001	Dominant
HCS							
NGCCT–ICA	6189	1230	10.201	0.172			
NGCCT only	6004	1154	10.203	0.170	–185	0.002	Dominates NGCCT–ICA
ICA only	6804	1170	10.210	0.169	800	0.008	102,208
Intolerance beta-blockers							
NGCCT–ICA	6455	1298	11.541	0.150			
ICA only	7009	1217	11.542	0.149	554	0.000	6,278,463
NGCCT only	6312	1218	11.542	0.152	–697	0.000	Dominant
Suspected overall							
NGCCT–ICA	5979	591	10.586	0.109			
NGCCT only	5813	557	10.590	0.110	–166	0.004	Dominates NGCCT–ICA
ICA only	6519	578	10.593	0.109	706	0.003	235,333

In the worst-case scenario (*Table 68*) for the NGCCT, the complication rates are set at the lower limit of the 95% CI, the ICA-only strategy is the most effective strategy. The incremental QALYs gained by ICA only increased compared with the base-case analysis. When assessing the balance between costs and effects, in both scenarios NGCCT only remains the most favourable strategy.

Scenario analysis covariates used in risk equation for obese subgroup

A study by Oreopoulos *et al.*[106] examines the association between obesity and HRQoL in patients with CAD. It gives a good representation of an obese population with CAD (BMI of 25–30 kg/m², $n = 2310$; BMI of 30–35 kg/m², $n = 1331$; BMI of 35–40 kg/m², $n = 446$; BMI of > 40 kg/m², $n = 178$). The baseline characteristics that were found in the Oreopoulos *et al.* study[106] are similar to the baseline characteristics used in our model. The baseline characteristics in the model are based on the systematic review and on the EUROPA trial. Not all covariates for the risk equations are presented in the Oreopoulos *et al.* study[106] but gender, diabetes, existing vascular disease and

TABLE 65 Scenario analysis: NGCCT £207, known CAD population

Strategy	Costs (£)		QALYs		iCosts	iQALYs	ICER
	Mean	SE	Mean	SE			
Obese							
ICA only	29,710	935	8.847	0.471			
NGCCT–ICA	29,238	928	8.851	0.469	−471	0.004	Dominates ICA only
NGCCT only	29,309	928	8.870	0.463	70	0.019	3727
Arrhythmias							
ICA only	27,437	898	6.567	0.498			
NGCCT only	27,762	941	6.592	0.502	325	0.025	12,894
NGCCT–ICA	27,127	904	6.602	0.495	−635	0.010	Dominant
HHR							
ICA only	30,418	1161	11.226	0.379			
NGCCT–ICA	30,094	1157	11.248	0.377	−324	0.022	Dominates ICA only
NGCCT only	30,465	1174	11.249	0.378	371	0.001	295,660
HCS							
ICA only	31,132	1062	9.262	0.549			
NGCCT only	30,865	1084	9.302	0.545	−267	0.040	Dominates ICA only
NGCCT–ICA	30,685	1058	9.302	0.543	−181	0.000	Dominant
Intolerance to beta-blockers							
ICA only	29,346	998	10.013	0.401			
NGCCT–ICA	29,023	1005	10.033	0.398	−324	0.020	Dominates ICA only
NGCCT only	29,385	1014	10.046	0.387	362	0.014	26,423
Previous stent							
ICA only	28,461	843	8.727	0.359			
NGCCT only	28,729	884	8.729	0.360	268	0.003	100,271
NGCCT–ICA	28,103	854	8.739	0.354	−626	0.009	Dominant
Previous CABG							
ICA only	28,473	845	8.722	0.364			
NGCCT only	28,598	1025	8.734	0.357	125	0.012	10,450
NGCCT–ICA	28,117	851	8.744	0.367	−481	0.010	Dominant
Known overall							
ICA only	28,268	510	9.52	0.29			
NGCCT–ICA	27,920	494	9.54	0.28	−348	0.020	Dominates ICA only
NGCCT only	28,296	511	9.54	0.29	376	0.004	103,297

previous MI are presented. We have performed scenario analyses within the obese group to study the effect of changing these covariates. The baseline values used in the obese known subgroup are existing vascular disease (stroke, TIA and peripheral vascular disease) 9.8%, female 34.1%, previous MI 64.7% and diabetes milletus proportion 34.1%. These values were changed to the following: existing vascular disease 7.5% and 13.5%; female 30%; previous MI 50% and diabetes milletus proportion 60%. These analyses (results not shown) show that these changes have no impact on our conclusions.

TABLE 66 Scenario analysis: prior likelihood, suspected population 0.3

Strategy	Costs (£)		QALYs		iCosts	iQALYs	ICER
	Mean	SE	Mean	SE			
Obese							
NGCCT–ICA	9314.3	308.61	10.366	0.172			
NGCCT only	9028.2	301.17	10.37	0.1723	−286	0.004	Dominates NGCCT–ICA
ICA only	9927.5	327.33	10.388	0.1669	899	0.018	50,007
Arrhythmias							
NGCCT–ICA	9124.8	301.97	9.2579	0.1771			
NGCCT only	8895.4	307.44	9.2593	0.1773	−229	0.001	Dominates NGCCT–ICA
ICA only	9612.3	529.68	9.3023	0.1726	717	0.043	16,655
HHR							
NGCCT–ICA	10,036	326.32	10.828	0.1568			
NGCCT only	9786.7	330.37	10.83	0.1572	−249	0.002	Dominates NGCCT–ICA
ICA only	10,538	332.76	10.84	0.1544	752	0.009	80,684
HCS							
NGCCT only	8839.8	303.35	10.036	0.1776			
NGCCT–ICA	9111.6	546.38	10.039	0.1771	272	0.003	82,843
ICA only	9706	317.08	10.056	0.1711	594	0.017	34,761
Intolerance to beta-blockers							
NGCCT–ICA	9453.2	639.39	11.413	0.1482			
NGCCT only	9238	332.08	11.418	0.1503	−215	0.005	Dominates NGCCT–ICA
ICA only	9984.8	344.16	11.419	0.1457	747	0.000	5,935,679
Suspected overall							
NGCCT only	9061	172	10.44	0.11			
NGCCT–ICA	9355	232	10.44	0.11	294	0.001	294,000
ICA only	9790	182	10.46	0.11	435	0.015	29,000

TABLE 67 Best-case scenario analysis: upper limit complication rates in suspected CAD population

Strategy	Costs (£)		QALYs		iCosts	iQALYs	ICER
	Mean	SE	Mean	SE			
Obese							
NGCCT–ICA	6288	1207	10.503	0.167			
NGCCT only	6097	1174	10.505	0.166	−192	0.002	Dominates NGCCT–ICA
ICA only	6965	1191	10.512	0.164	868	0.006	138,953
Arrhythmias							
NGCCT only	6051	1144	9.420	0.174			
NGCCT–ICA	6199	1170	9.423	0.174	147	0.003	52,093
ICA only	6746	1184	9.448	0.168	547	0.025	22,017
HHR							
ICA only	7373	1256	10.962	0.154			
NGCCT–ICA	6785	1285	10.963	0.156	−587	0.001	Dominates ICA only
NGCCT only	6619	1249	10.963	0.156	−166	0.000	Dominant

continued

TABLE 67 Best-case scenario analysis: upper limit complication rates in suspected CAD population (*continued*)

Strategy	Costs (£) Mean	SE	QALYs Mean	SE	iCosts	iQALYs	ICER
High coronary calcium score							
NGCCT–ICA	6167	1221	10.196	0.171			
NGCCT only	5983	1146	10.197	0.172	−184	0.001	Dominates NGCCT–ICA
ICA only	6823	1161	10.203	0.167	841	0.006	141,072
Intolerance to beta-blockers							
ICA only	7001	1200	11.539	0.150			
NGCCT–ICA	6401	1279	11.540	0.152	−601	0.001	Dominates ICA only
NGCCT only	6266	1202	11.541	0.153	−135	0.001	Dominant
Suspected overall							
NGCCT only	5795	553	10.585	0.109			
NGCCT–ICA	5962	576	10.587	0.111	167	0.002	83,500
ICA only	6547	565	10.591	0.108	585	0.004	146,250

TABLE 68 Worst-case scenario analysis: lower limit complication rates in suspected CAD

Strategy	Costs (£) Mean	SE	QALYs Mean	SE	iCosts	iQALYs	ICER
Obese							
NGCCT–ICA	6285	1225	10.514	0.163			
NGCCT only	6093	1191	10.515	0.163	−192	0.001	Dominates NGCCT–ICA
ICA only	6957	1208	10.522	0.160	864	0.007	122,501
Arrhythmias							
NGCCT only	6050	1148	9.426	0.174			
NGCCT–ICA	6200	1176	9.426	0.175	150	0.001	290,135
ICA only	6745	1183	9.455	0.168	545	0.029	18,689
HHR							
NGCCT–ICA	6811	1297	10.967	0.158			
NGCCT only	6645	1267	10.968	0.158	−166	0.001	Dominates NGCCT–ICA
ICA only	7389	1269	10.970	0.155	744	0.002	366,638
High coronary calcium score							
NGCCT only	5991	1152	10.199	0.171			
NGCCT–ICA	6175	1220	10.200	0.171	184	0.000	512,161
ICA only	6824	1164	10.210	0.166	649	0.011	60,086
Intolerance to beta-blockers							
NGCCT–ICA	6406	1284	11.545	0.151			
NGCCT only	6272	1204	11.545	0.149	−134	0.000	Dominates NGCCT–ICA
ICA only	7002	1207	11.546	0.148	730	0.001	583,943
Suspected overall							
NGCCT–ICA	5992	586	10.590	0.110			
NGCCT only	5800	557	10.591	0.108	−192	0.001	Dominates NGCCT–ICA
ICA only	6579	571	10.600	0.106	779	0.009	86,556

Cost-effectiveness of new-generation cardiac computed tomography in congenital heart disease

Model structure

The main model structure of the YRM for patients with congenital heart disease is identical to the structure discussed in detail above (see *York Radiation Model*). For the patients with congenital heart disease a number of scenario analyses were conducted, for example varying the age of cancer incidence. These are variations only in key parameters, not in the model structure. Further details are provided below. Regarding the potentially repetitive nature of the imaging in patients with congenital heart disease, experts emphasised that, owing to radiation exposure considerations, these patients are mostly imaged with echocardiography and MRI. We therefore assumed that the NGCCT would be used in a single instance for treatment planning, rather than for ongoing monitoring.

Model parameters

Base case

In the base case for patients with congenital heart disease, the key parameters of the YRM (i.e. utility, costs per scan, probability of cancer incidence given radiation, and cancers models) remain the same as for patients with CAD. The only difference is in the radiation doses for patients with congenital heart disease. These were based on an expert opinion, accounting for the particular diagnostic circumstances of patients with congenital heart disease (*Table 69*). We used these results to define five different age groups: 1-year-olds (infants), 5- to 10-year-olds (young children) and 25- to 35-year-olds (adults).

Patients with congenital heart disease can suffer from a range of cyanotic or non-cyanotic heart diseases. The timing of diagnosis and treatment and, hence, the use of a CT, depends on the particular lesion in question, but in most cases occurs in the first years of life. Depending on the lesion, further investigations and treatment might be necessary later in life. For aortic arch abnormalities (double aortic arch, vascular ring), for example a CT is undertaken at the time of diagnosis, usually in the first year of life. Similarly, for pulmonary atresia with MAPCAs either echocardiography, followed by cardiac catheterisation with invasive angiography or cross-sectional imaging (MRI or CT), is carried out in the first year of life and then again as required but often at the age of 2 or 3 years; for total anomalous pulmonary venous drainage/scimitar, echocardiography followed by cross-sectional imaging (MRI or CT) is undertaken at time of diagnosis and often again immediately before surgery (age 2–3 years). For lesions with both a vascular and airway component a CT may be carried out at diagnosis, which is usually soon after birth. In some cases, where a lesion has been previously treated using stents or pacemakers, MRI is unsuitable and patients require the use of CT when clinically indicated.

No clear evidence exists on to what extent NGCCT reduces the radiation dose at each scan. The general, NGCCT favourable assumption, based on information from one expert (see *Appendix 7*) was to assume a reduction of 50% compared with standard 64-slice CT.

TABLE 69 Radiations dose (baseline and range) for diagnosis in patients with congenital heart disease with a CT scan based on disease-specific expert reply (in millisieverts)

Age group	CT64	NGCCT
Very small children	1.6 (1–4)	0.8 (0.5–2)
Medium-sized children	3 (1–8)	1.5 (0.5–4)
Adults	6 (4–25)	3 (1–12)

Scenario analysis

In the scenario analyses a number of key parameters for patients with congenital heart disease were varied. These were (a) using the minimum radiation dose, (b) the maximum radiation dose, (c) an earlier age at cancer diagnosis, and (d) using the Biological Effects of Ionizing Radiation (BEIR) model for the effects of radiation on cancer incidence. Lastly, we ran (e) a scenario combining the least favourable assumption for the comparator, i.e. an *NGCCT-friendly* scenario that uses maximum radiation dose for a 64-slice CT scan, early onset of cancer, and the BEIR cancer radiation model.

The values for the (a) minimum and (b) maximum scenarios were based on the data shown in *Table 64*. The values for (c), the earlier age at cancer incidence scenario, were taken from the cancer model in the YRM.[61] The earlier age with the corresponding disease costs and remaining QALYs is shown in *Table 70*. Note that for the age group of patients with congenital heart disease (age at exposure < 40 years), the YRM takes the incidence age of 40 years for breast cancer by default. The values for the BEIR model (*Table 71*) were published by the National Research Council for a 1999 US population.[107] The BEIR study developed a more conservative risk model to estimate the relationship between exposure to ionising radiation and harmful health effects, primarily based on the cancer incidence data from the Life Span Study for the period 1958–98 and based on Dosimetry System 2002 (DSO2) dosimetry data.[61]

For all of the scenarios, the uncertainty in the costs and remaining QALYs of the cancer module are modelled via a PSA. The values for this are shown in *Table 46*. For prostate cancer no data for the uncertainty exists. In addition, we varied for all scenarios (including the base case) the price of a 64-slice CT scan; the alternative value is shown in *Table 72*.

Base-case results

Table 73 shows the intermediate result of the probability of lifetime cancer incidence for a given patient, group for the average radiation dose and the ranges as given by expert survey (HPA radiation/cancer model, assuming 50% male patients). The probability depends on overall radiation dose and age at exposure. *Table 74* shows the absolute QALYs for each age group by

TABLE 70 Mean total costs and mean QALYs lost due to cancer, discounted at 3.5% per annum to age at cancer diagnosis assuming an early age at cancer incidence

Cancer	Age at diagnosis (years)	Costs of cancer (£)	QALYs lost due to cancer
Lung	55	22,331	1.2145
Colorectal	55	14,321	3.8124
Prostate	55	12,389	2.6152

TABLE 71 Probability for lifetime incidence of cancer for an exposure to 10 mSv according to the BEIR model for age groups indicated for NGCCT[61]

Age at exposure (years)	Risk of all cancers (for exposure to 10 mSv)	
	Male	Female
1	0.002414	0.004497
5	0.001816	0.003377
10	0.001445	0.002611
25	0.000832	0.001356
35	0.000667	0.000976
60	0.000489	0.000586

TABLE 72 Cost per scan for 64-slice CT in scenario analysis

Strategy	Costs per scan (£)
64-slice CT	105.55

TABLE 73 Probability of lifetime cancer for different ages in the base-case scenario for patients with congenital heart disease

Age (years)	64-slice CT	NGCCT	Difference
1	0.00018	0.00000908	0.0000907
5	0.00034	0.00017	0.0001702
10	0.000269	0.000135	0.0001345
25	0.000425	0.000213	0.0002127
35	0.000347	0.000174	0.0001737

TABLE 74 Absolute QALYs for both strategies in the base-case scenario for congenital heart disease (SD in parenthesis)

Age (years)	64-slice CT	NGCCT	Difference
1	24.696847 (0.000007)	24.696918 (0.000003)	−0.000071
5	24.377658 (0.000014)	24.377807 (0.000007)	−0.000149
10	23.911911 (0.000012)	23.912049 (0.000006)	−0.000138
25	21.930976 (0.000032)	21.931331 (0.000016)	−0.000355
35	20.042644 (0.000035)	20.043041 (0.000016)	−0.000397

scanner type. NGCCT leads to higher overall QALYs because of the lower probability of cancer. The number of patients needed to be scanned in each age group to gain 1 QALY (in absolute terms) is shown in *Table 75*.

The costs caused by radiation-attributable cancer are shown in *Table 76*. *Table 77* shows the maximum admissible cost that makes an NGCCT cost-effective, only accounting for the costs of radiation-induced cancer, for two different threshold values, i.e. a willingness to pay per gained QALY of £20,000 or £30,000, respectively. *Table 78* shows the ICERS for the base-case scenario using two different costs for a 64-slice CT scan (£132.66 and £105.55, respectively); the price for the NGCCT is identical in both cases.

Sensitivity analysis and scenario analysis results

In this section the results for the sensitivity analysis and different scenario analysis are presented. In the sensitivity analysis the inputs for the age at cancer incidence, expected disease costs and the expected remaining QALYs are varied (for details see *Table 46*). The key parameters for the scenario analysis are outlined above.

Table 79 shows the intermediate results of the probability of lifetime cancer incidence given radiation dose and age at exposure for the five patient groups using the BEIR model, and assuming 50% male patients.

Sensitivity analysis

In *Figure 24* the cost-effectiveness plane for the five different age groups of the base-case scenario is shown. The sensitivity analysis accounts for the uncertainty of the mean age of incidence,

TABLE 75 Number of patients needed to scan (NGGCT) to gain 1 QALY, compared with 64-slice CT, in the base-case scenario

Age (years)	Difference in QALYs between NGCCT and CT64	No. of patients to be scanned
1	−0.000071	14,085
5	−0.00015	6711
10	−0.00014	7246
25	−0.00036	2817
35	−0.0004	2519

TABLE 76 Mean absolute radiation-induced cancer costs (£) of base case for patients with congenital heart disease (SD in parentheses)

Age (years)	CT64	NGCCT	Difference
1	0.42 (0.002873076)	0.21 (0.001513261)	0.21
5	0.89 (0.006429484)	0.45 (0.003215453)	0.44
10	0.83 (0.005951270)	0.41 (0.003132579)	0.42
25	2.15 (0.016340907)	1.07 (0.008268757)	1.08
35	2.41 (0.020106730)	1.20 (0.010022409)	1.21

SD, standard deviation.

TABLE 77 Threshold analysis showing the maximal additional price per patient that is admissible to make a NGCCT scan cost-effective

| Age (years)	Threshold value (£)	
	20,000	30,000
1	1.62	2.32
5	3.43	4.92
10	3.18	4.56
25	8.16	11.70
35	9.13	13.10

TABLE 78 Incremental cost-effectiveness ratio for base-case scenario (cost per NGCCT scan: £169.26)

Age (years)	ICER, price per CT64 scan	
	£133	£106
1	521,377	908,786
5	244,196	426,830
10	266,617	465,842
25	100,351	176,730
35	90,088	158,905

TABLE 79 Probability of lifetime cancer for different ages (BEIR radiation-cancer model)

Age (years)	CT64	NGCCT	Difference
1	0.0005528	0.0002764	0.000276
5	0.000779	0.0003895	0.00039
10	0.0006084	0.0003042	0.000304
25	0.0006561	0.0003281	0.000328
35	0.0004928	0.0002464	0.000246
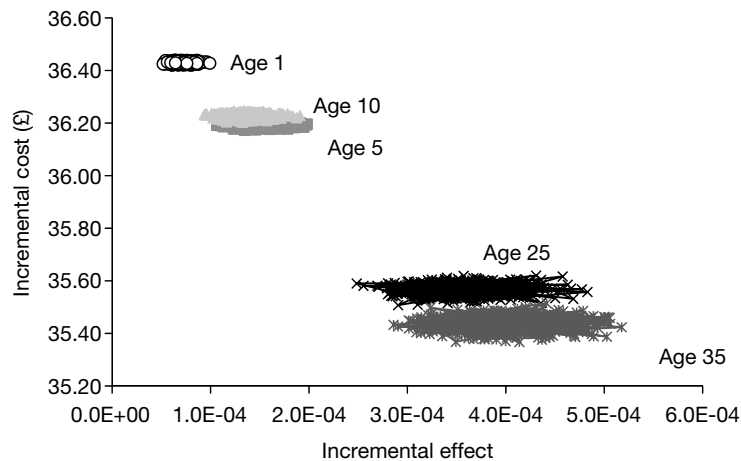
FIGURE 24 Cost-effectiveness plane for PSA of base-case scenario for five different age groups (note: origin not included).

disease cost of cancer, and remaining QALYs in the YRM cancer module. In *Table 80,* selected summary statistics of the outcome distribution of the PSA are shown.

Scenario analysis

In this section the results of the five different scenario analyses are shown. These were (a) using the minimum radiation dose, (b) the maximum radiation dose, (c) an earlier age at cancer diagnosis and (d) using the BEIR model for the effects of radiation on cancer incidence. Lastly, we ran (e) a scenario combining the least favourable assumption for the comparator, i.e. an *NGCCT-friendly* scenario that uses maximum radiation dose for a 64-slice CT scan, early onset of cancer, and the BEIR cancer-radiation model.

Tables 81 and *82* show the disease in the costs of radiation-induced cancer and the expected absolute QALYs for each age group in the five different scenario analyses. The corresponding differences are reported in *Tables 83* and *84*.

Tables 85 and *86* show the maximum admissible cost that makes an NGCCT cost-effective for two different threshold values, i.e. a willingness to pay per gained QALY £20,000 or £30,000, respectively. *Tables 87* and *88* report the ICERs for the scenario analyses in each age group, for a 64-slice CT price of £132.62 and £105.55, respectively.

TABLE 80 Summary statistic of the distribution of the incremental effects, the incremental costs, and the ICER of the PSA in the base-case scenarios

	Age (years)																
	1			5			10			25			35				
	Inc. effects	Inc. costs (£)	ICER (£)	Inc. effects	Inc. costs (£)	ICER (£)	Inc. effects	Inc. costs (£)	ICER	Inc. effects (£)	Inc. costs	ICER (£)	Inc. effects	Inc. costs (£)	ICER (£)		
Mean	0.000071	36.37	521,377	0.000150	36.16	244,196	0.000137	36.19	266,617	0.000357	35.53	100,351	0.000396	35.40	90,088		
SD	0.000008	1.31	56,292	0.000016	1.14	26,507	0.000014	1.14	28,460	0.000036	1.12	10,101	0.000039	1.12	8940		
Median	0.000070	36.43	519,204	0.000148	36.19	243,816	0.000137	36.23	264,819	0.000357	35.57	99,765	0.000395	35.44	89,765		
2.5th percentile	0.000057	36.42	425,904	0.000121	36.18	198,225	0.000111	36.21	220,195	0.000290	35.53	83,231	0.000324	35.39	74,202		
97.5th percentile	0.000085	36.44	640,876	0.000182	36.21	298,016	0.000164	36.24	324,597	0.000427	35.60	122,568	0.000477	35.48	108,808		
Minimum	0.000007	0.00	54,377	0.000016	0.01	25,622	0.000014	0.01	27,425	0.000034	0.02	9698	0.000037	0.02	8570		
Maximum	0.000099	36.44	708,734	0.000198	36.22	342,328	0.000190	36.25	388,872	0.000483	35.62	143,456	0.000517	35.51	124,102		

Inc., incremental; SD, standard deviation.

TABLE 81 Absolute radiation-induced cancer costs for scenario analysis in GBP

Age (years)	(a) Minimum		(b) Maximum		(c) Early cancer		(d) BEIR model		(e) NGCCT friendly	
	CT64	NGCCT	CT64	NGCCT	CT64	NGCCT	CT64	NGCCT	CT64	NGCCT
1	0.37 (0.00339)	0.18 (0.00163)	1.46 (0.01365)	0.73 (0.00701)	0.59 (0.00533)	0.29 (0.00278)	1.35 (0.008707)	0.67 (0.004586)	4.57 (0.039829)	2.28 (0.020124)
5	0.42 (0.00405)	0.21 (0.00200)	3.35 (0.03124)	1.67 (0.01585)	1.25 (0.01217)	0.63 (0.00566)	2.16 (0.014509)	1.08 (0.006838)	7.85 (0.067654)	3.92 (0.033607)
10	0.39 (0.00379)	0.20 (0.00188)	3.13 (0.03076)	1.56 (0.01484)	1.17 (0.01135)	0.59 (0.00576)	1.97 (0.013421)	0.99 (0.006649)	7.24 (0.064880)	3.62 (0.033030)
25	2.06 (0.01986)	1.03 (0.01018)	12.87 (0.12919)	6.44 (0.06335)	3.09 (0.03095)	1.54 (0.01509)	3.43 (0.024985)	1.72 (0.012502)	20.16 (0.190711)	10.08 (0.094329)
35	2.35 (0.02469)	1.18 (0.01215)	14.70 (0.15442)	7.35 (0.07540)	3.53 (0.03579)	1.76 (0.01790)	3.49 (0.028303)	1.74 (0.013855)	21.04 (0.212029)	10.52 (0.106989)

TABLE 82 Absolute QALYs for the five different age groups in the scenario analysis

Age (years)	(a) Minimum		(b) Maximum		(c) Early cancer		(d) BEIR model		(e) NGCCT friendly	
	CT64	NGCCT	CT64	NGCCT	CT64	NGCCT	CT64	NGCCT	CT64	NGCCT
1	24.6337635 (0.0000041)	24.6338588 (0.0000022)	24.6331895 (0.0000172)	24.6335726 (0.0000088)	24.6336489 (0.0000069)	24.6338016 (0.0000034)	24.696526 (0.000024)	24.696758 (0.000012)	24.631637 (0.000061)	24.632797 (0.000029)
5	24.3045185 (0.0000047)	24.3046284 (0.0000024)	24.3029834 (0.0000374)	24.3038604 (0.0000188)	24.3040802 (0.0000139)	24.3044091 (0.0000072)	24.377222 (0.000038)	24.377589 (0.000019)	24.300726 (0.000100)	24.302736 (0.000049)
10	23.8239917 (0.0000042)	23.8240945 (0.0000021)	23.8225465 (0.0000334)	23.8233723 (0.0000168)	23.8235788 (0.0000131)	23.8238886 (0.0000063)	23.911517 (0.000033)	23.911853 (0.000016)	23.820483 (0.000089)	23.822340 (0.000043)
25	21.7794578 (0.0000225)	21.7800067 (0.0000107)	21.7737154 (0.0001281)	21.7771307 (0.0000656)	21.7789115 (0.0000314)	21.7797323 (0.0000157)	21.930540 (0.000056)	21.931112 (0.000027)	21.770003 (0.000222)	21.775281 (0.000115)
35	19.8228249 (0.0000219)	19.8234595 (0.0000113)	19.8161715 (0.0001418)	19.8201349 (0.0000692)	19.8221934 (0.0000330)	19.8231420 (0.0000165)	20.042283 (0.000050)	20.042860 (0.000025)	19.812870 (0.000212)	19.818485 (0.000101)

TABLE 83 Differences in absolute radiation-induced cancer costs for scenario analysis between CT64 and NGCCT

| Age (years) | Costs (£) | | | | |
	(a) Minimum	(b) Maximum	(c) Early cancer	(d) BEIR model	(e) NGCCT friendly
1	−0.19	−0.73	−0.30	−0.68	−2.29
5	−0.21	−1.68	−0.62	−1.08	−3.93
10	−0.19	−1.57	−0.58	−0.98	−3.62
25	−1.03	−6.43	−1.55	−1.71	−10.08
35	−1.17	−7.35	−1.77	−1.75	−10.52

TABLE 84 Differences in absolute QALYs between CT64 and NGCCT

Age (years)	(a) Minimum	(b) Maximum	(c) Early cancer	(d) BEIR model	(e) NGCCT friendly
1	0.000095	0.000383	0.000153	0.000232	0.001160
5	0.000110	0.000877	0.000329	0.000367	0.002010
10	0.000103	0.000826	0.000310	0.000336	0.001857
25	0.000549	0.003415	0.000821	0.000572	0.005278
35	0.000635	0.003963	0.000949	0.000577	0.005615

TABLE 85 Threshold analysis showing the maximal additional price per patient that is admissible to make a NGCCT scan cost-effective at a willingness to pay of £20,000 for scenario analysis

| Age (years) | Cost £) | | | | |
	(a) Minimum	(b) Maximum	(c) Early cancer	(d) BEIR model	(e) NGCCT friendly
1	1.01	4.02	3.35	5.32	25.47
5	3.43	9.11	7.21	8.43	44.13
10	3.18	8.44	6.78	7.69	40.76
25	8.16	34.35	17.96	13.16	115.66
35	9.13	37.90	20.74	13.28	122.82

TABLE 86 Threshold analysis showing the maximal additional price per patient that is admissible to make a NGCCT scan cost-effective at a willingness to pay of £30,000 for scenario analysis

| Age (years) | (a) Minimum | (b) Maximum | (c) Early cancer | (d) BEIR model | (e) Benign |
	CT64	CT64	CT64	CT64	CT64
1	1.45	5.77	4.87	7.64	37.07
5	1.64	13.07	10.49	12.11	64.24
10	1.53	12.11	9.88	11.04	59.33
25	7.87	49.28	26.17	18.89	168.44
35	8.71	54.34	30.22	19.05	178.97

TABLE 87 Incremental cost-effectiveness ratio (£ per QALY gained) for scenario analysis with cost per NGCCT scan: £169.26 and cost per CT64 scan £132.62

Age (years)	(a) Minimum	(b) Maximum	(c) Early cancer	(d) BEIR model	(e) NGCCT friendly
1	785,466	194,919	224,93	154,879	27,907
5	692,360	84,492	103,409	96,738	15,279
10	745,225	91,383	109,900	106,332	16,705
25	142,272	20,197	40,323	61,025	4653
35	128,361	18,018	34,658	60,489	4297

TABLE 88 Incremental cost-effectiveness ratio for scenario analysis with cost per NGCCT scan: £169.26 and cost per CT64 scan £105.55

Age (years)	(a) Minimum	(b) Maximum	(c) Early cancer	(d) BEIR model	(e) NGCCT friendly
1	1,447,128	361,003	415,310	271,448	52,980
5	1,275,892	157,915	191,792	170,375	29,738
10	1,373,115	170,589	203,716	187,061	32,361
25	264,186	39,659	75,742	108,327	10,160
35	238,635	35,695	65,303	107,413	9474

Only in the NGCCT-friendly scenario do the ICERs decrease significantly, ranging from £28,000 per QALY gained for the youngest patients to £4300 per QALY gained for the adult patients. Looking at *Tables 83* and *84*, it is clear that of all key parameters, setting the radiation dose to the maximum of the range given by the expert has the highest impact on the cancer-related costs to be saved and QALYs to be gained. However, this upper value of the range of 25 mSv should be regarded with caution. It is very likely that the expert has implied a range of values ever used in his/her patient population, and it is very unlikely that it was implied that the *average* dosage could range from 4 to 25 mSv. The fact that for all other scenarios the ICER remains > £30,000 indicates that, even with the uncertainty about the various assumptions in mind, it can reasonably be concluded that the use of NGCCT instead of 64-slice CT in order to reduce radiation exposure is not cost-effective in this patient group.

Summary

In this chapter, we assessed the cost-effectiveness of NGCCT in two different populations (*Table 89*). The first is the comparison of NGCCT compared with ICA in difficult-to-image CAD patients and the second is the comparison of NGCCT compared with 64-slice CT in patients with congenital heart disease.

The CAD population was divided into two subpopulations: the suspected CAD population and the known CAD population. Patients suspected of CAD are patients who have chest pain or other symptoms suggestive of CAD. Patients with known CAD are patients who have previously been diagnosed with CAD and whose symptoms are no longer controlled by drug treatment and/or being considered for revascularisation. The use of NGCCT has different purposes in the two CAD populations: for the suspected CAD population the purpose is to diagnose patients with CAD and for the known CAD population the purpose is to aid decision-making regarding a revascularisation.

TABLE 89 Summary baseline cost-effectiveness

Strategy	Costs (£)	QALYs	iCosts	iQALYs	ICER
Suspected CAD					
NGCCT only	5808	10.588			
NGCCT–ICA	5950	10.590	142	0.002	71,000
ICA only	6534	10.597	584	0.007	83,429
Known					
ICA only	28,234	9.516			
NGCCT–ICA	27,785	9.537	−449	0.022	Dominates ICA only
NGCCT only	28,228	9.538	443	0.001	726,230

For the CAD population, five different models were combined to estimate the cost-effectiveness of the NGCCT:

1. a decision tree that models the diagnostic pathway
2. an alive–dead Markov model for 'healthy' patients without CAD[65]
3. a stroke model to estimate the impact of test and treatment-related stroke
4. a model for the prognosis of patients with CAD (the EUROPA model)[69]
5. a model to assess the impact of imaging due to radiation on cancer morbidity and mortality.[61]

The last of these five models, the YRM, was also used to assess the cost-effectiveness of the use of NGCCT to lower radiation exposure in patients with congenital heart disease.

The health economic analysis of the use of NGCCT in difficult-to-image patients with CAD showed that the use of NGCCT instead of invasive CA may be considered cost-effective. In patients with suspected CAD, the NGCCT-only strategy might be considered the most attractive. The ICER of NGCCT–ICA compared with NGCCT only is so high (£71,000) that it is unlikely to be considered cost-effective, given a conventional willingness-to-pay threshold of £20,000 to £30,000. In patients with known CAD, the most attractive strategy would be to perform a NGCCT with ICA; this scenario yields the highest cost saving and dominates ICA only. The ICER of NGCCT only compared with NGCCT–ICA is so high (£726,230) that it is unlikely to be considered cost-effective.

When taking uncertainty into account, these findings are confirmed. In the suspected population, in the range of thresholds of < £70,000, the NGCCT-only strategy has the highest probability of being cost-effective. For thresholds above £70,000, the three different strategies are more or less equivalent. For the patients with known CAD, the NGCCT–ICA strategy has the highest probability of being cost-effective, over the whole range of thresholds, whereas the ICA-only strategy has always the smallest probability of being cost-effective.

The key drivers behind these results are the percentage of patients being misclassified (as a results of test accuracy data and prevalence of disease) and the complication rate for ICA and revascularisation (see *Table 55*). In the ICA-only strategy, all patients are at risk for ICA-induced morbidity and mortality, whereas the TPs are also at risk for the revascularisation-induced

morbidity and mortality. In the NGCCT-only strategy, misclassification leads to FPs who undergo unnecessary revascularisations with the associated complications, whereas ICA complications cannot occur. Overall, in the population of suspected CAD, the NGCCT-only strategy has the lowest overall mortality rate – less than half of that of ICA only. To some extent, the same results apply for the known CAD population; here the overall mortality and morbidity is lowest in the NGCCT–ICA strategy. ICA only has the highest overall mortality and morbidity rate, regardless of the population.

As noted previously, it is important to realise that the percentage of patients being misclassified is a function of both diagnostic accuracy and the prior likelihood. If the prior likelihood increases, the percentage of FNs also increases while the percentage of FPs decreases. This explains to some extent why the results for the suspected CAD population are slightly different than for the known CAD population, even though for both populations the same accuracy was assumed.

Currently, there is uncertainty about the estimate of the cost price of a NGCCT scan, as we had to make various assumptions. Therefore, we performed a scenario analysis changing this cost price to £207 per scan, and this did not alter our conclusions.

The disaggregated results in *Tables 57* and *58* show that the inclusion of the reduced radiation effects has only very minimal impact on the outcomes.

The cost-effectiveness analysis of the use of NGCCT in congenital heart disease showed that, when only considering the radiation exposure, the use of NGCCT instead of 64-slice CT is not cost-effective in this group. The ICER ranged from £521,000 per QALY gained for the youngest patients to £90,000 per QALY gained for the adult patients. The reduction in radiation by replacing a single 64-slice CT scan by a NGCCT scan is small and leads to only a minor decrease in radiation-related cancer incidence, therefore it cannot justify the additional costs of the NGCCT scan.

Various scenarios were explored to assess the impact of the main assumptions. Only in the most unlikely scenario, i.e. an average radiation dose of 25 mSV for a 64-slice CT, do the ICERs decrease significantly. The fact that for all other scenarios the ICER remains > £30,000 indicates that, even with the uncertainty about the various assumptions in mind, it can reasonably be concluded that the use of NGCCT instead of 64-slice CT in order to reduce radiation exposure is not cost-effective in this patient group.

Chapter 5

Discussion

Statement of principal findings

Clinical effectiveness

All 24 studies (26 publications) included in the systematic review were diagnostic test accuracy studies that reported data on the performance of NGCCT in difficult-to-image patients with known or suspected CAD.

Where per-patient estimates of test accuracy were possible, these were generally high. The pooled estimates of sensitivity were 97.7% (95% CI 88.0% to 99.9%), 97.7% (95% CI 93.2% to 99.3%) and 96.0% (95% CI 88.8% to 99.2%), for patients with arrhythmias, patients with HHRs and patients with previous stent implantation(s), respectively. The corresponding pooled estimates of specificity were 81.7% (95% CI 71.6% to 89.4%), 86.3% (95% CI 80.2% to 90.7%) and 81.6% (95% CI 74.7% to 87.3%), respectively. The high per-patient estimates of sensitivity (> 95%) indicate that NGCCT could be used to reliably rule out significant stenosis and thus potentially avoid invasive investigations such as ICA in these patient groups. Furthermore, although there were no data specifically for beta-blocker-intolerant patients, it should be noted that no study reporting per-patient data for patients with HHRs used additional beta-blockers before imaging. Therefore, it may be inferred that NGCCT could reasonably be used to image patients who are intolerant to beta-blockers who could not otherwise be reliably imaged by 64-slice CT. With the exception of one small study, data on the accuracy of NGCCT in patients with high coronary calcium scores, previous bypass grafts, or obesity were limited to per-arterial segment or per-artery data. Sensitivity estimates remained high (> 90% in all but one study).

The majority of studies were judged to be at low risk of bias with respect to the reference standard domain of QUADAS-2; this reflects the specification, in the inclusion criteria of the review, of a single acceptable reference standard (ICA). Unclear ratings for this domain mainly reflected poor reporting of the interpretation of the reference standard and uncertainty as to whether or not those interpreting ICA were blinded to the index test results. The judgement of risk of bias with respect to patient selection was problematic and this is reflected in the high proportion of unclear ratings. The unclear rating frequently related to uncertainty surrounding the potential impact of inappropriate exclusions. Difficult-to-image patient groups were frequently reported as subgroups within larger studies, with those who had one or more additional criteria that may contribute further to difficulty in imaging being excluded from the study (e.g. a study reporting data for patients with HHR may have excluded patients with previous revascularisations). In addition, the numbers/proportion of patients excluded in this way were frequently not reported. Inclusion of multiple measurements per patient (per-arterial segment, per-artery or per-stent data) was a common problem in the index test domain. Where studies excluded non-diagnostic arterial segments from their analyses, the potential impact of these exclusions was frequently unclear because their distribution between patients was not reported.

No study reported data on changes to patient management or outcomes, test-related adverse events or patient preferences. No studies were identified of patients with congenital heart disease which met the inclusion criteria of the review.

Cost-effectiveness

The health economic analysis of the use of NGCCT in difficult-to-image patients with CAD showed that the use of NGCCT instead of invasive CA may be considered cost-effective. In patients with suspected CAD, the NGCCT-only strategy might be considered the most attractive. The ICER of NGCCT–ICA compared with NGCCT only is so high (£71,000) that it is unlikely to be considered cost-effective given a willingness-to-pay threshold of £20,000–30,000 per additional QALY. In patients with known CAD, the most attractive strategy would be to perform a NGCCT with ICA; this scenario yields the highest cost saving and dominates ICA only. The ICER of NGCCT only compared with NGCCT–ICA is so high (£726,230) that it is unlikely to be considered cost-effective. When taking uncertainty into account, these findings were confirmed. In the suspected population, in the range of thresholds of < £70,000, the NGCCT-only strategy has the highest probability of being cost-effective. For thresholds above £70,000, the three different strategies are more or less equivalent. For the patients with known CAD, the NGCCT–ICA strategy has the highest probability of being cost-effective over the whole range of thresholds, whereas the ICA-only strategy always has the smallest probability of being cost-effective.

The key drivers behind these results are the percentage of patients being misclassified (a function of both diagnostic accuracy and the prior likelihood) and the complication rate for ICA and revascularisation. Overall, in the population of suspected CAD, the NGCCT-only strategy has the lowest overall procedure-induced mortality rate, less than half that of ICA only. To some extent, the same results apply for the known CAD population; here the overall procedure-induced mortality and morbidity is lowest in the NGCCT–ICA strategy. ICA only has the highest overall procedure-induced mortality and morbidity rate. There is currently uncertainty about the estimate of the cost price of a NGCCT scan. Therefore, we performed a scenario analysis changing this cost price to £207 per scan, and this did not alter our conclusions.

The inclusion of the reduced radiation effects achievable using NGCCT compared with ICA has only very minimal impact on the outcomes.

The cost-effectiveness analysis of the use of NGCCT in congenital heart disease showed that, when only considering the radiation exposure, the use of NGCCT instead of 64-slice CT is not cost-effective in this group. The ICER ranged from £521,000 per QALY gained for the youngest patients to £90,000 per QALY gained for the adult patients. The reduction in radiation by replacing a single 64-slice CT scan by a NGCCT scan is small and leads to only a minor decrease in radiation-related cancer incidence, therefore it cannot justify the additional costs of the NGCCT scan.

Various scenarios were explored to assess the impact of the main assumptions. Only in the most unlikely scenario, i.e. an average radiation dose of 25 mSV for a 64-slice CT, do the ICERs decrease significantly. The fact that for all other scenarios the ICER remains > £30,000 indicates that, even with the uncertainty about the various assumptions in mind, it can reasonably be concluded that the use of NGCCT instead of 64-slice CT in order to reduce radiation exposure is not cost-effective in this patient group.

Strengths and limitations of assessment

Clinical effectiveness

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of clinical trials registers and conference abstracts to identify unpublished studies.

Because of the known difficulties in identifying test accuracy studies using study design-related search terms,[21] search strategies were developed to maximise sensitivity at the expense of reduced specificity. Thus, large numbers of citations were identified and screened, many of which did not meet the inclusion criteria of the review.

The possibility of publication bias remains a potential problem for all systematic reviews. Considerations may differ for systematic reviews of test accuracy studies. It is relatively simple to define a positive result for studies of treatment, for example a significant difference between the treatment and control groups, which favours treatment. This is not the case for test accuracy studies, which measure agreement between index test and reference standard. It would seem likely that studies finding greater agreement (high estimates of sensitivity and specificity) will be published more often. In addition, test accuracy data are often collected as part of routine clinical practice, or by retrospective review of records; test accuracy studies are not subject to the formal registration procedures applied to randomised controlled trials and are therefore more easily discarded when results appear unfavourable. The extent to which publication bias occurs in studies of test accuracy remains unclear; however, simulation studies have indicated that the effect of publication bias on meta-analytic estimates of test accuracy is minimal.[108] Formal assessment of publication bias in systematic reviews of test accuracy studies remains problematic and reliability is limited.[108] We did not undertake a statistical assessment of publication bias in this review. However, our search strategy included a variety of routes to identify unpublished studies and resulted in the inclusion of a number of conference abstracts, in which little documentation of study methodology and findings could be found.

Clear inclusion criteria were specified in the protocol for this review. Eligibility of studies for inclusion is therefore transparent. In addition, we have provided specific reasons for excluding any of the studies considered potentially relevant at initial citation screening (see *Appendix 5*). The review process followed recommended methods to minimise the potential for error and/or bias;[18] studies were independently screened for inclusion by two reviewers and data extraction and quality assessment were undertaken by one reviewer and checked by a second. Any disagreements were resolved by consensus.

All studies included in the review were test accuracy studies. Methodological quality was therefore assessed using QUADAS-2. The QUADAS tool is recommended for assessing the methodological quality of test accuracy studies,[18,20] and has been widely adopted by researchers and key organisations such as The Cochrane Collaboration, NICE in the UK, and the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) in Germany. It has been mentioned in more than 200 abstracts on the DARE database and has been cited more than 500 times. However, user experience and feedback have suggested potential improvements. A revised version of QUADAS (QUADAS-2) has recently been published. QUADAS-2 more closely resembles the approach and structure of the Cochrane risk of bias tool. It is structured into four key domains covering participant selection, index test, reference standard, and the flow of patients through the study (including timing of tests).[23] Each domain is rated for risk of bias (low, high or unclear) and the tool provides signalling questions, in each domain, to help reviewers in reaching a judgement. The participant selection, index test and reference standard domain are also separately rated for concerns regarding the applicability of the study to the review question (low, high or unclear). However, our assessment included only the risk of bias components of QUADAS-2, as it was considered that the inclusion criteria for this review were very specific to the review question and that questions of applicability were, therefore, not relevant. The review-specific guidance used in our QUADAS-2 assessment is reported in *Appendix 2*. We reported the results of our risk of bias assessment in full (see *Appendix 3*) and in summary in the results (see *Chapter 3*, *Results*). However, the usefulness of this assessment was limited by poor reporting of primary study methods.

There were a number of areas where problems caused by unclear reporting might be considered specific to this review. Because our assessment of test accuracy in patients with known or suspected CAD concerned only specific groups of patients who are known to be difficult to image using current (64-slice) CT technologies, the data included in our review were frequently derived from subgroup analysis reported as part of larger studies conducted in a general population of patients with CAD. One consequence of this was that patients with one or more additional criteria that might contribute further to difficulty in imaging were often excluded from these studies, for example a study of patients with suspected CAD that reported subgroup data for patients with HHRs might have excluded patients with previous revascularisations. In this scenario, judgement of the risk of bias is further complicated because, although the study may have reported the total number of patients excluded because of previous revascularisation, it is unlikely to have reported how many of these patients were in the HHR subgroup. It is therefore unclear what proportion of the relevant patient group (those with HHRs) have been inappropriately excluded. A further consideration in this review was the way in which data were reported, as many studies reported per-artery, per-stented lesion or per-segment data. These types of within-patient 'clustered' data are a common feature of test accuracy studies and are likely to result in a correlation between results within each patient, which should be accounted for in any statistical analyses.[109] Uncorrected estimates of sensitivity and specificity derived from such data are likely to be accurate, but imprecision will be underestimated.[109] The handling of non-diagnostic segments was also a particular issue for studies included in this review. The classification of non-diagnostic segments as positive for significant stenosis was adopted by many studies. If a patient is considered test positive when one or more segments with significant stenosis are identified, using this strategy will minimise the number of FN patients at the expense of increasing FPs. Thus, if NGCCT is being used to rule out patients from further invasive investigation, this strategy might reasonably be considered the most appropriate representation of how the test would be used in practice. However, it may result in overestimations of the sensitivity of NGCCT. By contrast, some studies in this review excluded non-diagnostic segments from their analyses. This approach is likely to produce inflated per-segment estimates of sensitivity and specificity and, if numbers of non-diagnostic segments or patients are not reported, ignores an important aspect of the practical utility of the test. For per-patient data, when a positive test is defined as one or more positive segments, exclusion of a non-diagnostic segment that is actually stenosed may result in misclassification of a positive patient as TN (if this is the only stenosed segment) or may have no effect (if multiple segments are stenosed).

Hierarchical or bivariate models are considered the optimal methods for estimating SROC curves.[18] Wherever possible, we have used the bivariate model[24] to generate pooled estimates of sensitivity and specificity for each difficult-to-image patient group considered. This model analyses sensitivity and specificity jointly, retaining the paired nature of the original data, and has been shown to produce equivalent results to the hierarchical SROC model in the absence of other study-level covariates.[25] There were no data sets of sufficient size (minimum 10) to allow statistical exploration of sources of heterogeneity by including additional covariables in the SROC model. In cases where a bivariate model could not be fitted because the number of studies was small (four), 2×2 data contained one or more zero values, and between-study heterogeneity was low, pooled estimates of sensitivity and specificity, with 95% CIs, were calculated using a random-effects model. In view of the known problems with meta-analysis of likelihood ratios with a bivariate model,[110] we have not included summary likelihood ratios and have instead adopted sensitivity and specificity as the primary outcomes for our review.[110]

Assessments of the diagnostic accuracy of NGCCT are underpinned by the assumption that the reference standard (ICA), against which NGCCT is being evaluated, is 100% sensitive and 100% specific. ICA has some limitations in that it can only provide information about abnormalities that narrow the vessel lumen; it is limited in its ability to accurately define the aetiology of

the obstruction or to detect the presence of early atherosclerotic disease.[11] When stenosis is present on ICA, pathological analyses almost always confirm findings, i.e. the assumption of 100% specificity is generally valid. However, the converse is not true; pathological studies have suggested that angiography underestimates the extent and severity of stenosis,[111–115] and the assumption of 100% sensitivity is therefore weaker. Several factors contribute to this problem: ICA provides two-dimensional visualisation, whereas coronary lesions are often geometrically complex; an adaptive phenomenon known as coronary remodelling (an outward displacement of the external vessel wall to compensate for narrowing), which occurs in the early stages of disease and may conceal atheroma on ICA; and frequent absence of a normal reference segment (in the presence of diffuse reference segment disease, per cent stenosis will underestimate the true extent of vessel narrowing).[11] If the assumption of 100% sensitivity for ICA does not hold and FNs do occur, one possible consequence for accuracy studies that use ICA as the reference standard would be underestimation of the true specificity of the index test. This would occur if the index test is better able to detect early stage or other disease missed by ICA and the numbers of FP index test results are thus overestimated. However, despite its limitations, ACC/AHA guidelines state that coronary angiography remains the accepted reference standard for assessment of anatomical coronary disease.[11]

The clinical applicability of accuracy data included in this review may have some limitations. NICE guidance on the assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin defines significant CAD on ICA as ≥ 70% diameter stenosis of at least one major epicardial artery segment or ≥ 50% diameter stenosis in the left main coronary artery.[63] By contrast, almost all of the studies included in this review considered the accuracy of NGCCT for the detection of significant CAD, which was defined as ≥ 50% diameter, regardless of the arteries assessed. However, the two studies that presented additional data for a threshold of > 75% diameter reduction[59] or ≥ 70% diameter reduction[38] both gave similar estimates of sensitivity and specificity for these thresholds and the 50% threshold.

The majority of included studies reported no information on funding; three[40,47,51] reported funding from NGCCT manufacturers.

Cost-effectiveness

In this study, we brought together various existing models, which have already been validated through peer review, to inform the assessment of the cost-effectiveness of NGCCT in difficult-to-image patients with CAD. The advantage of combining five different models into one overall model is that the combined model is broad enough to describe as well as possible the whole range from diagnostics to clinical pathway to complications and radiation. A disadvantage is that some of the models were developed for other study populations. The existing models needed to be adjusted for the known and suspected CAD difficult-to-image subgroups which introduces additional uncertainty.

We included procedure-induced morbidity, as well as mortality, as this is an important aspect of ICA. Throughout the model, we have used evidence to inform parameters that was UK relevant and as up to date and high quality as possible. Where evidence was not available through published studies or databases, for example for population characteristics, we used the most likely and plausible ranges based on expert opinion.

We found that the main drivers of our cost-effectiveness results were accuracy, prior likelihood and the complication rate for ICA, PCI and CABG. The uncertainty around the accuracy estimates was not very large, given the reasonably large number of studies conducted. However, as noted above (see *Model structure and methodology*), some limitations apply to these estimates. The estimates of the prior likelihood that we used were not derived from any studies. For the

suspected CAD group the estimate was based on the clinical guideline for chest pain of recent onset[63] and for the known CAD group on the value assumed in the CE-MARC study.[64] For the suspected CAD group, the likelihood estimate is actually more an assumption than an estimate. According to the NICE clinical guideline (CG95)[63] on the assessment and diagnosis of stable chest pain of recent onset, CT scans mainly play a part in the diagnostic path of patients with a prior likelihood of CAD of 10–29% and a non-zero calcium score. This likelihood is based on presence of certain clinical symptoms (suggestive of angina), and the risk factors age, gender, diabetes, smoking and hyperlipidaemia. For the likelihood estimate in the known CAD population, it is not entirely certain that the CE-MARC study and our study consider the exact same patient population. It is therefore possible that the actual prior likelihood in our known CAD population differs from that currently assumed in our model. Cost-effectiveness modelling for this assessment was based on patients with a prior likelihood of CAD of 10–29%, in accordance with the scope that was based on current NICE guidance. This guidance currently recommends ICA as the first-line investigation in patients where the estimated likelihood of CAD is 61–90% and functional imaging as the first-line investigation in patients where the estimated likelihood of CAD is 30–60%. Although the studies included in the systematic review component of this assessment rarely reported CAD risk factors separately for difficult-to-image patients (see *Appendix 4*), there was some indication that a significant proportion of these patients may be in the higher (30–90%) likelihood of CAD categories. With this consideration in mind and given the apparent accuracy of NGCCT in these populations, further modelling for higher prior likelihoods of CAD could be considered to inform future updates to NICE guidance.

Information on the final main driver, the complication rates, was derived from various sources. As the rate of MI resulting from a CABG was not available from data included in the literature review conducted for this assessment, we combined two studies identified for the purpose.[94,95] The overall complication rate (MI and stroke) taken from Serruys *et al.*[95] is based on a RCT. The authors presented only overall complication rates at 1 year of follow-up, and it seems likely that all of the reported events cannot fully be attributed to the procedure itself. Therefore, we used a 30-day complication rate based on the published survival curve, assuming that complications occurring in the first 30 days are induced by the procedure. An overestimation of the overall complication rate could have occurred. To estimate the MI rate, we subtracted the stroke rate reported by Tarakji *et al.*[94] from the overall complication rate presented in Serruys *et al.*[95] This method could have led to an inaccurate estimation of the MI rate for CABG. In contrast, the ICA-related mortality and morbidity were derived from an observational study in the UK, in which complications of diagnostic ICA were reported over a period of 10 years in 41 cardiac centres.[89] Thus, the reliability of the complication rates for ICA used in this model may be expected to be higher than for revascularisation. The British Cardiovascular Intervention Society (BCIS) was contacted to investigate the possibility of obtaining audit data on ICA-related complications; however, these data were not available at the time of our assessment. The PCI-induced morbidity reported in the BCIS database was approximately equal to that used in our model. The BCIS reported that PCI-related mortality was towards the lower limit of the CI applied in our sensitivity analyses. Given that our conclusions were unaltered if we took all uncertainty into account, using the BCIS data would not have changed these conclusions.

It was reassuring to see that the results were very similar across different subgroups of difficult-to-image patients. Had there been clear differences between the groups, questions would need to be answered in relation to implementation, i.e. do we recommend NGCCT for all difficult-to-image patients or only to a smaller subset. Furthermore, because the subgroup-specific outcomes were so similar, the impact of the relative weight of each subgroup, which was based on expert opinion, became small.

For the assessment of the cost-effectiveness of NGCCT in congenital heart disease, an important limitation is the fact that the current analysis considers only the effects of the lower radiation dose. However, we expect that inclusion of other factors, such as improved treatment planning, would have a limited impact on the current outcomes. An important reason for this is that it is likely that treatment (planning) be improved in only a fraction of patients, and in only a fraction of these would that lead on to improved health outcomes or reduction of costs.

Uncertainties

Clinical effectiveness

A major assumption underpinning this assessment is that the accuracy of NGCCT in the general population of patients with known or suspected CAD is equivalent to or better than that of 64-slice CT. The accuracy of 64-slice CT in the general population has been well established; recent systematic reviews have estimated the sensitivity and specificity of 64-slice CT, for the detection of ≥ 50% coronary artery stenosis, to be 92–99% and 89–92%, respectively.[3–5] It is therefore possible, although unlikely, that the use of NGCCT scanners would offer significant benefit over the use of a 64-slice CT scanner for most patients. There remains, however, the possibility that the radiation dose reduction protocols associated with NGCCT may negatively affect test accuracy. It was not part of the objectives of this review to systematically assess the accuracy of NGCCT in the general CAD population. However, a non-systematic sample of 10 studies which were excluded from the review at the full-paper-screening stage and which reported accuracy data in their abstracts indicated sensitivity and specificity estimates of 87–100% and 73–98%, respectively.[116–125]

None of the categories of difficult-to-image patients considered in this review was evaluated in large numbers of studies; the maximum was eight studies for patients with HHRs. Data were particularly sparse for obese patients and patients with previous bypass graft(s). There were no data specifically for beta-blocker-intolerant patients. However, it should be noted that no study reporting per-patient data for patients with HHRs used additional beta-blockers before scanning. It may therefore be inferred from the performance of NGCCT in patients with HHRs that these technologies could reasonably be used to image patients who are intolerant to beta-blockers who could not otherwise be reliably imaged by 64-slice CT.

As noted above (see *Strengths and limitations of assessment*, *Clinical effectiveness*), the effect on test accuracy of multiple difficult-to-image criteria within patients remains uncertain. Only two studies included in this review[52,58] reported data for patients with two distinct difficult-to-image criteria (HHR and previous revascularisation). Both of these studies reported sensitivity and specificity values > 90% and both excluded patients with arrhythmias.

In addition to test accuracy, an important consideration for the practical utility of NGCCT in difficult-to-image patient groups is the proportion of these patients in whom NGCCT imaging is non-diagnostic. Few of the studies in this assessment reported these data; where numbers of non-diagnostic images were reported, these were often for the whole study population, rather than the difficult-to-image subgroup. Three studies did report subgroup-specific non-diagnostic image rates in different populations; these were 5% for patients with arrhythmias,[47] 6.8% for patients with HHR[39] and 9% for patients with previous stent implantation.[40] Although these studies indicate that the proportions of otherwise difficult-to-image patients who would remain 'non-diagnostic', even with the use of NGCCT, are likely to be low, further studies are needed to confirm this.

It should be further noted that although this review provides reasonable evidence on the accuracy of NGCCT in difficult-to-image patients groups, no studies were identified which reported the effects of scanning with NGCCT on patient management or outcomes in these patients. The ultimate aim of any research on clinical tests should be to determine impact upon patient management and outcome. These data are essential to fully inform both clinical decision-making and policy decision-making.

We were unable to identify any studies reporting data on the effects of NGCCT scanning on management and outcomes for patients with congenital heart disease. The potential impact of the introduction of NGCCT in this patient group therefore remains an unknown quantity. In practice, if NGCCT were to be introduced on the basis of evidence of its effectiveness and cost-effectiveness in difficult-to-image patients with known or suspected CAD, it is likely that these scanners would also be used opportunistically in patients with complex congenital heart disease.

This assessment treats the specified NGCCT scanners [Discovery CT750 HD (GE Healthcare), Brilliance iCT (Philips Healthcare), Somatom Definition Flash (Siemens Healthcare) and Aquilion ONE (Toshiba Medical Systems)] as equivalent technologies. However, it should be noted that 20 of the 24 studies included in the systematic review reported using Somatom Definition; three studies did not specify the instrument used,[36–38] although the authors of one of these[37] had used Somatom Definition in an earlier study, which was also included in this review.[39] One study reported using Aquilion ONE for the assessment of in-stent restenosis[40] and found per-patient estimates of sensitivity and specificity of 100% (95% CI 71.5% to 100%) and 81.0% (95% CI 65.9% to 91.4%), consistent with the reported estimates for Somatom.

Cost-effectiveness

As noted above (see *Uncertainties*, *Clinical effectiveness*), we have assumed the accuracy of the various NGCCTs to be the same. In the health economic analysis, the same assumption has been made regarding radiation dosages and cost prices. Potential differences in any of these factors might lead to different conclusions for the various NGCCTs.

An important part of the CAD model, i.e. the EUROPA model, is based on risk equations that enabled the calculation of patient-specific transition probabilities. However, we applied the model to a cohort of 'average' patients, all with the average age, for a certain percentage male, for a certain percentage currently using calcium channel blockers, etc. This was done because the combination of five separate models used to model the current decision problem made patient-level simulation impossible. As a result, we removed one source of variation: the results that we found may well be different for certain subgroups of patients, such as younger or older patients.

An important factor in the final results in the CAD population is the percentage of patients misclassified. In the ICA strategy this percentage is '0', whereas the NGCCT strategies both lead to patients incorrectly classified as negative. In the model it has been assumed that these patients will in time be correctly identified as positive. A key benefit of correct identification is the increased HRQoL of a TN compared with a FN during this period, as well as the marginally reduced risk of experiencing a CV event. Therefore, an accurate estimate of the time until correct identification is important, but will be difficult to obtain. Probably the best source of information at this time would be expert elicitation, but this has its own difficulties, as the cardiologists would need to be able to distinguish between those who were originally misidentified (i.e. true FN) and those who were originally correctly identified as not having CAD (TN) but who developed CAD in the interim.

Chapter 6

Conclusions

Implications for service provision

The results of our systematic review suggest that NGCCT may provide sufficiently accurate anatomical information for the diagnosis and assessment of CAD in some or all difficult-to-image patient groups. These technologies may be particularly useful in ruling out patients from further invasive investigations. However, data were sparse, particularly for obese patients, patients with high coronary calcium and those with previous bypass grafts.

The limited available data indicate that the proportions of otherwise difficult-to-image patients in whom imaging would remain 'non-diagnostic', even with the use of NGCCT, are likely to be low. However, further studies are needed to confirm this.

In a recent report it was stated that, in the next 3 years, half of the CT scanners and MRIs in the UK will need to be replaced.[86] Assuming that our cost price estimate for NGCCT is realistic, the results of the economic evaluation of new-generation cardiac CT suggest that it is likely to be considered cost-effective for difficult-to-image patients with CAD, at current levels of willingness to pay in the NHS. Although ICA can diagnose these patients with certainty, this comes at the cost of procedure-induced mortality and morbidity. Overall, taking uncertainty into account, we may conclude that strategies including NGCCT are cost saving while yielding approximately the same number of QALYs. Whether NGCCT should be used with or without ICA depends on the CAD population. However, it is important to remember that our results are valid only within the group of difficult-to-image patients with CAD; they are not be extrapolated to the whole population of patients with known or suspected CAD, as for these patients non-invasive 64-slice CT remains a good option.

Suggested research priorities

All studies included in our systematic review were test accuracy studies conducted in difficult-to-image patient groups with known or suspected CAD. The test accuracy study design compares the results of a new test (index test) with those of the reference standard (which are assumed always to be correct); it is therefore inherently not capable of comparing tests in terms of their ultimate impact on patient outcome. The studies included in this review compare NGCCT with the reference standard (ICA) purely in terms of its ability to detect a predefined level of stenosis (usually 50%). They do not provide any indication of the contribution of NGCCT to therapeutic decision-making or subsequent impact on patient outcomes. The ideal study to address these questions would be a large, multicentre RCT, in which patients are randomised to receive therapeutic planning and/or treatment based on different imaging strategies (e.g. NGCCT, ICA, or NGCCT and ICA); evaluation in more than one centre is preferred, in order to minimise performance bias. Recognising that the establishment of large-scale RCTs is particularly problematic in rapidly evolving fields such as vascular imaging, one possible compromise strategy might be to establish a multicentre tracker study. Such a study should enable the collection of data comparing numbers of misdiagnoses, clinical outcomes and HRQoL resulting from

alternative imaging strategies. Such a study would also be the ideal set-up to provide a more robust assessment of the cost-effectiveness of the various diagnostic strategies.

In addition, test accuracy data were relatively sparse and further, high-quality accuracy studies, particularly for obese patients, patients with high coronary calcium and those with previous bypass grafts are needed to confirm the findings of our systematic review. Studies should include and fully report details of patients with more than one difficult-to-image criterion, so that the important issues of the potential cumulative impact on accuracy of multiple criteria can be fully assessed. Studies should also report the numbers of patients in whom NGCCT is non-diagnostic. QUADAS-2 assessment highlighted limitations in the reporting of many studies included in our review; future evaluations of NGCCT should follow the STARD guidelines for reporting test accuracy studies.[126,127]

This assessment was unable to identify any studies that assessed changes to patient management/outcome (subsequent to NGCCT) in patients with complex congenital heart disease. If NGCCT is introduced on the basis of evidence in CAD patients and is opportunistically used in congenital heart disease patients, 'before-and-after' population studies might offer some insight into the impact of introducing NGCCT upon treatment decisions and/or outcomes for patients with complex conditions. When well designed, such studies might also inform the cost-effectiveness of NGCCT in this population.

In the clinical guideline *Chest pain of recent onset*,[63] one of the recommendations was to establish a national registry for people who are undergoing initial assessment for stable angina.[63] It was mentioned that accurate assessment of the likelihood of coronary disease is needed to inform the cost-effective choice of investigative technologies. The data on which the estimated likelihood of CAD are currently based date from 1979 in a US population and may not be applicable to contemporary UK populations. We saw in our study that the prior likelihood of CAD is one of the main drivers of the cost-effectiveness results, and thus, such a registry could increase robustness of the health economic findings.

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Contributions of authors

Marie Westwood and Heike Raatz planned and performed the systematic review and interpretation of evidence.

Maiwenn Al, Laura Burgers, Ken Redekop and Stefan Lhachimi planned and performed the cost-effectiveness analyses and interpreted results.

Nigel Armstrong contributed to planning and interpretation of cost-effectiveness analysis and acquisition of input data for modelling.

Kate Misso devised and performed the literature searches and provided information support to the project.

Jos Kleijnen and Hans Severens provided senior advice and support to the systematic review and cost-effectiveness analyses, respectively.

All parties were involved in drafting and/or commenting on the report.

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Appendix 1

Literature search strategies

Clinical effectiveness search strategies

MEDLINE (OvidSP): 1 January 2000 to week 2 February 2011

Searched 17 February 2011.

1. Somatom definition flash.ti,ab,ot,hw. (4)
2. DSCT.ti,ab,ot,hw. (244)
3. (Aquilion-1 or Aquilion-one).ti,ab,ot,hw. (9)
4. Brilliance ict.ti,ab,ot,hw. (1)
5. (Discovery ct750 or Discovery ct-750).ti,ab,ot,hw. (1)
6. (640row$ or 640-row$ or 640-detect$ or 640slice$ or 640 slice$).ti,ab,ot,hw. (2)
7. (320row$ or 320-row$ or 320-detect$ or 320slice$ or 320 slice$).ti,ab,ot,hw. (59)
8. (256row$ or 256-row$ or 256-detect$ or 256slice$ or 256 slice$).ti,ab,ot,hw. (67)
9. (128row$ or 128-row$ or 128-detect$ or 128slice$ or 128 slice$).ti,ab,ot,hw. (40)
10. ('2' adj2 (energy or source$)).ti,ab,ot,hw. (2402)
11. (Dual$ adj2 (energy or source$) adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computed or tomograph$)).ti,ab,ot,hw. (1137)
12. (High definition adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computer or tomograph$)).ti,ab,ot,hw. (165)
13. modern cone-beam dual-source spiral.ti,ab,ot,hw. (1)
14. (high pitch dual spiral adj3 (CT or scan$ or imag$ or technique$ or protocol$ or DSCT or multidetect$ or multi-detect$ or computer or tomograph$)).ti,ab,ot,hw. (1)
15. or/1-14 (3962)
16. heart defects, congenital/ or aortic coarctation/ or cor triatriatum/ or eisenmenger complex/ or "isolated noncompaction of the ventricular myocardium"/ or leopard syndrome/ or marfan syndrome/ or "tetralogy of fallot"/ or "trilogy of fallot"/ or turner syndrome/ (59,436)
17. exp Coronary Disease/ or myocardial ischemia/ or exp myocardial infarction/ (289,267)
18. ((pulmonary or aortic or aorta or coronary or cardiac or valve) adj2 (stenosis or atresia)).ti,ab,ot,hw. (49,077)
19. (congenital$ adj2 arter$ adj2 (defect$ or deform$ or malform$ or anomal$ or abnormal$ or disease$)).ti,ab,ot,hw. (460)
20. (congenital$ adj2 heart adj2 (defect$ or deform$ or malform$ or anomal$ or abnormal$ or disease$)).ti,ab,ot,hw. (43,228)
21. (CAD or IAA or VSD or CHD or LVOT or PVOD or UVH or TAPVD or TAPVR or PAPVD or PAPVR or MAPCA or MAP-CA).ti,ab,ot. (34,019)
22. (TOF or TAPVC or COA or IAA or SS or PAPVC).ti,ab,ot. (63,756)
23. (Lutembacher$ adj2 (syndrome or complex)).ti,ab,ot,hw. (156)
24. (trilogy adj2 fallot).ti,ab,ot,hw. (54)
25. (Interrupt$ adj3 aortic arch).ti,ab,ot,hw. (920)
26. (tetralogy adj2 fallot).ti,ab,ot,hw. (8363)
27. total$ anomalous pulmonary venous connection$.ti,ab,ot,hw. (500)
28. Bicuspid aortic valve$.ti,ab,ot,hw. (1167)
29. Double inlet left ventricle$.ti,ab,ot,hw. (165)
30. (Coarctat$ adj3 aorta).ti,ab,ot,hw. (3560)

31. (Co-arctat$ adj3 aorta).ti,ab,ot,hw. (3)
32. Interrupt$ aort$.ti,ab,ot,hw. (616)
33. (Scimitar adj2 (syndrome or complex)).ti,ab,ot,hw. (450)
34. Partial$ anomalous pulmonary venous connect$.ti,ab,ot,hw. (229)
35. Total$ anomalous pulmonary venous connect$.ti,ab,ot,hw. (500)
36. (Shone$ adj2 (syndrome or complex or anomaly or defect$ or deform$ or malform$ or abnormal$)).ti,ab,ot,hw. (66)
37. (Marfan$ adj2 (syndrome or complex)).ti,ab,ot,hw. (5278)
38. Marfans.ti,ab,ot,hw. (1930)
39. (eisenmenger$ adj2 (syndrome or complex)).ti,ab,ot,hw. (989)
40. univentric$ heart$.ti,ab,ot,hw. (507)
41. uni-ventric$ heart$.ti,ab,ot,hw. (3)
42. ((coronary or heart) adj2 disease).ti,ab,ot,hw. (240,566)
43. (MI or IHD).ti,ab,ot,ab. (24,125)
44. (isch?emic heart disease$ or myocardi$ isch?em$ or angina$).ti,ab,ot,hw. (106,061)
45. ((right or double) adj2 aort$ arch$).ti,ab,ot,hw. (1350)
46. (aberrant subclavian arter$ or aberrant sub-clavian arter$).ti,ab,ot,hw. (122)
47. (Vascular ring or pulmonary arter$ sling or anomalous coronary arter$).ti,ab,ot,hw. (1066)
48. truncus arteriosus.ti,ab,ot,hw. (1369)
49. common arterial trunk.ti,ab,ot,hw. (127)
50. (superior cavopulmonary anastamosis or superior cavo-pulmonary anastamosis).ti,ab,ot,hw. (2)
51. arterial switch.ti,ab,ot,hw. (912)
52. (total cavopulmonary connection$ or total cavo-pulmonary connection$).ti,ab,ot,hw. (449)
53. partial$ anomalous pulmonary venous drainage.ti,ab,ot,hw. (135)
54. (cardiac adj2 (tumo?r$ or cancer$ or malignan$ or neoplas$)).ti,ab,ot,hw. (2451)
55. (DAA or TCPC).ti,ab,ot. (555)
56. (Kawasaki adj2 (disease$ or disorder$ or syndrome$)).ti,ab,ot,hw. (3596)
57. major aorto-pulmonary collateral arter$.ti,ab,ot,hw. (26)
58. Coronary Aneurysm/ (2461)
59. ((cardiac$ or cardio$ or heart$ or aort$ or coronary) adj4 (heterotax$ or laterality or isomerism)).ti,ab,ot,hw. (215)
60. Truncus Arteriosus/ (127)
61. Coronary Vessel Anomalies/ (5958)
62. Truncus Arteriosus, Persistent/ (606)
63. exp Norwood Procedures/ (1630)
64. Aortic Aneurysm/ (16,383)
65. ((rastelli or mustard or senning or le compte) adj4 (cardiac$ or cardio$ or heart$ or aort$ or coronar$)).ti,ab,ot,hw. (72)
66. ((fontan or hemifontan or hemi-fontan or glenn or norwood) adj3 (procedure$ or operation$ or method$ or approach$)).ti,ab,ot,hw. (2926)
67. exp Heart Neoplasms/ (11,963)
68. exp Teratoma/ (16,305)
69. Myxoma/ (5162)
70. (aortic root or myxoma$ or angiomyxoma$).ti,ab,ot,hw. (12,088)
71. or/16-70 (605,347)
72. animals/ not (animals/ and humans/) (3,450,666)
73. 71 not 72 (542,288)
74. 15 and 73 (370)
75. **limit 74 to yr="2000 -Current" (339)**

MEDLINE In-Process and Other Non-Indexed Citations (OvidSP): 1 January 2000 to 16 February 2011, MEDLINE Daily Update (OvidSP): 1 January 2000 to 16 February 2011

Searced 17 February 2011.

1. Somatom definition flash.ti,ab,ot,hw. (0)
2. DSCT.ti,ab,ot,hw. (23)
3. (Aquilion-1 or Aquilion-one).ti,ab,ot,hw. (0)
4. Brilliance ict.ti,ab,ot,hw. (0)
5. (Discovery ct750 or Discovery ct-750).ti,ab,ot,hw. (0)
6. (640row$ or 640-row$ or 640-detect$ or 640slice$ or 640 slice$).ti,ab,ot,hw. (0)
7. (320row$ or 320-row$ or 320-detect$ or 320slice$ or 320 slice$).ti,ab,ot,hw. (17)
8. (256row$ or 256-row$ or 256-detect$ or 256slice$ or 256 slice$).ti,ab,ot,hw. (7)
9. (128row$ or 128-row$ or 128-detect$ or 128slice$ or 128 slice$).ti,ab,ot,hw. (7)
10. ('2' adj2 (energy or source$)).ti,ab,ot,hw. (412)
11. (Dual$ adj2 (energy or source$) adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computed or tomograph$)).ti,ab,ot,hw. (109)
12. (High definition adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computer or tomograph$)).ti,ab,ot,hw. (20)
13. modern cone-beam dual-source spiral.ti,ab,ot,hw. (0)
14. (high pitch dual spiral adj3 (CT or scan$ or imag$ or technique$ or protocol$ or DSCT or multidetect$ or multi-detect$ or computer or tomograph$)).ti,ab,ot,hw. (0)
15. or/1-14 (565)
16. heart defects, congenital/ or aortic coarctation/ or cor triatriatum/ or eisenmenger complex/ or "isolated noncompaction of the ventricular myocardium"/ or leopard syndrome/ or marfan syndrome/ or "tetralogy of fallot"/ or "trilogy of fallot"/ or turner syndrome/ (24)
17. exp Coronary Disease/ or myocardial ischemia/ or exp myocardial infarction/ (86)
18. ((pulmonary or aortic or aorta or coronary or cardiac or valve) adj2 (stenosis or atresia)).ti,ab,ot,hw. (715)
19. (congenital$ adj2 arter$ adj2 (defect$ or deform$ or malform$ or anomal$ or abnormal$ or disease$)).ti,ab,ot,hw. (20)
20. (congenital$ adj2 heart adj2 (defect$ or deform$ or malform$ or anomal$ or abnormal$ or disease$)).ti,ab,ot,hw. (741)
21. (CAD or IAA or VSD or CHD or LVOT or PVOD or UVH or TAPVD or TAPVR or PAPVD or PAPVR or MAPCA or MAP-CA).ti,ab,ot. (2141)
22. (TOF or TAPVC or COA or IAA or SS or PAPVC).ti,ab,ot. (3935)
23. (Lutembacher$ adj2 (syndrome or complex)).ti,ab,ot,hw. (1)
24. (trilogy adj2 fallot).ti,ab,ot,hw. (0)
25. (Interrupt$ adj3 aortic arch).ti,ab,ot,hw. (26)
26. (tetralogy adj2 fallot).ti,ab,ot,hw. (132)
27. total$ anomalous pulmonary venous connection$.ti,ab,ot,hw. (15)
28. Bicuspid aortic valve$.ti,ab,ot,hw. (65)
29. Double inlet left ventricle$.ti,ab,ot,hw. (3)
30. (Coarctat$ adj3 aorta).ti,ab,ot,hw. (115)
31. (Co-arctat$ adj3 aorta).ti,ab,ot,hw. (1)
32. Interrupt$ aort$.ti,ab,ot,hw. (19)
33. (Scimitar adj2 (syndrome or complex)).ti,ab,ot,hw. (12)
34. Partial$ anomalous pulmonary venous connect$.ti,ab,ot,hw. (10)
35. Total$ anomalous pulmonary venous connect$.ti,ab,ot,hw. (15)
36. (Shone$ adj2 (syndrome or complex or anomaly or defect$ or deform$ or malform$ or abnormal$)).ti,ab,ot,hw. (3)
37. (Marfan$ adj2 (syndrome or complex)).ti,ab,ot,hw. (123)

38. Marfans.ti,ab,ot,hw. (25)
39. (eisenmenger$ adj2 (syndrome or complex)).ti,ab,ot,hw. (27)
40. univentric$ heart$.ti,ab,ot,hw. (15)
41. uni-ventric$ heart$.ti,ab,ot,hw. (0)
42. ((coronary or heart) adj2 disease).ti,ab,ot,hw. (5009)
43. (MI or IHD).ti,ab,ot,ab. (1336)
44. (isch?emic heart disease$ or myocardi$ isch?em$ or angina$).ti,ab,ot,hw. (2059)
45. ((right or double) adj2 aort$ arch$).ti,ab,ot,hw. (50)
46. (aberrant subclavian arter$ or aberrant sub-clavian arter$).ti,ab,ot,hw. (2)
47. (Vascular ring or pulmonary arter$ sling or anomalous coronary arter$).ti,ab,ot,hw. (40)
48. truncus arteriosus.ti,ab,ot,hw. (26)
49. common arterial trunk.ti,ab,ot,hw. (2)
50. (superior cavopulmonary anastamosis or superior cavo-pulmonary anastamosis).ti,ab,ot,hw. (0)
51. arterial switch.ti,ab,ot,hw. (33)
52. (total cavopulmonary connection$ or total cavo-pulmonary connection$).ti,ab,ot,hw. (21)
53. partial$ anomalous pulmonary venous drainage.ti,ab,ot,hw. (1)
54. (cardiac adj2 (tumo?r$ or cancer$ or malignan$ or neoplas$)).ti,ab,ot,hw. (107)
55. (DAA or TCPC).ti,ab,ot. (53)
56. (Kawasaki adj2 (disease$ or disorder$ or syndrome$)).ti,ab,ot,hw. (115)
57. major aorto-pulmonary collateral arter$.ti,ab,ot,hw. (3)
58. Coronary Aneurysm/ (0)
59. ((cardiac$ or cardio$ or heart$ or aort$ or coronary) adj4 (heterotax$ or laterality or isomerism)).ti,ab,ot,hw. (10)
60. Truncus Arteriosus/ (0)
61. Coronary Vessel Anomalies/ (3)
62. Truncus Arteriosus, Persistent/ (0)
63. exp Norwood Procedures/ (0)
64. Aortic Aneurysm/ (16)
65. ((rastelli or mustard or senning or le compte) adj4 (cardiac$ or cardio$ or heart$ or aort$ or coronar$)).ti,ab,ot,hw. (2)
66. ((fontan or hemifontan or hemi-fontan or glenn or norwood) adj3 (procedure$ or operation$ or method$ or approach$)).ti,ab,ot,hw. (88)
67. exp Heart Neoplasms/ (4)
68. exp Teratoma/ (4)
69. Myxoma/ (1)
70. (aortic root or myxoma$ or angiomyxoma$).ti,ab,ot,hw. (394)
71. or/16-70 (13,434)
72. animals/ not (animals/ and humans/) (1216)
73. 71 not 72 (13,398)
74. 15 and 73 (34)
75. **limit 74 to yr="2000-Current" (33)**

EMBASE (OvidSP): 1 January 2000 to week 6 2011

Searched 17 February 2011.

1. Somatom definition flash.ti,ab,ot,hw. (11)
2. DSCT.ti,ab,ot,hw. (333)
3. (Aquilion-1 or Aquilion-one).ti,ab,ot,hw. (19)
4. Brilliance ict.ti,ab,ot,hw. (4)
5. (Discovery ct750 or Discovery ct-750).ti,ab,ot,hw. (2)

6. (640row$ or 640-row$ or 640-detect$ or 640slice$ or 640 slice$ or 320row$ or 320-row$ or 320-detect$ or 320slice$ or 320 slice$).ti,ab,ot,hw. (155)

7. (256row$ or 256-row$ or 256-detect$ or 256slice$ or 256 slice$).ti,ab,ot,hw. (92)

8. (128row$ or 128-row$ or 128-detect$ or 128slice$ or 128 slice$).ti,ab,ot,hw. (73)

9. ('2' adj2 (energy or source$)).ti,ab,ot,hw. (2472)

10. (Dual$ adj2 (energy or source$) adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computed or tomograph$)).ti,ab,ot,hw. (1437)

11. (High definition adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computer or tomograph$)).ti,ab,ot,hw. (212)

12. modern cone-beam dual-source spiral.ti,ab,ot,hw. (0)

13. (high pitch dual spiral adj3 (CT or scan$ or imag$ or technique$ or protocol$ or DSCT or multidetect$ or multi-detect$ or computer or tomograph$)).ti,ab,ot,hw. (1)

14. or/1-13 (4512)

15. congenital heart malformation/ or cor triatriatum/ or coronary vessel malformation/ or eisenmenger complex/ or heterotaxy syndrome/ (29,152)

16. fallot tetralogy/ (8913)

17. exp aorta anomaly/ (17,993)

18. coronary artery anomaly/ (2536)

19. scimitar syndrome/ (387)

20. LEOPARD syndrome/ (248)

21. Marfan syndrome/ (5781)

22. heart atrium septum defect/ (9190)

23. Turner syndrome/ (7509)

24. exp coronary artery disease/ (167,530)

25. exp heart infarction/ (198,634)

26. heart muscle ischemia/ (58,741)

27. arterial trunk/ (735)

28. mucocutaneous lymph node syndrome/ (5745)

29. exp heart aneurysm/ (8434)

30. norwood procedure/ (477)

31. aorta aneurysm/ or aorta dissecting aneurysm/ or aorta sinus aneurysm/ (16,981)

32. teratoma/ (16,384)

33. exp myxoma/ (6377)

34. heart tumor/ (7896)

35. mustard operation/ (376)

36. ((pulmonary or aortic or aorta or coronary or cardiac or valve) adj2 (stenosis or atresia)).ti,ab,ot,hw. (50,571)

37. (congenital$ adj2 arter$ adj2 (defect$ or deform$ or malform$ or anomal$ or abnormal$ or disease$)).ti,ab,ot,hw. (521)

38. (congenital$ adj2 heart adj2 (defect$ or deform$ or malform$ or anomal$ or abnormal$ or disease$)).ti,ab,ot,hw. (46,328)

39. (CAD or IAA or VSD or CHD or LVOT or PVOD or UVH or TAPVD or TAPVR or PAPVD or PAPVR or MAPCA or MAP-CA).ti,ab,ot. (44,393)

40. (TOF or TAPVC or COA or IAA or SS or PAPVC).ti,ab,ot. (72,919)

41. (Lutembacher$ adj2 (syndrome or complex)).ti,ab,ot,hw. (140)

42. (trilogy adj2 fallot).ti,ab,ot,hw. (29)

43. (Interrupt$ adj3 aortic arch).ti,ab,ot,hw. (989)

44. (tetralogy adj2 fallot).ti,ab,ot,hw. (9728)

45. total$ anomalous pulmonary venous connection$.ti,ab,ot,hw. (551)

46. Bicuspid aortic valve$.ti,ab,ot,hw. (1610)

47. Double inlet left ventricle$.ti,ab,ot,hw. (176)

48. (Coarctat$ adj3 aorta).ti,ab,ot,hw. (9144)

49. (Co-arctat$ adj3 aorta).ti,ab,ot,hw. (3)
50. Interrupt$ aort$.ti,ab,ot,hw. (680)
51. (Scimitar adj2 (syndrome or complex)).ti,ab,ot,hw. (502)
52. Partial$ anomalous pulmonary venous connect$.ti,ab,ot,hw. (255)
53. Total$ anomalous pulmonary venous connect$.ti,ab,ot,hw. (551)
54. (Shone$ adj2 (syndrome or complex or anomaly or defect$ or deform$ or malform$ or abnormal$)).ti,ab,ot,hw. (84)
55. (Marfan$ adj2 (syndrome or complex)).ti,ab,ot,hw. (6455)
56. Marfans.ti,ab,ot,hw. (2031)
57. (eisenmenger$ adj2 (syndrome or complex)).ti,ab,ot,hw. (1340)
58. univentric$ heart$.ti,ab,ot,hw. (593)
59. uni-ventric$ heart$.ti,ab,ot,hw. (6)
60. ((coronary or heart) adj2 disease).ti,ab,ot,hw. (335,859)
61. (isch?emic heart disease$ or myocardi$ isch?em$ or angina$).ti,ab,ot,hw. (164,773)
62. (MI or IHD).ti,ab,ot. (32,623)
63. (isch?emic heart disease$ or myocardi$ isch?em$ or angina$).ti,ab,ot,hw. (164,773)
64. ((right or double) adj2 aort$ arch$).ti,ab,ot,hw. (1466)
65. (aberrant subclavian arter$ or aberrant sub-clavian arter$).ti,ab,ot,hw. (139)
66. (Vascular ring or pulmonary arter$ sling or anomalous coronary arter$).ti,ab,ot,hw. (3918)
67. truncus arteriosus.ti,ab,ot,hw. (1200)
68. common arterial trunk.ti,ab,ot,hw. (153)
69. (superior cavopulmonary anastamosis or superior cavo-pulmonary anastamosis).ti,ab,ot,hw. (2)
70. arterial switch.ti,ab,ot,hw. (1117)
71. total cavopulmonary connection$ or total cavo-pulmonary connection$).ti,ab,ot,hw. (553)
72. partial$ anomalous pulmonary venous drainage.ti,ab,ot,hw. (142)
73. (DAA or TCPC).ti,ab,ot. (729)
74. (Kawasaki adj2 (disease$ or disorder$ or syndrome$)).ti,ab,ot,hw. (4378)
75. major aorto-pulmonary collateral arter$.ti,ab,ot,hw. (34)
76. ((cardiac$ or cardio$ or heart$ or aort$ or coronary) adj4 (heterotax$ or laterality or isomerism)).ti,ab,ot,hw. (275)
77. ((rastelli or mustard or senning or le compte) adj4 (cardiac$ or cardio$ or heart$ or aort$ or coronar$)).ti,ab,ot,hw. (80)
78. ((fontan or hemifontan or hemi-fontan or glenn or norwood) adj3 (procedure$ or operation$ or method$ or approach$)).ti,ab,ot,hw. (4106)
79. (aortic root or myxoma$ or angiomyxoma$).ti,ab,ot,hw. (13,782)
80. or/15-79 (805,212)
81. animal/ or animal experiment/ (3,045,231)
82. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (4,666,017)
83. or/81-82 (4666017)
84. exp human/ or human experiment/ (12,216,815)
85. 82 not (82 and 84) (3,748,300)
86. 80 not 85 (725,233)
87. 14 and 86 (560)
88. **limit 87 to yr="2000 -Current" (527)**

Cochrane Database of Systematic Reviews (Internet) Issue 1 : 2011, 2000–11; Cochrane Central Register of Controlled Trials (CENTRAL) Issue 1 : 2011, 2000–11

Searched 17 February 2011.

#1   (Somatom definition flash):ti,ab,kw (0)
#2   DSCT:ti,ab,kw (4)
#3   (Aquilion-1 or Aquilion-one):ti,ab,kw (0)
#4   (Brilliance near ict):ti,ab,kw (0)
#5   "Discovery ct750":ti,ab,kw (0)
#6   "Discovery ct-750":ti,ab,kw (0)
#7   (640row* or 640-row* or 640-detect* or 640slice* or 640-slice* or 320row* or 320-row* or 320-detect* or 320slice* or 320-slice*):ti,ab,kw (0)
#8   (256row* or 256-row* or 256-detect* or 256slice* or 256-slice*):ti,ab,kw (0)
#9   (128row* or 128-row* or 128-detect* or 128slice* or 128-slice*):ti,ab,kw (1)
#10   ("2" near/2 (energy or source*)):ti,ab,kw (185)
#11   (Dual* near/2 (energy or source*) near/3 (CT or scan* or DSCT or imag* or multidetect* or multi-detect* or computed or tomography*)):ti,ab,kw (50)
#12   (High definition near/3 (CT or scan* or DSCT or imag* or multidetect* or multi-detect* or computer or tomography*)):ti,ab,kw (7)
#13   (modern cone-beam dual-source spiral):ti,ab,kw (0)
#14   (high pitch dual spiral near/3 (CT or scan* or imag* or technique* or protocol* or DSCT or multidetect* or multi-detect* or computer or tomography*)):ti,ab,kw (0)
#15   (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) (242)
#16   (#15), from 2000 to 2011 (**168**)

CDSR search retrieved three references.
CENTRAL search retrieved 154 references.

Database of Abstracts of Reviews of Effects (Internet) 1 January 2000 to 15 February 2011, NHS Economic Evaluation Database (Internet) 1 January 2000 to 15 February 2011 and Health Technology Assessment Database (Internet) 1 January 2000 to 15 February 2011

Searched: 5 February 2011.

#1   (Somatom NEAR definition NEAR flash) (0)
#2   DSCT:ti (0)
#3   DSCT (0)
#4   (Aquilion-1 OR Aquilion-one) (0)
#5   (Brilliance NEAR ict) (0)
#6   "Discovery ct750" 0
#7   "Discovery ct-750" (0)
#8   (640slice* OR 640-slice* or 640row* or 640-row* or 640-detect*) (0)
#9   (256slice* OR 256-slice* or 256row* or 256-row* or 256-detect*) (2)
#10   (128slice* OR 128-slice* or 128row* or 128-row* or 128-detect* or 320slice* OR 320-slice* or 320row* or 320-row* or 320-detect*) (0)
#11   ("2" NEAR energy) (88)
#12   ("2" NEAR source*) (411)
#13   (Dual* NEAR energy NEAR CT) (2)
#14   (Dual* NEAR energy NEAR scan*) (9)
#15   (Dual* NEAR energy NEAR imag*) (5)

#16 (Dual* NEAR energy NEAR multidetect*) (0)
#17 (Dual* NEAR energy NEAR multi-detect*) (0)
#18 (Dual* NEAR energy NEAR Computed) (16)
#19 (Dual* NEAR energy NEAR tomograph*) (21)
#20 (Dual* NEAR source NEAR CT) (1)
#21 (Dual* NEAR source NEAR scan*) (0)
#22 (Dual* NEAR source NEAR imag*) (1)
#23 (Dual* NEAR source NEAR multidetect*) (0)
#24 (Dual* NEAR source NEAR multi-detect*) (0)
#25 (Dual* NEAR source NEAR Computed) (0)
#26 (Dual* NEAR source NEAR tomograph*) (0)
#27 (High NEAR definition NEAR CT) (0)
#28 (High NEAR definition NEAR scan*) (0)
#29 (High NEAR definition NEAR imag*) (2)
#30 (High NEAR definition NEAR multidetect*) (0)
#31 (High NEAR definition NEAR multi-detect*) (0)
#32 (High NEAR definition NEAR Computed) (0)
#33 (High NEAR definition NEAR tomograph*) (0)
#34 (modern NEAR cone-beam NEAR dual-source NEAR spiral) (0)
#35 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 (525)
#36 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 (527)
#37 #36 RESTRICT YR 2000 2011 (**415)**

DARE search retrieved 181 references.
NHS EED search retrieved 182 references.
HTA search retrieved 52 references.

Science Citation Index (Web of Science): 1 January 2000 to 5 March 2011

Searched 9 March 2011.

#16 2,853 #14 not #15
    Databases=SCI-EXPANDED Timespan=2000-2011
#15 >100,000 TS=(cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep)
    Databases=SCI-EXPANDED Timespan=2000-2011
#14 3,079 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
    Databases=SCI-EXPANDED Timespan=2000-2011
#13 9 TS=(high SAME pitch SAME dual SAME spiral SAME (CT or scan* or imag* or technique* or protocol* or DSCT or multidetect* or multi-detect* or computer or tomograph*))
    Databases=SCI-EXPANDED Timespan=2000-2011
#12 1 TS=(modern SAME cone-beam SAME dual-source SAME spiral)
    Databases=SCI-EXPANDED Timespan=2000-2011
#11 401 TS=(High SAME definition SAME (CT or scan* or DSCT or imag* or multidetect* or multi-detect* or computer or tomograph*))
    Databases=SCI-EXPANDED Timespan=2000-2011
#10 2,443 TS=(Dual* SAME (energy or source*) SAME (CT or scan* or DSCT or imag* or multidetect* or multi-detect* or computed or tomograph*))
    Databases=SCI-EXPANDED Timespan=2000-2011

#9　121 TS=(128slice* or 128-slice* or 128row* or 128-row* or 128-detect* or 320slice* OR
　　　320-slice* or 320row* or 320-row* or 320-detect*)
　　　Databases=SCI-EXPANDED Timespan=2000-2011

#8　100 TS=(256slice* or 256-slice* or 256row* or 256-row* or 256-detect*)
　　　Databases=SCI-EXPANDED Timespan=2000-2011

#7　3 TS=(640slice* or 640-slice* or 640row* or 640-row* or 640-detect*)
　　　Databases=SCI-EXPANDED Timespan=2000-2011

#6　1 TS=(Discovery SAME ct-750)
　　　Databases=SCI-EXPANDED Timespan=2000-2011

#5　0 TS=(Discovery SAME ct750)
　　　Databases=SCI-EXPANDED Timespan=2000-2011

#4　1 TS=(Brilliance SAME ict)
　　　Databases=SCI-EXPANDED Timespan=2000-2011

#3　5 TS=(Aquilion-1 or Aquilion-one)
　　　Databases=SCI-EXPANDED Timespan=2000-2011

#2　186 TS=DSCT
　　　Databases=SCI-EXPANDED Timespan=2000-2011

#1　4 TS=(Somatom SAME definition SAME flash)
　　　Databases=SCI-EXPANDED Timespan=2000-2011

Clinicaltrials.gov (Internet)

http://clinicaltrials.gov/ct2/search/advanced.

Searched 9 March 2011.

Advanced search option: search terms box.

Search terms	Intervention	Results
Somatom	–	3
DSCT	–	11
Aquilion	–	0
Brilliance	–	3
ct750	–	0
Ct-750	–	0
640-slice OR 640slice or 640row or 640-row or 640-detect	–	0
256-slice OR 256slice or 256row or 256-row or 256-detect	–	0
128-slice OR 128slice or 128row or 128-row or 128-detect or 320slice OR 320-slice or 320row or 320-row or 320-detect	–	0
dual energy	–	224
dual source	–	26
–	High definition	80
High pitch dual spiral	–	1
Total		348

metaRegister of Controlled Trials (Internet)

www.controlled-trials.com/mrct/search.html.

Searched 9 March 2011.

Intervention	Results
Somatom or DSCT or Aquilion or Brilliance or ct750 or Ct-750	4
640-slice OR 640slice or 640row or 640-row or 640-detect	54
256-slice OR 256slice or 256row or 256-row or 256-detect	91
128-slice OR 128slice	0
128row or 128-row	0
128-detector	0
320slice OR 320-slice	0
320row or 320-row	1
320-detector	0
dual energy	189
dual source	3
high definition	9
high pitch dual spiral	0
Total	**351**

World Health Organization International Clinical Trials Registry Platform (Internet)

www.who.int/ictrp/en/.

Searched 9 March 2011.

Advanced search option:

- Recruitment status = ALL
- Date limit: 1 January 2000 to 9 March 2011.

Intervention	Results
Somatom or DSCT or Aquilion or Brilliance or ct750 or Ct-750	5
640-slice OR 640slice or 640row or 640-row or 640-detector	0
256-slice OR 256slice or 256row or 256-row or 256-detector	0
128-slice OR 128slice or 128row or 128-row or 128-detector	0
320slice OR 320-slice or 320row or 320-row or 320-detector	5
dual energy	11
dual source	7
High definition	6
high pitch dual spiral	1
Total	**35**

Electronic searching of conference abstracts

American College of Cardiology (Internet)

All dates.

www.cardiosource.org/Meetings/Previous-Meetings-OLD.aspx.

Searched 22 March 2011.

Search terms	Results
128+row	96
256+row	112
320+row	86
640+row	21
128+slice	202
256+slice	249
320+slice	141
640+slice	249
128+detector	91
256+detector	96
320+detector	82
640+detector	23
Aquilion	26
Brilliance ict	1
Somatom+definition+flash	2
DSCT	21
high+pitch+dual+spiral	33
modern cone-beam dual-source spiral	2
Total	1533

European Society of Cardiology (Internet)

All dates.

www.escardio.org/congresses/past_congresses/Pages/past-ESC-congresses.aspx.

Searched 22 March 2011.

Search terms	Results
256 row	4
320 row	16
640 row	0
128 row	1
256 slice	16
320 slice	26
640 slice	0
128 slice	17
256 detector	5
320 detector	18
640 detector	0
128 detector	6
Aquilion	24
DSCT	41
Dual and energy and CT	15
Dual and energy and scan	9
dual and source and scan	43
high pitch dual spiral	8
Somatom	26
Total	275

Society of Cardiovascular Computed Tomography (Internet): 2006–7, 2009–10

www.scct.org/annualmeeting/2010/index.cfm.

Searched 22 March 2011.

Search terms	2010	2009	2008	2007	2006
128 row	0	0	–	–	0
256 row	0	0	–	–	0
320 row	6	2	–	–	0
640 row	0	0	–	–	0
128 slice	2	0	–	–	0
256 slice	1	3	–	–	0
320 slice	3	0	–	–	0
640 slice	0	0	–	–	0
128 detector	1	0	–	–	0
256 detector	0	0	–	–	0
320 detector	3	1	–	–	0
640 detector	0	0	–	–	0
Aquilion	0	2	–	–	0
Brilliance	0	0	–	–	0
Somatom	0	0	–	–	0
DSCT	0	1	–	–	0
high pitch spiral	2	1	–	–	0
Dual source	20	12	–	–	0
Dual energy	5	3	–	–	0
Total by year	43	25	–	1	0
Total	*69*				

Note: No free content or full abstracts, therefore could only browse abstract titles in programme.

2010 = www.scct.org/annualmeeting/2010/Abstracts_Accepted.pdf
2009 = www.scct.org/annualmeeting/2009/2009PrelimProgram.pdf
2008 = no free access to programme or abstract lists.
*2007 = www.scct.org/annualmeeting/2007/meetingbrochure.pdf
2006 = www.scct.org/annualmeeting/meeting_brochure.pdf

*Unable to search or copy within PDF, therefore browsed listings.

American Heart Association (Internet): 2007–10

Searched 22 March 2011.

2010 = http://circ.ahajournals.org/content/vol122/21_MeetingAbstracts/
2009 = http://circ.ahajournals.org/content/vol120/18_MeetingAbstracts/
2008 = http://circ.ahajournals.org/content/vol118/18_MeetingAbstracts/
2007 = http://circ.ahajournals.org/content/vol116/16_MeetingAbstracts/
2006 = unable to locate searchable abstracts

Search terms	2010	2009	2008	2007
"128 row*"	0	0	0	0
"256 row*"	1	1	1	3
"320 row*"	0	0	2	0
"640 row*"	3	0	0	0
"128 slice*"	3	1	0	0
"256 slice*"	0	0	0	1
"320 slice*"	9	2	3	0
"640 slice*"	0	0	0	0
detector*	25	25	29	26
Aquilion	4	6	1	0
Brilliance	0	2	2	4
Somatom	2	2	4	6
DSCT	1	3	8	9
"high pitch spiral"	1	1	0	0
"Dual source"	11	12	15	10
"Dual energy"	6	10	7	1
Total by year	66	65	72	60
Total	*263*			

Cost-effectiveness search

MEDLINE (OvidSP): 1 January 2000 to week 2 March 2011

Searched 18 March 2011.

1. economics/ (25,965)
2. exp "costs and cost analysis"/ (154,360)
3. economics, dental/ (1814)
4. exp "economics, hospital"/ (17,009)
5. economics, medical/ (8379)
6. economics, nursing/ (3839)
7. economics, pharmaceutical/ (2194)
8. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (327,719)
9. (expenditure$ not energy).ti,ab. (13,900)
10. (value adj1 money).ti,ab. (18)
11. budget$.ti,ab. (14,162)
12. or/1-11 (439,089)
13. ((energy or oxygen) adj cost).ti,ab. (2243)
14. (metabolic adj cost).ti,ab. (578)
15. ((energy or oxygen) adj expenditure).ti,ab. (12,794)

16.　or/13-15 (15,012)

17.　12 not 16 (435,668)

18.　letter.pt. (707,514)

19.　editorial.pt. (270,646)

20.　historical article.pt. (271,900)

21.　or/18-20 (1,237,508)

22.　17 not 21 (411,802)

23.　Somatom definition flash.ti,ab,ot,hw. (4)

24.　DSCT.ti,ab,ot,hw. (250)

25.　(Aquilion-1 or Aquilion-one).ti,ab,ot,hw. (9)

26.　Brilliance ict.ti,ab,ot,hw. (1)

27.　(Discovery ct750 or Discovery ct-750).ti,ab,ot,hw. (1)

28.　(640row$ or 640-row$ or 640-detect$ or 640slice$ or 640 slice$).ti,ab,ot,hw. (2)

29.　(320row$ or 320-row$ or 320-detect$ or 320slice$ or 320 slice$ or 256row$ or 256-row$ or 256-detect$ or 256slice$ or 256 slice$).ti,ab,ot,hw. (130)

30.　(128row$ or 128-row$ or 128-detect$ or 128slice$ or 128 slice$).ti,ab,ot,hw. (42)

31.　('2' adj2 (energy or source$)).ti,ab,ot,hw. (2425)

32.　(Dual$ adj2 (energy or source$) adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computed or tomograph$)).ti,ab,ot,hw. (1160)

33.　(High definition adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computer or tomograph$)).ti,ab,ot,hw. (167)

34.　modern cone-beam dual-source spiral.ti,ab,ot,hw. (1)

35.　(high pitch dual spiral adj3 (CT or scan$ or imag$ or technique$ or protocol$ or DSCT or multidetect$ or multi-detect$ or computer or tomograph$)).ti,ab,ot,hw. (1)

36.　or/23-35 (4014)

37.　animals/ not (animals/ and humans/) (3,467,241)

38.　36 not 37 (3093)

39.　22 and 38 (124)

40.　limit 39 to yr="2000 -Current" (86)

Costs filter

CRD. NHS EED Economics Filter: MEDLINE (Ovid) monthly search (Internet). York: Centre for Reviews and Dissemination; 2010 (accessed 13 January 2011). Available from: www.crd.york. ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED

MEDLINE In-Process and Other Non-Indexed Citations (Ovid SP): 1 January 2000 to 17 March 2011, MEDLINE Daily Update (Ovid SP): 1 January 2000 to 17 March 2011

Searched 18 March 2011.

1.　economics/ (4)

2.　exp "costs and cost analysis"/ (92)

3.　economics, dental/ (0)

4.　exp "economics, hospital"/ (8)

5.　economics, medical/ (0)

6.　economics, nursing/ (0)

7.　economics, pharmaceutical/ (1)

8.　(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (22,066)

9.　(expenditure$ not energy).ti,ab. (661)

10.　value adj1 money).ti,ab. (2)

11.　budget$.ti,ab. (1260)

12. or/1-11 (23,355)
13. ((energy or oxygen) adj cost).ti,ab. (147)
14. (metabolic adj cost).ti,ab. (36)
15. ((energy or oxygen) adj expenditure).ti,ab. (513)
16. or/13-15 (674)
17. 12 not 16 (23,148)
18. letter.pt. (16,125)
19. editorial.pt. (9820)
20. historical article.pt. (136)
21. or/18-20 (26,064)
22. 17 not 21 (22,849)
23. Somatom definition flash.ti,ab,ot,hw. (0)
24. DSCT.ti,ab,ot,hw. (21)
25. (Aquilion-1 or Aquilion-one).ti,ab,ot,hw. (0)
26. Brilliance ict.ti,ab,ot,hw. (0)
27. (Discovery ct750 or Discovery ct-750).ti,ab,ot,hw. (0)
28. (640row$ or 640-row$ or 640-detect$ or 640slice$ or 640 slice$).ti,ab,ot,hw. (0)
29. (320row$ or 320-row$ or 320-detect$ or 320slice$ or 320 slice$ or 256row$ or 256-row$ or 256-detect$ or 256slice$ or 256 slice$).ti,ab,ot,hw. (22)
30. (128row$ or 128-row$ or 128-detect$ or 128slice$ or 128 slice$).ti,ab,ot,hw. (8)
31. ('2' adj2 (energy or source$)).ti,ab,ot,hw. (424)
32. (Dual$ adj2 (energy or source$) adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computed or tomograph$)).ti,ab,ot,hw. (109)
33. (High definition adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computer or tomograph$)).ti,ab,ot,hw. (22)
34. modern cone-beam dual-source spiral.ti,ab,ot,hw. (0)
35. (high pitch dual spiral adj3 (CT or scan$ or imag$ or technique$ or protocol$ or DSCT or multidetect$ or multi-detect$ or computer or tomograph$)).ti,ab,ot,hw. (0)
36. or/23-35 (579)
37. animals/ not (animals/ and humans/) (1590)
38. 36 not 37 (577)
39. 22 and 38 (11)
40. **limit 39 to yr="2000-Current" (10)**

Costs filter

CRD. NHS EED Economics Filter: MEDLINE (Ovid) monthly search (internet). York: Centre for Reviews and Dissemination; 2010 (accessed 13 January 2011). Available from: www.crd.york. ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED

EMBASE (OvidSP): 1 January 2000 to week 11 2011

Searched 21 March 2011.

1. health-economics/ (29,992)
2. exp economic-evaluation/ (164,874)
3. 3 exp health-care-cost/ (158,402)
4. exp pharmacoeconomics/ (135,363)
5. or/1-4 (379,713)
6. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (423,085)
7. (expenditure$ not energy).ti,ab. (16,910)

8. (value adj2 money).ti,ab. (886)

9. budget$.ti,ab. (17,926)

10. or/6-9 (441,343)

11. 5 or 10 (667,209)

12. letter.pt. (722,150)

13. editorial.pt. (367,790)

14. note.pt. (437,051)

15. or/12-14 (1,526,991)

16. 11 not 15 (597,817)

17. (metabolic adj cost).ti,ab. (639)

18. ((energy or oxygen) adj cost).ti,ab. (2509)

19. ((energy or oxygen) adj expenditure).ti,ab. (14,898)

20. or/17-19 (17,385)

21. 16 not 20 (593,880)

22. animal/ or animal experiment/ (3,061,249)

23. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (4,692,356)

24. or/22-23 (4,692,356)

25. exp human/ or human experiment/ (12,289,869)

26. 24 not (24 and 25) (3,767,804)

27. 21 not 26 (568,041)

28. Somatom definition flash.mp. (12)

29. DSCT.mp. (352)

30. (Aquilion-1 or Aquilion-one).mp. (22)

31. Brilliance ict.mp. (4)

32. (Discovery ct750 or Discovery ct-750).mp. (2)

33. (640row$ or 640-row$ or 640-detect$ or 640slice$ or 640 slice$ or 128row$ or 128-row$ or 128-detect$ or 128slice$ or 128 slice$).mp. (80)

34. (320row$ or 320-row$ or 320-detect$ or 320slice$ or 320 slice$ or 256row$ or 256-row$ or 256-detect$ or 256slice$ or 256 slice$).mp. (261)

35. ('2' adj2 (energy or source$)).mp. (2503)

36. (Dual$ adj2 (energy or source$) adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computed or tomograph$)).mp. (1500)

37. (High definition adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computer or tomograph$)).mp. (218)

38. modern cone-beam dual-source spiral.mp. (1)

39. (high pitch dual spiral adj3 (CT or scan$ or imag$ or technique$ or protocol$ or DSCT or multidetect$ or multi-detect$ or computer or tomograph$)).mp. (1)

40. or/28-39 (4631)

41. 27 and 40 (166)

42. **limit 41 to yr="2000-Current" (132)**

Costs filter

CRD. NHS EED Economics Filter: EMBASE (Ovid) weekly search (Internet). York: Centre for Reviews and Dissemination; 2010 (accessed 17 March 2011). Available from: www.crd.york.ac.uk/crdweb/html/helpdoc.htm#embase

Paediatric Economic Database Evaluation (Internet): 2000–9

http://pede.ccb.sickkids.ca/pede/search.jsp.

Searched 21 March 2011.

Searched 'Title, Abstract, or Keywords', 2000–9.

Search term: 'Title, Abstract, or Keywords'	Records retrieved
high definition	0
Somatom	0
DSCT	0
Aquilion	0
brilliance	0
Discovery	0/3
Rows	0
Row	0/1
Slice	0
Slices	0
Detector	0/2
Detectors	0
dual source	0
dual sources	0
dual energy	0
modern cone-beam	0
high pitch dual spiral	0
2 source	0
2 sources	0
2 energy	0
Total	0

The Paediatric Economic Database Evaluation (PEDE) search retrieved **0** records.

Health Economics Evaluation Database (Internet)

Up to 21 March 2011.

http://onlinelibrary.wiley.com/book/10.1002/9780470510933.

Searched 21 March 2011.

Compound search, (all data), 2000–11.

high definition OR Somatom OR DSCT OR Aquilion OR brilliance
OR
Discovery ct750 OR Discovery ct-750
OR
row OR rows OR detector* OR slice*
OR
dual source OR dual energy OR dual sources
OR
modern cone-beam dual-source spiral

OR
high pitch dual spiral
OR
'2 energy' OR '2 source' OR '2 sources'

HEED search retrieved 18 records.

Guidelines search

G-I-N: International Guidelines Library (Internet)

www.g-i-n.net, 2005 to 16 March 2011.

Searched 16 March 2011.

Limited to 2005–11, English language only.

Terms searched	Hits
Free-text: angiogra*	7
Free-text: arteriogra*	0
Free-text: cardiac AND catheter*	6
Free-text: coronary AND catheter*	3
Total (prior to deduplication)	16

National Guidelines Clearinghouse (Internet)

www.guideline.gov/.

Searched 16 March 2011.

Advanced search:

Terms searched	Hits
((catheter* or coronary or cardiac) and (angiogra* or arteriogra*)) or ((coronary or cardiac) and (catheter*))	**138**

National Institute for Health and Clinical Excellence Guidance (Internet)

http://guidance.nice.org.uk/.

Searched 16 March 2011.

Terms searched	Hits
Angiography	18
Angiogra*	0
Arteriogra*	0
Arteriography	0
catheter*	32/97
catheterisation	7/18
catheterization	0
Total	57

Turning Research into Practice database (Internet)

www.tripdatabase.com/.

Searched 16 March 2011.

Limited to Guidelines only: 2005–11.

Terms searched	Hits
(Angiography or Arteriography) from:2005 to:2011	118

Health Technology Assessment database (Internet): 2005–11

www.york.ac.uk/inst/crd/.

Searched 16 March 2011.

#1   (coronary NEAR angiogra*) OR (coronary NEAR arteriogra*) OR (coronary NEAR catheter*) (391)

#2   (cardiac NEAR angiogra*) OR (cardiac NEAR arteriogra*) OR (cardiac NEAR catheter*) (246)

#3   (catheter* NEAR angiogra*) OR (catheter* NEAR arteriogra*) (59)

#4   #1 or #2 or #3 RESTRICT YR 2005 2011 (250)

HTA search retrieved **34** references.

Appendix 2

Study-specific guide to completion of QUADAS-2

The version of QUADAS-2 used in this assessment included only the risk of bias components, as it was considered that the inclusion criteria matched the review question and that questions of applicability were, therefore, not relevant.

Before starting the risk of bias assessment, we considered the relevance of each signalling question to our review, as well as the potential need for additional questions. Further criteria were then defined, as needed, to ensure consistent application of signalling questions and to help in the judgement of the risk of bias. Many signalling questions were not further specified and the answer was judged to be 'yes' if it was clearly reported in the study. If the answer to a signalling question was not clearly reported the question was judged as 'unclear' unless specified differently. 'No' was answered if it was clear from the reporting that an aspect was not fulfilled. An additional question (question 3) was added to domain 2 'index test' to record the potential bias introduced where studies include multiple measurements per patient. Details of the assessment criteria used are reported below.

Domain 1: patient selection

Question 1: Was a consecutive or random sample of patients enrolled?

- 'yes' → low risk of bias
- 'unclear' → unclear risk of bias
- 'no' → high risk of bias

Question 2: Was a case–control design avoided?

- 'yes' → low risk of bias
- 'unclear' → unclear risk of bias
- 'no' → high risk of bias

Question 3: Did the study avoid inappropriate exclusions?

- 'no' for < 10% of patients or 'yes' → low risk of bias
- 'unclear' → unclear risk of bias
- 'no' for ≥ 10% of patients → high risk of bias

Domain 2: index test

Question 1: Were the index test results interpreted without knowledge of the results of the reference standard?

Question 2: Did the study prespecify the threshold for a positive result?

Question 3: Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?

The same criteria applied to each of the three signalling questions:

- 'yes' → low risk of bias
- 'unclear' → unclear risk of bias
- 'no' → high risk of bias

Domain 3: reference standard

Question 1: Is the reference standard likely to correctly classify the target condition?

The use of a reference standard, likely to correctly classify the target condition (i.e. coronary angiography), was an inclusion criterion, hence the answer to this question was always 'yes'.

- 'yes' → low risk of bias

Question 2: Were the reference standard results interpreted without knowledge of the results of the index test?

- 'yes' → low risk of bias
- 'unclear' → unclear risk of bias
- 'no' → high risk of bias

Domain 4: flow and timing

Question 1: Was there an appropriate interval between index test and reference standard?

The time interval between index and reference standard had to be ≤ 3 months in order to be judged as 'adequate'.

- 'no' but only for < 10% of patients or 'yes' → low risk of bias
- the answer was judged to be 'unclear' if the time interval was not reported or if it was unclear what proportion of patients had an inadequate time interval between index test and reference standard → unclear risk of bias
- 'no' for ≥ 10% of patients → high risk of bias

Question 2: Did all patients receive a reference standard?

- 'no' but only for < 10% of patients or 'yes' → low risk of bias
- 'unclear' → unclear risk of bias
- 'no' for ≥ 10% of patients → high risk of bias

Question 3: Did patients receive the same reference standard?
As ICA was the only reference standard allowed in the inclusion criteria this item was always answered with 'yes' → low risk of bias.

Question 4: Were all patients included in the analysis?

- 'no' but only for < 10% of patients or 'yes' → low risk of bias
- 'yes', or < 10% of patients excluded, but unclear how exclusion of non-diagnostic segments may have affected per-patient results → unclear risk of bias
- 'unclear' → unclear risk of bias
- 'no' for ≥ 10% of patients → high risk of bias

The following criteria were used to reach a per-domain judgement of risk of bias:

- If at least one of the signalling questions of a domain had an answer associated with a high risk of bias the domain was judged to have a high risk of bias.
- If the answer to any of the signalling questions was 'unclear' and the answers to the remaining questions were 'yes', the risk of bias was judged to be unclear.
- The answer to all the signalling questions had to be 'yes' in order for the domain to be judged as having a low risk of bias.

Appendix 3

Quality assessment: QUADAS-2 results

Completed QUADAS-2 assessments for all included studies:

Study ID: Alkadhi 2008[41]

Domain 1: patient selection

Describe methods of patient selection:
Consecutive patients with chest pain, negative or equivocal stress test, intermediate risk of CAD and stable clinical conditions referred for ICA

Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: LOW**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Two independent observers who were blinded to clinical information and reference standard results. Disagreements resolved by consensus

Both per-patient and per-segment data were reported; non-diagnostic segments were classified as positive

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: LOW**

Domain 3: reference standard
A. Risk of bias

Describe the reference standard and how it was conducted and interpreted:
ICA, interpreted by one experienced observer, who was aware of clinical history but blind to CT results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing
A. Risk of bias

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
All patients received both tests

Describe the time interval between index and reference standard and any actions taken:
10 ± 6 days (median 8 days, range 1–22 days)

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

Study ID: Brodoefel 2008[46]

Domain 1: patient selection

Describe methods of patient selection:
Patients scheduled for ICA for suspected CAD or CAD progression. Seven patients with previous bypass surgery were excluded. Total number of included patients: 100, HHR 30, HCS 47

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Two observers who were blinded to clinical information and reference standard results, decisions reached by consensus. Data were reported by segment only and it was not clear how non-diagnostic segments were classified. Where there were multiple lesions per segment, the segment was classified by the worst stenosis

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	No
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: HIGH**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
ICA, interpreted by one observer, who was blind to CT results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
Initial reasons for exclusion: refusal/withdrawal of consent (8), impaired renal function (2), previous bypass surgery (7), acute coronary syndrome necessitating immediate ICA (1). One patient with a normal CTA withdrew consent and did not receive the reference standard (excluded after enrolment). All other patients received both tests. However, it was not clear whether or not non-diagnostic segments were included in the analyses

Describe the time interval between index and reference standard and any actions taken:
All CT studies were performed the day before ICA

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	No
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: LOW**

CTA, computed tomography angiography.

Study ID: Brodoefel 2008[42]

Domain 1: patient selection

Describe methods of patient selection:
Patients scheduled for ICA for suspected CAD or CAD progression. Thirteen patients with bypass surgery were excluded. Total number of included patients: 125, obese patients: 44. It was not clear how many, if any, of the 13 excluded patients were in the obese category

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Two observers who were blinded to clinical information and reference standard results, decisions reached by consensus. Data were reported by segment only and it was not clear how non-diagnostic segments were classified. Where there were multiple lesions per segment, the segment was classified by the worst stenosis

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	No
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: HIGH**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
ICA, interpreted by one observer, who was blind to CT results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
Of 145 screened patients 20 were excluded due to refusal of consent (10), withdrawal of consent (2), impaired renal function (3), previous bypass surgery (13), acute coronary syndrome necessitating immediate ICA (2)

All other patients received both tests and all segments appeared to have been included in the analysis; however, it was unclear how non-diagnostic segments were classified
Describe the time interval between index and reference standard and any actions taken:

All CT studies were performed the day before CT

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

Study ID: de Graaf 2010[40]

Domain 1: patient selection

Describe methods of patient selection:
Patients with previous stent implantation, who were being assessed for recurrent chest pain and who received both CT and ICA. Some other 'difficult-to-image' subgroups were excluded; in particular, three patients with increased heart rate and contraindications to beta-blockers were excluded (total included: 53 patients)

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Two observers who were blinded to reference standard results, decisions reached by consensus. Data were reported per stent and per patient and non-diagnostic stents and patients with at least one non-diagnostic stent were classified as positive. Overlapping stents were classified as one stent

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: LOW**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
ICA, interpreted by one observer, who was blind to CT results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
All patients received both tests and all segments and patients were included in the analyses

Describe the time interval between index and reference standard and any actions taken:
Time between CT and ICA was 14 ± 21 days and no interventions or changes to clinical condition occurred between examinations

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

Study ID: LaBounty 2010[38]

Domain 1: patient selection

Describe methods of patient selection:
Abstract only, consecutive patients, stented patients likely to be a subgroup

Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Two blinded observers, disagreements resolved by a third observer. Only per-stent data were extractable

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	No
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: HIGH**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
ICA, interpreted by one blinded observer

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
Analyses were 'intention to diagnose', no further details reported
Describe the time interval between index and reference standard and any actions taken:
No details reported

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Leber 2007[43]

Domain 1: patient selection

Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: LOW**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Two investigators assessed CT, no details reported. CT was done before ICA. Data were reported per segment and per patient

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: UNCLEAR**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
No details of angiography interpretation were reported

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: UNCLEAR**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
One patient was excluded from analysis owing to non-diagnostic CT imaging. Non-diagnostic segments ($n = 16$) were excluded from the analysis but it was not clear how many of these were in patients with HHR and/or AF. If all non-diagnostic segments were in patients with HHR and/or AF the maximum proportion of excluded segments would be 2.5%. In addition, it was not clear how non-diagnostic segments were distributed between patients and hence how their exclusion may have affected per-patient results

Describe the time interval between index and reference standard and any actions taken:
Time between CT and ICA was 1 day

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Lin 2010[44]

Domain 1: patient selection

Was a consecutive or random sample of patients enrolled?	No
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: HIGH**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Two independent observers, blinding not reported

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: UNCLEAR**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
ICA, interpreted by one observer, who was blind to CT results. Data were recorded per patient, per segment and per vessel

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
Nine patients were excluded because the time between index test and reference standard was > 3 months. The rest of the included patients received both tests and all segments and patients appear to have been included in the analyses

Describe the time interval between index and reference standard and any actions taken:
Time between CT and ICA was < 3 months

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

Study ID: Marwan 2010[47]

Domain 1: patient selection

Describe methods of patient selection:
Consecutive patients with AF; 10 patients with rapid AF (HR > 100 b.p.m.) unresponsive to beta-blockers or calcium channel blockers and 14 patients with difficulty in holding their breath were excluded

Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: HIGH**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Two independent observers, blinding not reported but performed before ICA. Both per-patient and per-segment data were reported and non-diagnostic segments were classified as positive

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: UNCLEAR**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
Evaluated by independent observer, no blinding reported, performed after CT

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: UNCLEAR**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
All included patients received both tests and all segments and patients appear to have been included in the analyses

Describe the time interval between index and reference standard and any actions taken:
Time between CT and ICA was < 24 hours

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

Study ID: Meng 2009[48]

Domain 1: patient selection

Describe methods of patient selection:
Consecutive patients with suspected CAD. Patients with previous stent implantation or bypass surgery were excluded. Not reported if any patients met exclusion criteria

Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Two independent observers, blind to reference standard results and clinical details. Only segment or per-artery data were reported for difficult-to-image patient groups

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	No
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: HIGH**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
One experienced cardiologist who was not involved in CT interpretation

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
Non-diagnostic segments were excluded from the analyses (25/1558 for all patients) but it was not clear how many non-diagnostic segments were in the HHR and HCS groups. If all non-diagnostic segments were in the smallest group (HCS), maximum possible proportion would be 7%. One patient was excluded but it is not clear whether this patient was in either the HHR ($n = 50$) or HCS ($n = 17$) groups.

Describe the time interval between index and reference standard and any actions taken:
Time between CT and ICA was < 24 hours

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Oncel 2007[49]

Domain 1: patient selection

Describe methods of patient selection:
Consecutive patients with AF and suspected CAD. Exclusion criteria were previous stent implantation or bypass graft, inability to follow breath-hold instructions, but no patients were excluded on the basis of these criteria

Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: LOW**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Two independent observers, blind to reference standard results. Data were reported per patient, per artery and per segment

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: LOW**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
One experienced cardiologist who was blinded to CT results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
Non-diagnostic segments were excluded from the analyses (13/225), approximately 6% of total. It was not clear how non-diagnostic segments were distributed between patients and hence how their exclusion may have affected per-patient results

Describe the time interval between index and reference standard and any actions taken:
Time between CT and ICA was 1 day

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Oncel 2008[50]

Domain 1: patient selection

Describe methods of patient selection:
Consecutive patients with suspected in-stent restenosis. Patients with inability to breath-hold were excluded. Numbers not reported

Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Two independent observers, blind to reference standard results and clinical data. Data were reported per stent and per patient

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: LOW**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
One experienced cardiologist who was blinded to CT results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
All patients and stents appeared to have been included in the analysis

Describe the time interval between index and reference standard and any actions taken:
Time between CT and ICA was 1 day

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

Study ID: Pflederer 2009[51]

Domain 1: patient selection

Describe methods of patient selection:
Consecutive patients with suspected in-stent restenosis. Lesions with more than one implanted stent [two or more stents implanted in bifurcation lesions, contiguous or slightly overlapping stents, and stent-in-stent implantation, any stent diameter of <3.0 mm, and stents implanted in bypass grafts (31 patients)] were excluded as were patients with AF ($n = 6$) with a total of 112 patients included

Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: HIGH**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Two experienced observers jointly classified images; blinding was not reported. Data were reported per stent and per patient and non-diagnostic stents were classified as positive for the per-patient analysis

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: UNCLEAR**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
One experienced cardiologist who was blinded to CT results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
All patients who met the inclusion criteria appear to have been included in the analysis. Fifteen stents were not included in the analysis; it was unclear how these were distributed between patients and hence how the per-patient analysis may have been affected

Describe the time interval between index and reference standard and any actions taken:
Time between CT and ICA was 1 day

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Pflederer 2010[34]

Domain 1: patient selection

Describe methods of patient selection:
Previously revascularised patients who were scheduled for ICA

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK:UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Abstract only, no detail of interpretation reported. Data reported per stent and per bypass graft

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	No
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: HIGH**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
Abstract only, no detail of interpretation reported

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: UNCLEAR**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
All patients appear to have been included in the analyses

Describe the time interval between index and reference standard and any actions taken:
NR

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Pugliese 2011[52,53]

Domain 1: patient selection

Describe methods of patient selection:
Patients with chest pain and previous stent implantation. Some other difficult-to-image subgroups were excluded (six for irregular heart rhythm/AF, total included 100)

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Index test was interpreted blind to the reference standard results. Data were reported per stented lesion

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	No
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: HIGH**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
Two experienced readers evaluated the DSCT studies independently; the readers were unaware of the findings of conventional angiography

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
A total of 133 patients with chest pain after stent implantation were referred for conventional angiography; 33 were excluded, four because of renal impairment, three owing to contrast allergy, six due to AF/irregular heart rate, and 20 did not give informed consent. All included patients/stented lesions appear to have been included in the analysis. Non-diagnostic segments were classified as positive

Describe the time interval between index and reference standard and any actions taken:
NR

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Rist 2009[54]

Domain 1: patient selection

Describe methods of patient selection:
Patients with chronic AF, referred for CT angiography

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Scans interpreted by two observers, blind to clinical information and other test results. Data were reported per segment and per patient

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: LOW**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
Interpreted by a single observer blind to CT results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study or describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2x2 table:
21/68 participants received the reference standard; all of these patients appear to have been included in the analysis. Non-diagnostic segments ($n=81$) were excluded and it was not clear how many of these were in patients included in the diagnostic accuracy analysis (maximum possible proportion 22.3%). The selection criteria for the 21 patients with the reference standard were unclear

Describe the time interval between index and reference standard and any actions taken:
Mean time between CT and ICA was 20 ± 26 days (range 1 to 97 days)

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	No
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: HIGH**

Study ID: Rixe 2009[35]

Domain 1: patient selection

Describe methods of patient selection:
Consecutive patients with suspected CAD and AF

Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: LOW**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Abstract only, no detail of interpretation reported. Data reported per patient and per segment. Data were evaluated by two experts in consensus. Unassessable segments were considered to be positive

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: UNCLEAR**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
Abstract only, no detail of interpretation reported

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: UNCLEAR**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
All patients appear to have been included in the analyses; non-diagnostic segments were classified as positive

Describe the time interval between index and reference standard and any actions taken:
NR

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Ropers 2007[39]

Domain 1: patient selection

Describe methods of patient selection:
Consecutive patients referred for coronary angiography for suspected CAD. Patients with HHR were included but patients not in sinus rhythm and patients with previous stent implantation or bypass graft were excluded (numbers not reported)

Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Scans interpreted by one observer, blind to clinical information and reference standard results. Data were reported per segment, per artery and per patient

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: LOW**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
Interpreted by a separate single observer, blinding not reported

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: UNCLEAR**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
All patients were included in the analyses, non-diagnostic segments/arteries/patients were classified as positive

Describe the time interval between index and reference standard and any actions taken:
Mean time between CT and ICA was 1.4 days (range 0–11 days)

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

Study ID: Ropers 2008[37]

Domain 1: patient selection

Describe methods of patient selection:
Patients with previous bypass graft. Abstract only, no further details reported. For the graft based analysis only the patent grafts were assessed for stenosis by the authors. With the information given this could be corrected for the graft based results but it is unclear if and how this affected the patient and the segment based analysis

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Abstract only, no details of interpretation reported

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: UNCLEAR**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
Abstract only, no details of interpretation reported

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: UNCLEAR**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 x 2 table:
All patients were included in the per-patient and bypass graft analyses; non-diagnostic segments and occluded grafts were excluded from the per-segment analysis. It was not clear how these were distributed between patients and therefore how the per-patient analysis may have been affected

Describe the time interval between index and reference standard and any actions taken:
Time between CT and ICA was not reported

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Scheffel 2006[55]

Domain 1: patient selection

Describe methods of patient selection:
Patients who had undergone ICA for suspected CAD. Patients with irregular heart rates were not excluded. Patients with previous stent implantation or bypass graft were excluded (numbers not reported)

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Scans interpreted by two independent observers, blinding not reported. Data were reported per segment

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	No
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: HIGH**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
Interpreted by a separate single observer, blind to CT results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
All patients/segments appear to have been included in the analyses, although it was not clear how non-diagnostic segments were classified

Describe the time interval between index and reference standard and any actions taken:
Mean time between CT and ICA was 14 ± 9 days

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

Study ID: Tsiflikas 2010[56,57]

Domain 1: patient selection

Describe methods of patient selection:
Patients without stable sinus rhythm, scheduled for ICA. Seventeen stented segments were excluded (total included 536)

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Index test interpreted blind to reference standard results and clinical information. Only per-segment data were available

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	No
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: HIGH**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
Interpreted blind to index test

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
All patients who met the inclusion criteria received the index test and reference standard, but not all segments appear to have been included in the analysis (unclear how non-diagnostic segments were classified). It was not clear how the possible exclusion of segments may have affected per-patient analysis. Segments with very poor image quality or stents were excluded and there were inconsistencies in the numbers of segments reported

Describe the time interval between index and reference standard and any actions taken:
Examination with quantitative coronary angiography within 1 day after DSCT

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Van Mieghem 2007[36]

Domain 1: patient selection

Describe methods of patient selection:
Symptomatic patients scheduled for invasive angiography, who had previous PCI with large diameter (≥ 3 mm) stents. Patients with previous bypass graft were excluded (numbers not reported)

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
No details of how index test results were interpreted were reported

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: UNCLEAR**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
No details of how reference standard results were interpreted were reported

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: UNCLEAR**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
All patients appeared to have been included in the analysis. Both in-stent restenoses and native vessel stenoses were included in the analysis
Describe the time interval between index and reference standard and any actions taken:
NR

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Study ID: Weustink 2009[45]

Domain 1: patient selection

Describe methods of patient selection:
Consecutive patients with suspected or known CAD. Patients with AF ($n=6$) or previous revascularisation ($n=103$), i.e. total of 109 patients (10.5%) were excluded

Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: HIGH**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
Observers were blinded for reference standard

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: LOW**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
Interpreted blind to CT results

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
1143 consecutive patients were enrolled who met the inclusion criteria. 155 were excluded because they gave no informed consent (52) or had a CABG (103). Of the 988 patients referred for CTCA 61 were excluded based on the exclusion criteria (35 patients due to renal dysfunction, 12 with known contrast allergy, 6 AF with fast ventricular response and 8 due to scan failure). Of the 927 patients still in the study 444 (48%) had the reference standard. It was not reported how those patients were selected

Describe the time interval between index and reference standard and any actions taken:
The reference standard was performed within 4 weeks before or after CT

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	No
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: HIGH**

Study ID: Weustink 2009[58]

Domain 1: patient selection

Describe methods of patient selection:
Symptomatic patients after revascularisation. Patients in AF were excluded [$n = 2$ (3.3%)]

Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: LOW**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:
CT scans interpreted by two observers. The radiologists were blinded to the results of the reference standard. Full-accuracy data are only available for segment based data

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	No
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: HIGH**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:
Interpreted by one cardiologist, blind to CT results

Is the reference standard likely to correctly classify the target condition?	Yes
SOWere the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing
A. Risk of bias

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:
Of 58 consecutive patients after surgical revascularisation 6 were excluded: 1 due to a known allergy to iodinated contrast material, 2 due to impaired renal function, 2 due to AF, and 1 due to logistic inability to undergo a CT scan before ICA

Describe the time interval between index and reference standard and any actions taken:
ICA was performed within 4 weeks of CTCA

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: LOW**

Study ID: Zhang 2010[59]

Domain 1: patient selection

Describe methods of patient selection:	
Consecutive patients with suspected CAD who underwent both dual-source CTCA and CAG and gave informed consent were included. Patients not in sinus rhythm, obese patients and patients with high coronary calcium were not excluded, but patients with previous stent (4) or bypass surgery (none) were excluded (total included: 113, HCS: 12, HHR: 70); it was unclear how the four excluded patients were distributed between these two groups	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	**RISK: UNCLEAR**

Domain 2: index test

If more than one index test was used, please also complete the comparative study domain.

Describe how the index test results were interpreted:	
Interpreted blind to reference standard	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Did the study prespecify the threshold for a positive result?	Yes
Did the study avoid using multiple data sets per patient (reporting of per-segment data only)?	Yes
Could methods used to conduct or interpret the index test have introduced bias?	**RISK: LOW**

Domain 3: reference standard

Describe the reference standard and how it was conducted and interpreted:	
Interpreted blind to CT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could methods used to conduct or interpret the reference standard have introduced bias?	**RISK: LOW**

Domain 4: flow and timing

Draw a flow chart for the study *or* describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table:	
Information partially contradictory	
121 patients with suspected CAD gave informed consent and had both CTCA and CAG. Six patients were excluded because they did not meet the inclusion criteria (four because of stent follow-up, one who did not receive a CAG because of occluded iliac arteries, one due to chest pain during examination); 113 patients were included (for two patients information on why they were excluded from the study was lacking)	
Describe the time interval between index and reference standard and any actions taken:	
Range: 1–155 days, mean: 18 ± 29 days	
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive a reference standard?	Unclear
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: UNCLEAR**

Appendix 4

Data extraction tables

Details of the methods and interpretation of the index test (assessed technology) and reference standard used in included studies

Study ID	Index test (assessed technology) details	Reference standard details
Alkadhi 2010[41]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany *Use of beta-blockers*: 46 patients continued their baseline treatment with beta-blockers, no additional medication for heart rate control was given *Contrast agent*: 80 ml of iodixanol (Visipaque 320, 320 mg/ml, GE Healthcare, Buckinghamshire, UK), intravenously, flow rate of 5 ml/second, followed by 30 ml of saline. Scans performed from tracheal bifurcation to diaphragm *Scan parameters*: detector collimation $2 \times 32 \times 0.6\,mm^3$, slice collimation $2 \times 64 \times 0.6\,mm^3$, gantry rotation time 330 milliseconds, pitch 0.2–0.5, tube current time product 350 milliamps (mA) per rotation, and tube potential 120 kilovolts (kV) *Interpretation*: Two independent observers, who were blinded to clinical history and reference standard results, interpreted all images. Both readers rated image quality as diagnostic or non-diagnostic. Non-diagnostic segments were classified as FP. Positive stenosis was defined as diameter reduction of $>50\%$, measured with an electronic calliper tool. Any disagreements between observers were resolved by consensus	*Catheter angiography*: 'Standard techniques', with at least two views in different planes for each artery (no further details reported) *Interpretation*: One experienced observer who was aware of clinical history, but blinded to CT results, assessed all angiograms. Positive stenosis was defined as diameter reduction of $>50\%$
Brodoefel 2008[42]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany *Use of beta-blockers*: 94 patients had baseline treatment with beta-blockers. No additional beta-blockers were given *Contrast agent*: 80 ml of iomeprol (Imeron 400, Altana, Konstanz, Germany), i.v., flow rate of 5 ml/second, followed by 60 ml of chaser bolus *Scan parameters*: collimation $32 \times 0.6\,mm$, slice acquisition $64 \times 0.6\,mm$, gantry rotation time 330 milliseconds, pitch 0.2–0.43, tube current 400 mA per rotation, and tube voltage 120 kV *Interpretation*: Two experienced readers, who were blinded to reference standard results and clinical information, assessed images by consensus. Positive stenosis was defined as diameter reduction of $\geq 50\%$. Where there were multiple lesions per segment, the segment was classified by the worst stenosis	*Catheter angiography*: Transfemoral and transradial Judkins technique, two or more projections for the right coronary artery and six or more projections for the left coronary artery, performed by two experienced cardiologists *Interpretation*: One observer who was blinded to CT results assessed all angiograms. Positive stenosis was defined as diameter reduction of $\geq 50\%$

Study ID	Index test (assessed technology) details	Reference standard details
Brodoefel 2008[46]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany *Use of beta-blockers*: 75% of the total patient population (not reported for HHR or HCS subgroups) were routinely taking beta-blockers; no additional beta-blockers were administered to any patient *Contrast agent*: 80 ml of iomeprol (Imeron 400, Altana, Konstanz, Germany), i.v., flow rate of 5 ml/second, followed by 60 ml of chaser bolus *Scan parameters*: Collimation 32×0.6 mm, slice acquisition 64×0.6 mm, gantry rotation time 330 milliseconds, pitch 0.2–0.43, tube current 400 mA per rotation, and tube voltage 120 kV *Interpretation*: Two experienced observers, who were blinded to reference standard results and clinical information, assessed images by consensus. Positive stenosis was defined as diameter reduction of $\geq 50\%$. Where there were multiple lesions per segment, the segment was classified by using the worst stenosis	*Catheter angiography*: Transfemoral and transradial Judkins technique, two or more projections for the right coronary artery and six or more projections for the left coronary artery, preformed by two experienced cardiologists *Interpretation*: One observer who was blinded to CT results assessed all angiograms. Positive stenosis was defined as diameter reduction of $\geq 50\%$. Where there were multiple lesions per segment, the segment was classified by using the worst stenosis
De Graaf 2010[40]	*CT scanner*: Aquilion ONE, Toshiba Medical Systems, Otawara, Japan *Use of beta-blockers*: Metoprolol was administered orally, 1 hour before data acquisition, to all patients with HR of > 65 b.p.m., unless contraindicated. Patients with a heart rate between 65 and 75 b.p.m. received 50 mg metoprolol; patients with HR $\geq$ 75 b.p.m. received 100 mg metoprolol *Contrast agent*: Triphasic injection of 60–80 ml of iomeprol (Iomeron 400, Bracco, Milan, Italy), flow rate of 5 or 6 ml/second, followed by 20 ml of 50% contrast/saline mix and finally 25 ml of saline at 3 ml/second *Scan parameters*: Gantry rotation time 350 milliseconds, tube current 400–580 mA (dependent upon BMI), and tube voltage 100–135 kV (dependent upon BMI). All images were acquired during a 5-second breath hold *Interpretation*: Two experienced observers, who were blinded to reference standard results, assessed images by consensus. Overlapping stents were considered to represent a single stent. Significant in-stent restenosis was defined as lumen reduction of $\geq 50\%$, or the presence of significant stent edge (< 5 mm from edge) stenosis. Reduced run-off distal to the stent was also judged to suggest in-stent stenosis. In patient-based analysis, the CTA was deemed non-diagnostic if patients had one or more uninterpretable stents; non-diagnostic stents were classified as positive	*Catheter angiography*: 'Standard techniques,' no further details reported *Interpretation*: One experienced observer, blinded to CT results. Positive stenosis was defined as lumen reduction $\geq 50\%$, or the presence of significant stent edge (< 5 mm from edge) stenosis in the view with the most severe luminal narrowing
LaBounty 2010[38]	*CT scanner*: 128-slice, dual source, manufacturer not specified. Later confirmed by the manufacturer to have used Discovery CT750HD *Use of beta-blockers*: NR *Contrast agent*: No details reported *Scan parameters*: No details reported *Interpretation*: Two blinded, experienced observers interpreted images and disagreements were resolved by a third observer. Positive stenosis was defined as diameter reduction of $\geq 50\%$	*Catheter angiography*: No details reported *Interpretation*: Blinded, experienced core laboratory. Positive stenosis was defined as diameter reduction of $\geq 50\%$
Leber 2007[43]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany *Use of beta-blockers*: No patients received beta-blockers prior to imaging *Contrast agent*: Body weight adapted (1.25 ml/kg Ultravist 370, Schering, Berlin, Germany) i.v. at a constant rate to give an injection time of 20 seconds, followed by 100 ml of saline at 5 ml/second *Scan parameters*: Collimation 0.6 mm, 64 slices, gantry rotation time 330 milliseconds, pitch 0.2–0.44, tube current 560 mA per rotation, and tube voltage 120 kV *Interpretation*: Two independent investigators assessed the DSCT images. Positive stenosis was defined as diameter reduction of > 50%	*Catheter angiography*: Judkins approach using 4F catheters and acquiring standard projections *Interpretation*: No details of who interpreted angiograms were reported. Positive stenosis was defined as diameter reduction > 50%

Study ID	Index test (assessed technology) details	Reference standard details
Lin 2010[44]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany *Use of beta-blockers*: No patients received beta-blockers prior to imaging *Contrast agent*: Continuous injection of 50–70 ml of iopamidol (Iopamiro 370 mg I/ml, Bracco, Milano, Italy) according to patient size, flow rate of 5–7 ml/second, followed by 50 ml of saline *Scan parameters*: Collimation 32 × 0.6 mm, slice acquisition 64 × 0.6 mm, gantry rotation time 330 milliseconds, pitch 0.2–0.43, tube current 400 mA per rotation, and tube voltage 120 kV *Interpretation*: All images were evaluated and classified by two independent readers. Positive stenosis was defined as diameter reduction of > 50%	*Catheter angiography*: Recorded in three orthogonal projections after intracoronary injection of 100 mg nitroglycerine *Interpretation*: Single observer, blind to CT results. Stenotic severity was defined as narrowest diameter divided by diameter of the nearest distal normal segment. Positive stenosis was defined as diameter reduction of > 50%
Marwan 2010[47]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany *Use of beta-blockers*: 46 (77%) participants were on long-term beta-blockers. In addition, three (5%) participants received 100 mg of atenolol orally, before imaging, and 21 (35%) received i.v. metoprolol (5–20 mg) before scanning. Eight patients (13.3) received diltiazem *Contrast agent*: 60–110 ml of iopromide (370 mg iodine/ml, Ultravist 370, Schering, Berlin, Germany), flow rate of 6 ml/second, followed by 50 ml of saline *Scan parameters*: Collimation 2 × 64 × 0.6 mm, rotation time 330 milliseconds, pitch 0.2–0.43, tube current 360 or 400 mA (dependent upon patient BMI), and tube voltage 100 or 120 kV (dependent upon patient BMI) *Interpretation*: All images were jointly assessed by two readers, each with > 3 years' experience in coronary CT angiography. Positive stenosis was defined as diameter reduction of > 50%. Patients with one or more unevaluable vessel were classified as positive because the presence of stenosis could not be ruled out. Patients in whom all vessels were evaluable and no significant stenosis was found were classified as negative	*Catheter angiography*: 'Standard projections' after intracoronary injection of 0.2 mg isosorbide dinitrate *Interpretation*: Projections were evaluated offline by an independent observer. Stenosis was determined from two orthogonal views. Positive stenosis was defined as diameter reduction of ≥ 50%
Meng 2009[48]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany *Use of beta-blockers*: No beta-blockers were administered for scanning *Contrast agent*: Continuous injection of 80 ml bolus of iohexol (350 mg iodine/ml, Amersham Heath, Princeton, NJ), flow rate of 5 ml/second, followed by 50 ml of saline *Scan parameters*: Detector collimation 32 × 0.6 mm, slice acquisition 64 × 0.6 mm, gantry rotation time 330 milliseconds, pitch 0.2–0.5, tube current 400 mA per rotation, and tube voltage 120 kV *Interpretation*: All images were independently assessed by two observers, blind to clinical details and ICA results and any disagreements were resolved by consensus. Positive stenosis was defined as diameter reduction of > 50%	*Catheter angiography*: Standard Judkins technique, two or more projections for the right coronary artery and six or more projections for the left coronary artery *Interpretation*: One experienced cardiologist who was blinded to CT results assessed all angiograms. Positive stenosis was defined as diameter reduction of > 50%
Oncel 2007[49]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany *Use of beta-blockers*: No additional medication for heart rate control given *Contrast agent*: Bolus 70 ml of iopromidum (Ultravist 350/ml, Schering, Berlin, Germany), flow rate of 6 ml/second, followed by 50 ml bolus of saline at 5 ml/second *Scan parameters*: with collimation, 64 × 0.6-mm slice thickness, rotation time 0.33 seconds, pitch 0.26–0.45, tube current 900 mA, and tube voltage 120 kV *Interpretation*: All images were assessed by two radiologists with 5 years cardiac CT experience each, who were blind to ICA results. Positive stenosis was defined as diameter reduction > 50%. Vessels with poor or non-evaluable image quality were excluded from analysis. In per vessel/patient analysis the presence of any significant lesion was considered positive	*Catheter angiography*: 'Standard techniques', no details reported *Interpretation*: One experienced cardiologist who was blinded to CT results assessed all angiograms. Positive stenosis was defined as diameter reduction > 50%

Study ID	Index test (assessed technology) details	Reference standard details
Oncel 2008[50]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany *Use of beta-blockers*: No beta-blockers were given before scanning *Contrast agent*: Bolus 70 ml of iomeprol (400 mg I/ml Iomeron, Bracco, Italy), flow rate of 6 ml/second, followed by 50 ml bolus of saline at 5 ml/second *Scan parameters*: Collimation 32 × 0.6 mm, slice acquisition 64 × 0.6 mm, gantry rotation time 330 milliseconds, pitch 0.2–0.47, tube current 390 mA per rotation and tube voltage 120 kV *Interpretation*: All images were assessed by two independent radiologists with 5 years' cardiac CT experience each, who were blind to ICA results and clinical information. Any disagreements were resolved by consensus. Positive in-stent restenosis was defined as diameter reduction of ≥ 50%. Persistent stenosis was defined as ≥ 50% narrowing, 5 mm proximal and distal to the stent	*Catheter angiography*: 'Standard techniques', no details reported *Interpretation*: One experienced cardiologist (at least 10 years' angiography experience), who was blinded to CT results, assessed all angiograms. Positive stenosis was defined as diameter reduction of ≥ 50% anywhere within the stent or within the 5-mm segment proximal or distal to the stent margins
Pflederer 2009[51]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany *Use of beta-blockers*: Patients with a heart rate of > 65 b.p.m. received 100 mg atenolol orally 45–60 minutes before DSCT. If heart rate remained > 65 b.p.m. up to four doses of metoprolol 5 mg were given intravenously *Contrast agent*: Bolus 60–95 ml of iopromide (370 mg I/ml Ultravist 3070, Schering, Berlin, Germany), flow rate of 6 ml/second, followed by 50 ml bolus of saline at 6 ml/second *Scan parameters*: Collimation 0.6 mm, simultaneous collection of 2 × 64 slices, gantry rotation time 330 ms, pitch 0.2–0.43, tube current 400 mA and tube voltage 120 kV *Interpretation*: All images were jointly assessed by two readers with > 3 years' cardiac CT experience. Each stent was first classified as assessable or not assessable. Assessable stents were evaluated for stenosis. Positive in-stent restenosis was defined as diameter reduction of ≥ 50%. For patient based assessment non-assessable stents were classified as having in-stent restenosis using DSCT	*Catheter angiography*: To acquire two or more projections of the stented coronary segment *Interpretation*: One experienced observer who was blinded to CT results assessed all angiograms. Positive stenosis was defined as diameter reduction ≥ 50%. Diagnostic accuracy was calculated for assessable stents
Pflederer 2010[34]	*CT scanner*: Somatom Definition FLASH, Siemens Healthcare, Forchheim, Germany *Use of beta-blockers*: NR *Contrast agent*: 60–90 ml, intravenously, unspecified contrast agent, flow rate of 6 ml/second *Scan parameters*: collimation 2 × 128 × 0.6 mm, gantry rotation time 280 milliseconds. No further details reported *Interpretation*: No details of who interpreted scans were reported. Positive stenosis was defined as diameter reduction > 50%	*Catheter angiography*: No details reported *Interpretation*: No details of who interpreted angiograms were reported. Positive stenosis was defined as diameter reduction of > 50%
Pugliese 2008[52] and Pugliese 2007[53]	*CT scanner*: Somatom Definition, Siemens, Forchheim, Germany *Use of beta-blockers*: 70 (70%) of patients were on treatment with beta-blockers, none received additional beta-blockers prior to scanning *Contrast agent*: 60–100 ml contrast agent (Iomeron 400 mg/ml, Bracco, Italy) was injected into the antecubital vein at a flow rate of 5.0 ml/second, followed by a saline chaser (40 ml) *Scan parameters*: Collimation 2 × 32 × 0.6-mm, gantry rotation time 330 ms, pitch 0.20–0.43, tube current 412 mA/rotation, and tube voltage 120 kV *Interpretation*: Two experienced readers evaluated the DSCT studies independently; the readers were unaware of the findings of conventional angiography. Any disagreements were resolved by consensus. Positive in-stent restenosis was defined as ≥ 50% lumen diameter reduction. When multiple stents were implanted contiguously to treat one lesion, they were considered as one single stent. When stent lumen was uninterpretable and in-stent restenosis could not be excluded the stents were considered to have restenosis	*Catheter angiography*: No details reported *Interpretation*: A single observer, who was unaware of the CT results, examined the angiograms before contrast injection to identify the sites of stent implantation. Positive in-stent restenosis was defined as luminal narrowing of > 50%

Study ID	Index test (assessed technology) details	Reference standard details
Rist 2009[54]	*CT scanner*: Somatom Definition, Siemens Medical Systems, Forchheim, Germany *Use of beta-blockers*: Beta-blockers were not administered before the examination; 16 patients were receiving continuous beta-blocker treatment, which was not interrupted for the examination *Contrast agent*: Body weight adapted (1.25 ml/kg Ultravist, Iopromide 370 mgI/ml, Bayer-Schering, Berlin, Germany) i.v., mean volume 90 ml, mean flow rate 5.5 ml, followed by 50 ml saline *Scan parameters*: Collimation 0.6 mm, gantry rotation time 330 milliseconds, pitch 0.2–0.43, tube current time product 410 mA/rotation, effective tube current time product 360 mA, and tube voltage 120 kV *Interpretation*: All images were assessed by two experienced readers, blinded to clinical information and other test results. Positive stenosis per patient was defined as one or more significant diameter reduction ≥ 50%	*Catheter angiography*: Two or more projections for each coronary artery *Interpretation*: One independent observer, who was blinded to CT results, assessed all angiograms. Positive stenosis was defined as diameter reduction of ≥ 50%
Rixe 2009[35]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany *Use of beta-blockers*: Beta-blockers were not administered before the examination *Contrast agent*: No details reported *Scan parameters*: Collimation 64 × 0.6 mm, no further details *Interpretation*: No details of who interpreted scans were reported. Positive stenosis was defined as diameter reduction of > 50%. Un-assessable segments were regarded as having significant stenosis	*Catheter angiography*: No details reported *Interpretation*: No details of who interpreted angiograms were reported. Positive stenosis was defined as diameter reduction of > 50%
Ropers 2007[39]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany *Use of beta-blockers*: Beta-blockers were not administered before the examination; 34 patients were taking routinely beta-blockers, which were not discontinued for the examination *Contrast agent*: ≥ 60 ml (Omnipaque 350, Schering AGF, Berlin, Germany) i.v., flow rate 5 ml/second, followed by 50 ml of saline at 5 ml/second *Scan parameters*: Collimation 0.6 mm, 2 × 64 slices, gantry rotation time 330 ms, pitch 0.2–0.43, tube current 400 mA/tube, and tube voltage 120 kV *Interpretation*: All images were assessed by one observer, blinded to clinical information and ICA results. Each coronary segment was first classified as evaluable or not evaluable. In evaluable segments Positive stenosis was defined as diameter reduction of > 50%. Unevaluable segments were classified as positive	*Catheter angiography*: No details reported *Interpretation*: One observer, different from the CT observer. Positive stenosis was defined as diameter reduction of > 50%
Ropers 2008[37]	*CT scanner*: DSCT-Scanner, no details reported *Use of beta-blockers*: NR *Contrast agent*: NR *Scan parameters*: Collimation 0.6 mm, 2 × 64 slices, gantry rotation time 330 ms, no further details reported *Interpretation*: No details of who interpreted scans were reported. Positive stenosis was defined as diameter reduction of ≥ 50%	*Catheter angiography*: No details reported *Interpretation*: No details of who interpreted angiograms were reported. Positive stenosis was defined as diameter reduction of ≥ 50%

Study ID	Index test (assessed technology) details	Reference standard details
Scheffel 2006[55]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany	*Catheter angiography*: 'Standard techniques with multiple views stored', no details reported
	Use of beta-blockers: Beta-blockers were not administered before the examination. Three patients took beta-blockers as part of their baseline medication	*Interpretation*: Assessed by one experienced observer, blind to CT results. Positive stenosis was defined as diameter reduction of > 50%
	Contrast agent: Bolus 80 ml of iodixanol i.v. (Visipaque 320, 320 mg/ml, GE Healthcare, Buckinghamshire, UK), followed by 30 ml of saline at 5 ml/second	
	Scan parameters: Collimation 32 × 0.6 mm, 64 × 0.6 mm slice acquisition, gantry rotation time 330 milliseconds, pitch 0.2–0.39, tube current 80 mA per rotation and tube voltage 120 kV	
	Interpretation: All images were assessed by two independent readers and disagreements were resolved by consensus. Positive stenosis was defined as diameter reduction of > 50%	
Tsiflikas 2010[56] and Drosch[57]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany	*Catheter angiography*: No details reported
	Use of beta-blockers: 35 of 41 patients were on daily beta-blockers treatment. Additional beta blockers before scan NR	*Interpretation*: By one independent, experienced interventional cardiologist, using quantitative coronary analysis with automated vessel contour detection. The cardiologist was not aware of the CT results. In coronary segments with more than one lesion, the lesion with the most severe diameter reduction determined the test result. Positive stenosis was defined as > 50% diameter reduction
	Contrast agent: 70 ml (90 ml in patients with CABGs) Imeron 400mg iodine/ml at a flow-rate of 5 ml/second, followed by a saline chaser bolus (50 ml, flow-rate 5 ml/second)	
	Scan parameters: 0.6 mm collimation (cardiac mode), 330 milliseconds gantry rotation time, pitch 0.2–0.43 (automatically adapted to the patients' heart rate). Tube current for both tubes was 560 mA and tube voltage was 120 kV	
	Interpretation: All CT data sets were interactively assessed by two experienced observers who were not aware of patients' clinical information or the coronary angiographic findings. Positive stenosis was defined as > 50% diameter reduction	
Van Mieghem 2007[36]	*CT scanner*: DSCT (unspecified). No further details reported	*Catheter angiography*: No details reported
	Interpretation: Positive stenosis was defined as > 50% diameter reduction. No further details reported	*Interpretation*: Positive stenosis was defined as > 50% diameter reduction. No further details reported
Weustink 2009[58]	*CT scanner*: Somatom Definition Siemens Healthcare, Forchheim, Germany	*Catheter angiography*: No details reported
	Use of beta-blockers: No beta-blockers were administered before scanning	*Interpretation*: One experienced cardiologist, unaware of the results of the CTA, identified all graft segments, distal run-offs and native coronary segments. Lesions with ≥ 50% lumen diameter reduction in two orthogonal planes were considered positive for stenosis. Distal run-off segments supplied by occluded grafts were classified as native grafted segments. All graft and native coronary segments located distally to a total occlusion (100% lumen reduction) and not supplied by collaterals were classified as post-occlusion segments and were excluded from analysis. In addition, native grafted segments with a lumen diameter of < 1.5 mm were excluded
	Contrast agent: A bolus of iodinated contrast material (Ultravist 370, Schering AG, Berlin, Germany), which varied between 80 and 100 ml depending on the expected scan time, was injected in an antecubital vein followed by a saline chaser (40 ml; flow rate 4.0–5.0 ml/second)	
	Scan parameters: Collimation 2 × 32 × 0.6, rotation time 330 ms, pitch 0.20–0.53, tube current 380 mA/rotation, and tube voltage 120 kV	
	Area scanned: The scan range was extended to the level of the subclavian arteries in patients with internal mammary artery grafts	
	Interpretation: Two experienced radiologists blinded to ICA findings independently scored all CT data sets. Any disagreements were resolved by discussion. Positive stenosis was defined as ≥ 50% lumen diameter reduction	Stents with uninterpretable lumen were classified as having in-stent restenosis

Study ID	Index test (assessed technology) details	Reference standard details
Weustink 2009[45]	*CT scanner*: Somatom Definition Siemens Healthcare, Forchheim, Germany *Use of beta-blockers*: No beta-blockers were administered before scanning *Contrast agent*: A bolus of iodinated contrast material (370 mg/ml, Ultravist; Schering, Berlin, Germany), which varied between 60 and 100 ml, depending on the expected scan time, was injected (flow rate 5.5 ml/second) in an antecubital vein followed by a saline chaser (40 ml; flow rate 5.5 ml/second) *Scan parameters*: Two X-ray tubes, 32 detector rows of 0.6 mm each, rotation time 330 milliseconds, pitch 0.2–0.53, tube voltage 120 kV and full tube current 625 mA (independent of patient size) *Interpretation*: Two experienced observers, each with ≥ 5 years' experience in CT coronary angiography and unaware of the results of conventional coronary angiography, independently scored all CT coronary angiograms; any disagreements were resolved by consensus. Positive stenosis was defined as ≥ 50% lumen diameter reduction. Segments distal to a chronic total occlusion were excluded. An intention-to-diagnose design was used: all scanned patients, including all segments, were analysed even if the image quality was impaired	*Catheter angiography*: No details reported *Interpretation*: Three cardiologists, with ≥ 5 years' experience in interventional cardiology and unaware of the results of CT, assessed all angiograms. All segments, regardless of size, were included for comparison with CT coronary angiography. Positive stenosis was defined as lumen diameter reduction of ≥ 50%
Zhang 2010[59]	*CT scanner*: Somatom Definition, Siemens Medical Solutions, Forchheim, Germany) *Use of beta-blockers*: No beta-blockers were administered before scanning *Contrast agent:* Bolus of 80 ml of Ultravist (370 mg I/ml; Bayer Schering Pharma, Berlin, Germany) followed by 40 ml of saline solution injected into an antecubital vein via an 18-gauge catheter (injection rate 5 ml/second) *Scan parameters*: Rotation time of 0.33 seconds, tube voltage of 120 kV, effective tube current of 330 mA, adapted pitch value of 0.20–0.43 according to heart rate, slice thickness of 0.75 mm, a reconstruction increment of 0.5 mm *Interpretation*: Two experienced observers, who had 8 and 3 years' experience of interpretation of CTCA, respectively, and were unaware of the results of ICA, scored all DSCT coronary angiography data sets Positive stenosis was defined as ≥ 50% diameter reduction. A TP case was defined as having at least one worse than significant or severe stenosis in both per-patient and per-vessel analyses	*Coronary angiography*: CAG (INNOVA 3100, GE Healthcare, Waukesha, WI, USA) was performed according to 'standard techniques,' and multiple views were stored *Interpretation*: By one experienced observer with 10 years' experience in the interpretation of CAT results, who was unaware of the CTCA results Positive stenosis was defined as ≥ 50% diameter reduction. In the case of multiple abnormal segments per artery, the vessel was classified by the segment with the most severe irregularity. Patients were classified as positive for the presence of significant CAD if there was a significant stenosis in any artery

CTA, computed tomography angiography; i.v., intravenously.

Inclusion/exclusion criteria and participant characteristics of included studies

Study ID	Total participants (*n*), participant group (*n*)	Inclusion criteria	Exclusion criteria	Participant characteristics
Alkadhi 2010[41]	Total 150 HHR 75	Patients with chest pain and a negative or equivocal stress test but stable clinical conditions Only patients with an intermediate pre-test probability of CAD were included[128]	Renal insufficiency (creatinine level > 130 µmol/l), previous allergic reactions to iodinated contrast material, known CAD or an unstable clinical condition	*HHR*: Age (years) 63.5 ± 12.0 Male/female 51/24 BMI (kg/m^2) 26.2 ± 4.2 Obesity 27 (36.0%) HR 78.9 ± 9.4 b.p.m. Calcium score 568 ± 807 Type II diabetes mellitus 14 (18.7%) Family history CAD 8 (10.7%) Hyperlipidaemia 32 (42.7%) Symptomic angina 64 (85.3%)
Brodoefel 2008[42]	Total 125 Obese 44	Patients scheduled for catheter angiography for suspected CAD or suspected progression of known CAD	Renal insufficiency (serum creatinine level > 1.5 mg/dl), hyperthyroidism (basal TSH < 0.03 µl/l), known allergic reaction to iodinated contrast media, inability to follow breath-hold instruction, previous bypass surgery	*Obese*: Age (years) 63 Male/female 29/15 BMI (kg/m^2) 32.8 ± 2.5 HR 65.7 ± 12.1 b.p.m. Calcium score 741 ± 968 Diabetes mellitus 15 (34.1%) Hypertension 41 (93.2%)
Brodoefel 2008[46]	Total 100 HHR 30 HCS 47	Patients scheduled for catheter angiography for suspected CAD or suspected progression of known CAD	Renal insufficiency (serum creatinine level > 1.5 mg/dl), hyperthyroidism (basal TSH < 0.03 µl/l), known allergic reaction to iodinated contrast media, inability to follow breath-hold instruction, previous bypass surgery	*Total*: Age (years) 62 ± 10 Male/female 80/20 Adiposis 61 (61%) HR 64.9 ± 13.2 b.p.m. Calcium score 786.5 ± 965.9 Diabetes mellitus 24 (24%) Hypertension 85 (85%)
De Graaf 2010[40]	Total 53 With stents 53 (121 stents)	Patients with previous stent implantation, referred for evaluation of recurrent chest pain, who underwent both CT and ICA	(Supra)ventricular arrhythmias, renal failure (GFR < 30 ml/minute, known allergy to iodinated contrast media, severe claustrophobia, pregnancy, HHR in the presence of contraindications to beta-blockade	*Stented*: Age (years) 65 ± 13 Male/female 37/16 BMI (kg/m^2) 27 ± 3 HR 59 ± 12 b.p.m. Diabetes mellitus 12 (23%) Family history of CAD 16 (30%) Hypertension 43 (81%) Hypercholesterolaemia 45 (85%) Previous MI 28 (53%) Previous bypass graft 8 (15%)
LaBounty 2010[38]	Total 81 With stents, unclear (54 stents)	NR	NR	NR

Study ID	Total participants (*n*), participant group (*n*)	Inclusion criteria	Exclusion criteria	Participant characteristics
Leber 2007[43]	Total 90 HHR and/or AF 46	Patients referred for coronary angiography, who had negative or equivocal stress tests, no prior known CAD and intermediate pre-test probability of CAD[128]	Renal insufficiency, known allergy to iodinated contrast media, unstable clinical condition	*Total*: Age (years) 58 ± 8 Male/female 57/33 HR 73 (range 48 to 112) b.p.m. Diabetes mellitus 8 (8.9%) Family history of CAD 27 (30%) Hypertension 65 (72.2%) Hypercholesterolaemia 36 (40%) Angina 73 (81.1%) Permanent beta-blocker use 23 (25.6%)
Lin 2010[44]	Total 44 HHR 18	Patients suspected CAD and inconclusive cardiac stress test. Only patients with at least one significant stenosis on CT were advised to undergo ICA and these patients were eligible for inclusion in the study	Allergy to iodinated contrast material, renal insufficiency (creatinine level >120 µmol/l), pregnancy, haemodynamic instability, previous coronary stent implantation or bypass, >3 months between CT and ICA	*HR $\geq$ 70 b.p.m.*: Age (years) 59.2 ± 10.3 Male/female 13/5 BMI (kg/m^2) 26.6 ± 2.6 HR 80.1 ± 10.4 b.p.m. Diabetes mellitus 4 (22.2%) Family history of CAD 4 (22.2%) Hypertension 7 (38.9%) Angina 13 (72.2%)
Marwan 2010[47]	Total 60 AF 60	Patients with AF and absence of previously known CAD	Renal insufficiency (serum creatinine >1.4 mg/dl), inability to maintain adequate breath hold, rapid AF non-responsive to beta-blockers and calcium channel blockers (mean HR >100 b.p.m.)	*AF*: Age (years) 71 ± 7 Male/female 34/26 BMI (kg/m^2) 29 ± 5 HR 70 ± 15 b.p.m. Diabetes mellitus 16 (27%) Family history of CAD 10 (17%) Hypertension 56 (93%) Long-term beta-blockers 46 (77%) High likelihood of CAD 24 (40%) Intermediate likelihood of CAD 21 (35%)
Meng 2009[48]	Total 109 HHR 50 HCS 17	Patients with suspected CAD	Allergy to iodinated contrast media, thyroid disorder, renal insufficiency (creatinine level >120 µmol/l), pregnancy, haemodynamic instability, previous stent implantation or bypass graft	*Total*: Age (years) 63 ± 9 Male/female 68/41 BMI (kg/m^2) 26.9 ± 3.3 CCS (Agatston units) 226.5 HR 71.8 ± 13.2 b.p.m. Diabetes mellitus 15 (13.7%) Hypertension 75 (68.8%)
Oncel 2007[49]	Total 15 AF 15	Patients with AF who were suspected of having co-existing CAD and were scheduled to undergo ICA	Unstable clinical condition, known allergy to iodinated contrast media, elevated serum creatinine level (>1.5 mg/dl >132.6 µmol/l), previous stent implantation or bypass graft, inability to follow breath-hold instructions	*AF*: Age (years) 58.5 ± 9.1 Male/female 9/6 HR 83.7 ± 8.9 b.p.m.

Study ID	Total participants (*n*), participant group (*n*)	Inclusion criteria	Exclusion criteria	Participant characteristics
Oncel 2008[50]	Total 35 With stents 35 (48 stents)	Patients with suspected in-stent restenosis, based on symptoms or laboratory findings, who were scheduled to undergo ICA	Unstable clinical condition, known allergy to iodinated contrast media, renal insufficiency (serum creatinine level > 1.5 mg/dl), inability to follow breath-hold instructions	*With stents*: Age (years) 65 ± 8.2 Male/female 25/10 BMI (kg/m^2) 27.2 ± 3.6 Diabetes mellitus 8 (23%) Family history of CAD 18 (52%) Hypertension 21 (59%) Hypercholesterolaemia 24 (68%) Angina 22 (63%) Serum creatinine 1 ± 0.29 mg/dl
Pflederer 2009[51]	Total 112 With stents 112 (150 stents)	Patients with previous stent implantation, who were referred for ICA because of suspected progression of CAD	Known allergy to iodinated contrast media, renal insufficiency (serum creatinine > 1.5 mg/dl), possible pregnancy, in non-sinus rhythm, lesions with more than one implanted stent (two or more stents implanted in bifurcation lesions, contiguous or slightly overlapping stents, and stent-in-stent implantation), any stent diameter < 3.0 mm, and stents implanted in bypass grafts	*With stents*: Age (years) 65 ± 11 Male/female 70/42 BMI (kg/m^2) 28.0 ± 3.9 HR 60 ± 9 b.p.m.
Pflederer 2010[34]	Total 55 Revascularised 55 (42 bypass grafts and 78 stents)	Patients with previous revascularisation who were scheduled for ICA	NR	*Total*: HR 58 ± 7 b.p.m.
Pugliese 2008[52] and 2007[53]	Total: 100 Stent: 100 Stent + high HR: 31	Patients with chest pain and prior stent implantation	Serum creatinine level > 120 µmol/l, irregular heart rhythm, known allergy to iodinated contrast media	*All*: Age (years) 62 ± 10 Male/Female 78/22 Obesity (BMI $\geq$ 30 kg/m^2) 23 (23%) Diabetes mellitus 21 (21%) Family history of CAD 29 (29%) Hypertension ($\geq$ 160/95 or ongoing treatment) 45 (45%) Hypercholesterolaemia (> 200 mg/dl (5.18 mmol/l) 51 (51%)
Rist 2009[54]	Total 68 AF 68	Patients with chronic AF who were referred for CT coronary angiography	Hyperthyroidism (TSH level < 0.3 mU/l), renal insufficiency (serum creatinine level > 1.5 mg/dl), known allergy to iodinated contrast media, treatment with metformin, women who were nursing or in whom pregnancy could not be excluded	*AF*: Age (years) 64 ± 11 Male/female 55/13 HR 77 ± 25 b.p.m.
Rixe 2009[35]	Total 30 AF 30	Patients with AF and suspected CAD	NR	*AF*: Age (years) 64.9 ± 14 Male/female 21/9 HR 73 ± 16 b.p.m.

Study ID	Total participants (*n*), participant group (*n*)	Inclusion criteria	Exclusion criteria	Participant characteristics
Ropers 2007[39]	Total 100 HHR 44	Consecutive patients recruited for a first diagnostic angiogram for suspected CAD	Renal insufficiency (creatinine level > 1.5 mg/dl), in non-sinus rhythm, previously known CAD, previous stent implantation or bypass graft, acute coronary syndrome, haemodynamic instability	*HHR*: Age (years) 60 Male/female 29/15 BMI (kg/m^2) 28 HR 76 ± 9 b.p.m.
Ropers 2008[37]	Total 78 With bypass graft 78 (195 grafts)	Patients with previous bypass graft(s). No further details reported	NR	Age (years) 64 range 40–87 No further details reported
Scheffel 2006[55]	Total 30 HHR 13 HCS 15	Patients who had undergone ICA for suspected CAD. Patients with irregular heart rates were not excluded	Known allergy to iodinated contrast media, renal insufficiency (creatinine level > 120 µmol/l), pregnancy, haemodynamic instability, previous stent implantation or bypass graft	*HHR*: Age (years) 62.9 ± 13.3 Male/female 9/4 BMI (kg/m^2) 27.6 ± 3.5 HR 84.2 ± 8.4 b.p.m. Calcium score 674 ± 780 *HCS*: Age (years) 63.4 ± 8.9 Male/female 14/1 BMI (kg/m^2) 28.5 ± 4.4 HR 70.0 ± 15.1 b.p.m Calcium score 1483 ± 893 *Total*: Age (years) 63.1 ± 11.3 Male/female 24/6 BMI (kg/m^2) 28.3 ± 3.9 Obesity 23 (77%) HR 70.3 ± 14.2 b.p.m. Calcium score 821 ± 904 Diabetes mellitus 19 (63.3%) Family history of CAD 16 (53.3%) Hypertension 23 (76.7%) Angina 21 (70%)
Tsiflikas 2010[56] and Drosch 2008[57]	Total: 44 Arrhythmia: 44	Patients scheduled for ICA because of suspected or known CAD without stable sinus rhythm	Elevated serum creatinine levels of > 1.5 mg/dl, unstable angina, thyroid disease, pregnancy, or patients with previous allergic reactions to iodinated contrast media	*Arrhythmia*: Age (years): 68 ± 9 Male/Female 31/13 BMI (kg/m^2) 27.9 ± 4.3 Obesity 26 (59%) HR 69 ± 14 b.p.m. Calcium score 762 (range 0 to 4949.7) AF 25 (57%) Diabetes mellitus 9 (20%) Hypertension 38 (86%) Family history of CAD 31 (70%) Previous stent implantation 19 (41%) Previous bypass graft 5 (11%) Beta-blocker use 35 (85%)

Study ID	Total participants (*n*), participant group (*n*)	Inclusion criteria	Exclusion criteria	Participant characteristics
Van Mieghem 2007[36]	Total: 33 Stents: 33	Symptomatic patients, scheduled for ICA, who had previous PCI with large diameter (≥ 3 mm) stents	Previous bypass graft	NR
Weustink 2009[58]	Total: 52 CABG: 52 CABG + high HR: NR	Symptomatic patients after surgical revascularisation with sinus heart rhythm, able to breath-hold for 15 seconds, and no previous coronary intervention	Allergy to iodinated contrast media, impaired renal function (serum creatinine level > 120 μmol), AF, logistic inability to undergo a CT scan before ICA	*CABG*: Age (years) 66 ± 13.2 Male/Female 41/11 BMI (kg/m^2) 27.2 ± 5.8 HR 64.4 ± 14.3 b.p.m. Diabetes mellitus 19 (37) Family history of CAD 21 (40%) Hypertension 16 (31) Previous MI 22 (42%) Long-term beta-blockers 47 (90) Single bypass graft 11(21) Two bypass grafts 31 (60) Three bypass grafts 9 (17)
Weustink 2009[45]	Total 927 Intermediate HR: 170 HHR: 85	Symptomatic patients with suspected or known CAD	Previous surgical revascularisation, AF with fast ventricular response, known allergy to iodinated contrast media, impaired renal function (serum creatinine level > 120 μmol)	*Intermediate HR group*: Age (years): 61.0 ± 11.4 Male/Female 193/140 HR 71.9 ± 3.7 b.p.m. Long-term beta-blocker use 134 (40.2%) *High HR group:* Age (years) 56.2 ± 10.3 Male/Female 88/83 HR 88.8 ± 8.4 b.p.m. Long-term beta-blocker use 53 (31.0%)
Zhang 2010[59]	Total: 113 HCS: 12 Medium HR: 31 HHR: 39	Patients with suspected CAD no allergy to iodine-containing contrast medium; sufficient renal function (creatinine level ≥ 120 mol/l), haemodynamic stability, non-pregnant status for women of child-bearing age, and without previous stent or bypass surgery. Patients with non-sinus rhythm, obesity, or high coronary calcium were not excluded	Failure to undergo CCA due to occluded iliac arteries, chest pain during examination	*Total*: Age (years) 64 ± 12 Male/Female 82/31 Atypical angina 46 (40.7%) Typical angina 37 (32.7%) Unstable CAD 30 (26.5%)

GFR, glomerular filtration rate; NR, not reported.

Appendix 5

List of excluded studies with rationale

The following is a list of studies excluded at the full-paper-screening stage of the review, along with the reasons for their exclusion. Studies listed in submissions from manufacturers of NGCCT are labelled '**M**'.

The reasons for study exclusion are coded as follows:

- **population** The study did not include difficult-to-image CAD patients or patients with congenital heart disease, *or* data for these patients were not reported separately, *or* categories of difficult-to-image patients (e.g. obese, HHR, HCS) were not defined, as specified in *Chapter 4* (see *Search strategy*).
- **index test** The study did not assess the effectiveness of one of the four assessed technologies specified in *Chapter 4* (see *Search strategy*).
- **reference standard** The study was a diagnostic test accuracy study, which did not use ICA as the reference standard.
- **outcomes** The study did not report any of the outcomes specified in *Chapter 4* (see *Search strategy*) *or* for diagnostic test accuracy studies, insufficient data were reported to allow the construction of 2×2 contingency tables (numbers of TP, FN, FP and TN test results).
- **study design** The study design was not one of those specified in *Chapter 4* (see *Search strategy*) *or* the study included fewer than 10 participants in the relevant patient groups.

List of studies

1. Achenbach S, Marwan M, Schepis T, Pflederer T, Bruder H, Allmendinger T, *et al.* High-pitch spiral acquisition: a new scan mode for coronary CT angiography. *J Cardiovasc Comput Tomogr* 2009;**3**:117–21. – **outcomes, M**

2. Achenbach S, Ropers U, Kuettner A, Anders K, Pflederer T, Komatsu S, *et al.* Randomised comparison of 64-slice single- and dual-source computed tomography coronary angiography for the detection of coronary artery disease. *JACC Cardiovasc Imaging* 2008;**1**:177–86. – **population**

3. Anan I, Sakumu T, Fukuda K. [Diagnostic accuracy of dual-source CT cardiac imaging in patients with coronary artery disease.] *Jpn J Clin Radiol* 2009;**54**:170–5. – **outcomes**

4. Arnoldi E, Ramos-Duran L, Abro JA, Zwerner PL, Nikolaou K, Reiser MF, *et al.* Coronary CT angiography using prospective ECG triggering. *Radiologe* 2010;**50**:500–6. – **population**

5. Baumuller S, Leschka S, Desbiolles L, Stolzmann P, Scheffel H, Seifert B, *et al.* Dual-source versus 64-section CT coronary angiography at lower heart rates: comparison of accuracy and radiation dose. *Radiology* 2009;**253**:56–64. – **population**

6. Ben Saad M, Rohnean A, Sigal-Cinqualbre A, Adler G, Paul J-F. Evaluation of image quality and radiation dose of thoracic and coronary dual-source CT in 110 infants with congenital heart disease. *Pediatr Radiol* 2009;**39**:668–76. – **outcomes**

7. Bezerra HG, Loureiro R, Sarwar A, Rocha J, Pflederer T, Marwan M, *et al.* Defining the best approach for stenosis quantification by dual-source CT: a comparative study involving intravascular ultrasound and invasive coronary angiography. *Circulation* 2008;**118**:S845. – **reference standard**

8. Bradacova P, Zemanek D, Adla T, Veselka J. Dual-source computed tomography has a high negative predictive value in the evaluation of restenosis after the left main coronary artery stenting. *Am J Cardiol* 2010;**105**:8B. – **reference standard**

9. Burgstahler C, Brodoefel H, Reimann A, Tsiflikas I, Heuschmid M, Uysal I, *et al.* Dual-source CT in non-invasive coronary artery angiography: effect of heart rate, heart rate variability and calcification on image quality and diagnostic accuracy in an unselected patient population. *Circulation* 2007;**116**:1901. – **population**

10. Burgstahler C, Reimann A, Drosch T, Heuschmid M, Brodoefel H, Tsiflikas I, *et al.* Cardiac dual-source computed tomography in patients with severe coronary calcifications and a high prevalence of coronary artery disease. *J Cardiovasc Comput Tomogr* 2007;**1**:143–51. – **population** (HCS not defined as > 400)

11. Busch S, Nikolaou K, Johnson T, Rist C, Knez A, Reiser M, *et al.* [Quantification of coronary artery stenoses. Comparison of 64-slice and dual source CT angiography with cardiac catheterisation.] *Radiologe* 2007;**47**:295–300. – **population**

12. Chan J, Du L, Sarwar S, Khosa F, Kataoka M, Paicopolis M, *et al.* Whole heart coronary artery evaluation in one single heart beat using 320-slice multi-detector computed tomography. Presented at Royal Australian and New Zealand College of Radiologists, Australian Institute of Radiography, Faculty of Radiation Oncology, Australasian College of Physical Scientists and Engineers in Medicine Combined Scientific Meeting; Brisbane, Australia, 22–25 October 2009. *J Med Imaging Radiat Oncol* 2009;**53**:A105. – **population**

13. Chan J, Sarwar S, Khosa F, Kataoka M, Paicopoilis MC, Laham R, *et al.* Diagnostic accuracy of 320-slice multi-detector row computed tomography to detect coronary artery disease: a direct comparison to invasive coronary angiography. Presented at American College of Cardiology 58th Annual Scientific Session and i2 Summit: Innovation in Intervention, Orlando, USA, 29–31 September 2009. *J Am Coll Cardiol* 2009;**53**:A267–8. – **population**

14. Chang Gung Memorial Hospital. *The correlation of heart hemodynamic status between 320 multidetector computed tomography, echocardiography and cardiac catheterisation in patients with coronary artery disease. NCT01083134 (ongoing trial).* 2010. URL: http://ClinicalTrials.gov/show/NCT01083134 (accessed 11 May 2011) – **outcomes**

15. Chao SP, Law WY, Kuo CJ, Hung HF, Cheng JJ, Lo HM, *et al.* The diagnostic accuracy of 256-row computed tomographic angiography compared with invasive coronary angiography in patients with suspected coronary artery disease. *Eur Heart J* 2010;**31**:1916–23. – **outcomes** (2 × 2 data could not be extracted)**, M**

16. Chen BX, Ma FY, Wen ZY, Luo W, Zhao XZ, Kang F, *et al.* [Diagnostic value of 128-slice CT coronary angiography in comparison with invasive coronary angiography.] *Zhonghua Xin Xue Guan Bing Za Zhi* 2008;**36**:223–8. – **population**

17. Chen HW, Fang XM, Hu XY, Bao J, Hu CH, Chen Y, *et al.* Efficacy of dual-source CT coronary angiography in evaluating coronary stenosis: initial experience. *Clin Imaging* 2010;**34**:165–71. – **population**

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21. de Graaf FR, Schuijf JD, van Velzen JE, Kroft LJ, de Roos A, Reiber JHC, *et al.* Diagnostic accuracy of 320-row multidetector computed tomography coronary angiography in the non-invasive evaluation of significant coronary artery disease. *Eur Heart J* 2010;**31**:1908–15. – **population**

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32. Far Eastern Memorial Hospital. Effects of heart rates and variability of heart rates on image quality of dual-source CT coronary angiography. NCT00632918 (completed trial). 2008. URL: http://ClinicalTrials.gov/show/NCT00632918 (accessed 11 May 2011) – **outcomes**

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43. Hosch W, Heye T, Schulz F, Lehrke S, Schlieter M, Giannitsis E, *et al.* Image quality and radiation dose in 256-slice cardiac computed tomography: comparison of prospective versus retrospective image acquisition protocols. *Eur J Radiol* 2011;**80**:127–35. – **outcomes, M**

44. Hou Y, Yue Y, Guo W, Feng G, Yu T, Li G, *et al.* Prospectively versus retrospectively ECG-gated 256-slice coronary CT angiography: image quality and radiation dose over expanded heart rates. *Int J Cardiovasc Imaging* Epub 15 December 2010. – **reference standard, M**

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computed tomography. Presented at 9th International Conference of Non-Invasive Cardiovascular Imaging, Barcelona, Spain, 10–13 May 2009. *Eur Heart J* 2009;**11**:S3. – **population**

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47. Kepka C, Pregowski J, Kruk M. Dual source computed tomography in coronary imaging. *Postepy Kardiol Interwencyjnej* 2008;**4**:31–4. – **study design**

48. Klepzig H. Diagnostic accuracy of dual-source multi-slice CT-coronary angiography in patients with an intermediate pretest likelihood for coronary artery disease. *Eur Heart J* 2008;**29**:680. – **study design**

49. Ko B, Cameron J, Leung M, Lehman S, Hope S, Crossett M, *et al.* Adenosine stress perfusion imaging and coronary angiography using 320 slice computed tomography: a comparison with quantitative coronary angiography and fractional flow reserve. Presented at New Zealand Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand, Adelaide, Australia, 5–8 August 2010. *Heart Lung Circ* 2010;**19**:S163. – **population**

50. Ko B, Cameron JD, Leung M, Lehman SJ, Hope S, Crossett M, *et al.* Adenosine stress perfusion imaging and coronary angiography using 320 slice cardiac CT: a comparison with quantitative coronary angiography and fractional flow reserve. Presented at European Society of Cardiology (ESC) Congress, Stockholm, Sweden, 28 Aug to 1 September 2010. *Eur Heart J* 2010;**31**:152. – **population**

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54. Leber AW, Becker A, Tittus J, von Ziegler F, Becker C, Knez A. Noninvasive heart rate-independent coronary angiography using a new dual X-ray source CT. *Circulation* 2006;**114**:448. – **population**

55. Leschka S, Scheffel H, Desbiolles L, Plass A, Gaemperli O, Stolzmann P, *et al.* Combining dual-source computed tomography coronary angiography and calcium scoring: added value for the assessment of coronary artery disease. *Heart* 2008;**94**:1154–61. – **population**

56. Maluenda G, Goldstein MA, Lemesle G, Weissman G, Weigold G, Landsman MJ, *et al.* Perioperative outcomes in reoperative cardiac surgery guided by cardiac multidetector computed tomographic angiography. *Am Heart J* 2010;**159**:301–6. – **population, M**

57. Massachusetts General Hospital. Comparison of DSCT With IB-IVUS and angiography in the assessment of coronary artery disease. NCT00622167 (terminated trial). 2010. URL: http://ClinicalTrials.gov/show/NCT00622167 (accessed 11 May 2011) – **reference standard**

58. Motoyama S, Anno H, Sarai M, Sato T, Inoue K, Sanda Y, *et al.* Noninvasive coronary angiography using 256-slice multislice computed tomography. *Circulation* 2006;**114**:384. – **population**

59. Motoyama S, Anno H, Sarai M, Sato T, Sanda Y, Ozaki Y, *et al.* Noninvasive coronary angiography with a prototype 256-row area detector computed tomography system comparison with conventional invasive coronary angiography. *J Am Coll Cardiol* 2008;**51**:773–5. – **population**

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62. Nasis A, Leung MC, Antonis PR, Cameron JD, Meredith IT, Moir WS, *et al.* Diagnostic performance of 320-detector row CT coronary angiography: a comparison with invasive angiography. Presented at Transcatheter Cardiovascular Therapeutics Symposium, San Francisco, USA, 21–25 September 2009. *Am J Cardiol* 2009;**104**:68D. – **population**

63. Nieman K, Galema T, Neefjes L, Weustink A, Musters P, Moelker A, *et al.* Head-to-head comparison of coronary calcium imaging, computed tomography coronary angiography and exercise testing in real-world patients with stable chest pain. Presented at American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention, Atlanta, GA, USA, 14–16 March 2010. *J Am Coll Cardiol* 2010;**55**:A78, E729. – **population**

64. Opolski MP, Kepka C, Pregowski J, Kruk M, Dzielinska Z, Michalowska I, *et al.* Dual-source computed tomography angiography for assessment of native coronary circulation and bypass grafts in patients after bypass surgery. Presented at 5th Annual Scientific Meeting of the Society of Cardiovascular Computed Tomography, SCCT 2010, Las Vegas, NV, USA, 15–18 July 2010. *J Cardiovasc Comput Tomogr* 2010;**4**:S49. – **outcomes**

65. Opolski MP, Pregowski J, Kepka C, Kruk M, Pracon R, Ruzyllo W. Dual source computed tomography in visualisation of coronary artery anomalies. *Postepy Kardiol Interwencyjnej* 2008;**4**:133–45. – **outcomes**

66. Ou S-x, Li X-r, Peng G-m, Zhang L, Li S-n. [Imaging of congenital coronary artery anomalies by dual-source computed tomography angiography.] *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2010;**32**:690–4. – **outcomes**

67. Ovrehus KA, Jensen JK, Jensen JM, Bottcher M, Larsen HM, Botker HE, *et al.* Impact of dual source CT angiography on the number of unnecessary invasive coronary angiographies. *Am J Cardiol* 2008;**102**:97I. – **population**

68. Ovrehus KA, Munkholm H, Bottcher M, Botker Hans E, Norgaard BL. Coronary computed tomographic angiography in patients suspected of coronary artery disease: impact of observer experience on diagnostic performance and interobserver reproducibility. *J Cardiovasc Comput Tomogr* 2010;**4**:186–94. – **outcomes**

69. Peng Z-h, Huang J-y, Pu H, Bai L, Chen J-y, Li G, *et al.* [Comparison of coronary angiography with myocardial perfusion imaging in assessment of functionally relevant coronary artery lesion.] *Zhonghua Xin Xue Guan Bing Za Zhi* 2010;**38**:601–5. – **population**

70. Piers LH, Dikkers R, Willems TP, de Smet B, Oudkerk M, Zijlstra F, *et al.* Computed tomographic angiography or conventional coronary angiography in therapeutic decision-making. *Eur Heart J* 2008;**29**:2902–7. – **population**

71. Qin J, Liu L-Y, Meng X-C, Dong Y-X, Zhu J-M, Zheng Z-d, *et al.* [Clinical application of prospective electrocardiogram-gated 320-detector computed tomography coronary angiography.] *Zhonghua Yi Xue Za Zhi* 2010;**90**:3079–83. – **population**

72. Qin J, Zhu KS, Liu LY, Chen JW, Chen XZ, Shan H. [Initial application of coronary images from 320-slice dynamic volume MDCT.] *Zhonghua Yi Xue Za Zhi* 2010;**90**:478–81. – **population, M**

73. Reimann AJ, Tsiflikas I, Brodoefel H, Scheuering M, Rinck D, Kopp AF, *et al.* Efficacy of computer aided analysis in detection of significant coronary artery stenosis in cardiac using dual source computed tomography. *Int J Cardiovasc Imaging* 2009;**25**:195–203. – **population**

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75. Rocha-Filho JA, Shturman L, Rogers IS, Blankstein R, Okada DR, Mamuya WS, *et al.* Incremental value of adenosine-induced stress myocardial perfusion imaging using dual source computed tomography on coronary computed tomography angiography. Presented at American College of Cardiology 58th Annual Scientific Session and i2 Summit: Innovation in Intervention, Orlando, FL, USA, 29–31 March 2009. *J Am Coll Cardiol* 2009;**53**:A259. – **population**

76. Ropers D. Heart rate-independent dual-source computed tomography coronary angiography: growing experience. *J Cardiovasc Comput Tomogr* 2008;**2**:115–16. – **study design**

77. Ropers U, Karakaya S, Wechsel M, Anders K, Ropers D, Kuettner A, *et al.* Randomised comparison of dual source computed tomography and 64-slice multi-detector computed tomography for the detection of coronary artery stenoses. *Circulation* 2006;**114**:448. – **population**

78. Rosenblum D, Kutoloski K, Diaz PJ, Tamarkin S, Friedman D, Milner B. Brilliance iCT: initial experiences with the new generation of cardiovascular computed tomography. *MedicaMundi* 2008;**52**:25–30. – **study design, M**

79. Ruehm S, Lohan D, Krishnam M, Panknin C, Lell MM. Dual-source CT in congenital heart disease. *AJR Am J Roentgenol* 2007;**188**:A4. – **outcomes**

80. Ruzsics B, Gebregziabher M, Schoepf UJ, Lee H, Abro JA, Costello P, *et al.* Dual-energy CT of the heart for diagnosing coronary artery stenosis and myocardial ischaemia: comparison with SPECT. *Circulation* 2008;**118**:S838. – **population**

81. Ruzsics B, Lee H, Zwerner PL, Gebregziabher M, Costello P, Schoepf UJ. Dual-energy CT of the heart for diagnosing coronary artery stenosis and myocardial ischaemia-initial experience. *Eur Radiol* 2008;**18**:2414–24. – **population**

82. Ruzsics B, Schwarz F, Schoepf UJ, Lee YS, Bastarrika G, Chiaramida SA, *et al.* Comparison of dual-energy computed tomography of the heart with single photon emission computed tomography for assessment of coronary artery stenosis and of the myocardial blood supply. *Am J Cardiol* 2009;**104**:318–26. – **population**

83. Scheffel H, Stolzmann P, Karlo C, Trigo-Trindade P, Marincek B, Luescher TF, *et al.* Tako-tsubo phenomenon: dual-source computed tomography and conventional coronary angiography. *Cardiovasc Intervent Radiol* 2008;**31**:226–7. – **study design**

84. Schoenhagen P, Nagel E. Noninvasive assessment of coronary artery disease anatomy, physiology, and clinical outcome. *JACC Cardiovasc Imaging* 2011;**4**:62–4. – **study design**

85. Shyu KG, Chao SP, Law WY. The diagnostic accuracy of 256-row computed tomographic angiography compared with conventional coronary angiography in patients with suspected coronary artery disease. *Circulation* 2009;**120**:S381. – **population**

86.   Stolzmann P, Scheffel H, Leschka S, Plass A, Baumuller S, Marincek B, *et al.* Influence of calcifications on diagnostic accuracy of coronary CT angiography using prospective ECG triggering. *AJR Am J Roentgenol* 2008;**191**:1684–9. – **population** (HCS not defined as > 400)

87.   Sun ML. Diagnostic accuracy of dual-source CT coronary angiography with prospective ECG triggering on different heart rate patients. Presented at International Heart Forum, Beijing, China, 11–13 August 2010. *Cardiology* 2010;**117**:114–15. – **outcomes**

88.   Thai WE, Harper RW, Seneviratne S. Dynamic volume 320-slice CT in the assessment of patent ductus arteriosus for percutaneous closure. *Heart* 2010;**96**:321. – **study design**

89.   Thomas C, Brodoefel H, Tsiflikas I, Bruckner F, Reimann A, Ketelsen D, *et al.* Does clinical pretest probability influence image quality and diagnostic accuracy in dual-source coronary CT angiography? *Acad Radiol* 2010;**17**:212–18. – **population**

90.   Tsiflikas I, Brodoefel H, Reimann AJ, Thomas C, Ketelsen D, Schroeder S, *et al.* Coronary CT angiography with dual source computed tomography in 170 patients. *Eur J Radiol* 2010;**74**:161–5. – **population**

91.   Uehara M, Funabashi N, Ueda M, Murayama T, Takaoka H, Sawada K, *et al.* Quality of coronary arterial 320-slice computed tomography images in subjects with chronic atrial fibrillation compared with normal sinus rhythm. *Int J Cardiol* 2011;**150**:65–70. – **population, M**

92.   University Medical Centre Groningen. *Computed tomographic angiography or conventional coronary angiography in clinical decision-making. NCT00566059 (completed trial).* 2007. URL: http://ClinicalTrials.gov/show/NCT00566059 (accessed 11 May 2011) – **population**

93.   University of Aarhus, Danish Research Agency, Philips Medical Systems, Danish Heart Foundation. *Imaging of vulnerable plaques in coronary artery disease by multidetector computed tomography. NCT00482651 (ongoing trial).* 2011. URL: http://ClinicalTrials.gov/show/NCT00482651 (accessed 11 May 2011)– **index test**

94.   Wagdi P, Alkadhi H. The impact of cardiac CT on the appropriate utilisation of catheter coronary angiography. *Int J Cardiovasc Imaging* 2010;**26**:333–44. – **population**

95.   Wang Y, Zhang Z, Kong L, Song L, Merges RD, Chen J, *et al.* Dual-source CT coronary angiography in patients with atrial fibrillation: comparison with single-source CT. *Eur J Radiol* 2008;**68**:434–41. – **study design** (< 10 participants)

96.   Wang YN, Kong LY, Zhang ZH, Chen LB, Song L, Zhang SY, *et al.* [Diagnostic value of dual-source CT coronary angiography on the detection of coronary artery disease with myocardial perfusion defect.] *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2009;**31**:160–5. – **population**

97.   Weininger M, Nance J, Henzler T, Schmidt B, Costello P, Schoepf UJ. High temporal resolution dual-energy CT of the heart using a novel hybrid image reconstruction algorithm: initial experience. Presented at 5th Annual Scientific Meeting of the Society of Cardiovascular Computed Tomography, SCCT2010, Las Vegas, NV, USA, 15–18 July 2010. *J Cardiovasc Comput Tomogr* 2010;**4**:s1. – **population**

98.   Weustink AC, Mollet NR, Meijboom WB, Krestin GP, de Feyter PM. Diagnostic accuracy of dual source computed tomography coronary angiography in patients referred for conventional angiography. *Circulation* 2006;**114**:448. – **population**

99.   Weustink AC, Mollet NR, Meijboom WB, Otsuka M, Pugliese F, van Mieghem C, *et al.* Diagnostic accuracy of dual source coronary tomography coronary angiography in patients referred for conventional angiography. *J Am Coll Cardiol* 2007;**49**:114A. – **population**

100. Weustink AC, Schinkel AFL, van der Ent M, de Feyter PJ. Pre-procedural dual source 64-slice computed tomography in unprotected left main intervention. *JACC Cardiovasc Interv* 2009;**2**:470–1. – **study design**

101. Yang X, Gai L-y, Li P, Chen Y-d, Li T, Yang L. Diagnostic accuracy of dual-source CT angiography and coronary risk stratification. *Vasc Health Risk Manag* 2010;**6**:935–41. – **population**

102. Zemanek D, Adla T, Bradacova P, Hajek P, Veselka J. The role of the dual-source computed tomography in evaluation of restenosis after the left main coronary artery stenting, a comparison with coronary angiography and intravascular ultrasound. Presented at 22nd Annual Symposium of the Transcatheter Cardiovascular Therapeutics, Washington, USA, 21–25 September 2010. *J Am Coll Cardiol* 2010;**56**:B90. – **reference standard**

103. Zemanek D, Bradacova P, Adla T, Veselka J. The comparison of dual-source computed tomography, coronary angiography and intravascular ultrasound in the evaluation of restenosis after the left main coronary artery stenting. Presented at European Society of Cardiology, ESC Congress, Stockholm, Sweden, 28 August to 1 September 2010. *Eur Heart J* 2010;**31**:289. – **reference standard**

104. Zheng M, Li J, Xu J, Chen K, Zhao H, Huan Y. Dual-source computed tomographic coronary angiography: image quality and stenosis diagnosis in patients with high heart rates. *Tex Heart Inst J* 2009;**36**:117–24.

The following is a list of those studies provided in submissions from manufacturers of NGCCT, which were excluded at the title and abstract screening stage, along with the reasons for their exclusion.

1. Abdelkarim MJ, Ahmadi N, Gopal A, Hamirani Y, Karlsberg RP, Budoff MJ. Noninvasive quantitative evaluation of coronary artery stent patency using 64-row multidetector computed tomography. *J Cardiovasc Comput Tomogr* 2010;**4**:29–37. – **index test**

2. Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, *et al.* Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. *Eur Heart J* 2010;**31**:340–6. – **outcomes**

3. Bardo DME, Asamato J, Mackay CS, Minette M. Low-dose coronary artery computed tomography angiogram of an infant with tetralogy of fallot using a 256-slice multidetector computed tomography scanner. *Pediatr Cardiol* 2009;**30**:824–6. – **study design**

4. Choi SI, George RT, Schuleri KH, Chun EJ, Lima JAC, Lardo AC. Recent developments in wide-detector cardiac computed tomography. *Int J Cardiovasc Imaging* 2009;**25**:23–9. – **study design**

5. Dewey M, Zimmermann E, Wollenberg U, Rief M, Greupner J, Hamm B. Reduction of radiation dose of 320-row coronary computed tomography angiography through prior coronary calcium scanning. Presented at American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention, Atlanta, GA, USA, 14–16 May 2010. *J Am Coll Cardiol* 2010;**55**:A67, E627. – **study design**

6. Earls JP, Berman EL, Urban BA, Curry CA, Lane JL, Jennings RS, *et al.* Prospectively gated transverse coronary CT angiography versus retrospectively gated helical technique: improved image quality and reduced radiation dose. *Radiology* 2008;**246**:742–53. – **outcomes**

7. Efstathopoulos EP, Kelekis NL, Pantos I, Brountzos E, Argentos S, Grebac J, *et al.* Reduction of the estimated radiation dose and associated patient risk with prospective ECG-gated 256-slice CT coronary angiography. *Phys Med Biol* 2009;**54**:5209–22. – **outcomes**

8. Einstein AJ. Radiation risk from coronary artery disease imaging: how do different diagnostic tests compare? *Heart* 2008;**94**:1519–21. – **study design**

9. Faletra FF, D'Angeli I, Klersy C, Averaimo M, Klimusina J, Pasotti E, *et al.* Estimates of lifetime attributable risk of cancer after a single radiation exposure from 64-slice computed tomographic coronary angiography. *Heart* 2010;**96**:927–32. – **index test**

10. Gaudio C, Evangelista A, Pasceri V, Pannarale G, Varrica S, Romitelli S, *et al.* Visualisation of coronary arteries and coronary stents by low dose 320-slice multi-detector computed tomography in a patient with atrial fibrillation. *Int J Cardiol* Epub 20 March 2010. – **study design**

11. Gerber TC, Carr JJ, Arai AE, Dixon RL, Ferrari VA, Gomes AS, *et al.* Ionising radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. *Circulation* 2009;**119**:1056–65. – **study design**

12. Gosling O, Loader R, Venables P, Roobottom C, Rowles N, Bellenger N, *et al.* A comparison of radiation doses between state-of-the-art multislice CT coronary angiography with iterative reconstruction, multislice CT coronary angiography with standard filtered back-projection and invasive diagnostic coronary angiography. *Heart* 2010;**96**:922–6. – **outcomes**

13. Hameed TA, Teague SD, Vembar M, Dharaiya E, Rydberg J. Low radiation dose ECG-gated chest CT angiography on a 256-slice multidetector CT scanner. *Int J Cardiovasc Imaging* 2009;**25**:267–78. – **population**

14. Heilbron BG, Leipsic J. Submillisievert coronary computed tomography angiography using adaptive statistical iterative reconstruction: a new reality. *Can J Cardiol* 2010;**26**:35–6. – **study design**

15. Hein F, Meyer T, Hadamitzky M, Bischoff B, Albrecht W, Hendrich E, *et al.* Prospective ECG-triggered sequential scan protocol for coronary dual-source angiography: initial experience. *Int J Cardiovasc Imaging* 2009;**25**:231–9. – **study design**

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17. Husmann L, Valenta I, Gaemperli O, Adda O, Treyer V, Wyss CA, *et al.* Feasibility of low-dose coronary CT angiography: first experience with prospective ECG-gating. *Eur Heart J* 2008;**29**:191–7. – **study design**

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Appendix 6

The National Institute for Health and Clinical Excellence guidance relevant to treatment of congenital heart disease in childhood

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National Institute for Health and Clinical Excellence. *Transcatheter endovascular closure of perimembranous ventricular septal defect.* Interventional Procedure Guidance 336 [Internet]. London: NICE; 2010. URL: http://guidance.nice.org.uk/IPG336 (accessed 21 April 2011).

National Institute for Health and Clinical Excellence. *Endoscopic saphenous vein harvest for coronary artery bypass grafting.* Interventional procedure guidance 343 [Internet]. London: NICE; 2010. URL: http://guidance.nice.org.uk/IPG343 (accessed 21 April 2011).

Appendix 7

Details of input provided by experts

Assumption	Method of data collection	Expert
Initial treatment decision suspected CAD population	Personal communication	Professor Dr Leonard Hofstra, Department of Cardiology, Maastricht University Medical Centre
	Unpublished study	Joosen I, Versteylen M, Laufer E, Winkens M, Narula J, Hofstra L. The use of Framingham risk score, coronary calcium score and coronary computed tomographic angiography in patients with stable chest pain. Maastricht, Netherlands: Maastricht University Medical Centre; 2011
Radiation dose	Questionnaire	Ruth Clarke, Trainee Consultant Radiographer Mid Yorkshire NHS Trust
		Dr Simon Padley, Consultant Radiologist, Chelsea and Westminster Hospital and Royal Brompton and Harefield NHS Foundation Trust
Difficult-to-image subgroup proportions	Questionnaire	Ruth Clarke. Trainee Consultant Radiographer Mid Yorkshire NHS Trust
		Dr Simon Padley. Consultant Radiologist, Chelsea and Westminster Hospital and Royal Brompton and Harefield NHS Foundation Trust
		Dr Ramesh De Silva. Consultant Interventional Cardiologist, Bedford hospital NHS Trust
		Professor Dr Carl Roobottom, Professor of Radiology and Consultant Radiologist, Plymouth Hospitals NHS Trust
Role of NGCCT in treatment and diagnostics for congenital heart disease	Personal communication	Dr Owen Miller, Consultant in Paediatric and Fetal Cardiology, Evelina Children's Hospital
Acquisition cost and maintenance cost of NGCCT scans	Personal communication	Valarie Fone, Trust Imaging Services Manager, Royal Brompton and Harefield NHS Foundation Trust

Appendix 8

Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist

Section/topic	No.	Checklist item	Reported in:
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	Title page
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	Executive summary
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	*Chapter 1, Conditions and aetiologies*
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes and study design (PICOS)	*Chapter 2, Objectives*
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. website address) and, if available, provide registration information including registration number	Protocol available at: http://guidance.nice.org.uk/DT/3/FinalProtocol/pdf/English
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale	*Chapter 3, Inclusion and exclusion criteria*
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	*Chapter 3, Search strategy*
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	*Appendix 1*
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	*Chapter 3, Inclusion screening and data extraction*
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	*Chapter 3, Inclusion screening and data extraction*
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made	*Chapter 3, Inclusion screening and data extraction*
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was carried out at the study or outcome level), and how this information is to be used in any data synthesis	*Chapter 3, Inclusion screening and data extraction*
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means)	*Chapter 3, Inclusion screening and data extraction* and *Quality assessment*
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if undertaken, including measures of consistency (e.g. I^2) for each meta-analysis	*Chapter 3, Methods of analysis/synthesis*

Section/topic	No.	Checklist item	Reported in:
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies)	NA
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if carried out, indicating which were prespecified	NA
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	*Figure 1*
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations	*Appendix 4* and *Table 1*
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item no. 12)	*Appendix 3*, *Tables 2, 4, 6, 8 ,10, 12* and *14*
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group, (b) effect estimates and CIs, ideally with a forest plot	*Tables 3*, *5*, *7*, *9*, *11*, 13 and *15*
Synthesis of results	21	Present results of each meta-analysis undertaken, including CIs and measures of consistency	*Table 16*
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item no. 15)	*Figure 10*
Additional analysis	23	Give results of additional analyses, if done [e.g. sensitivity or subgroup analyses, meta-regression (see item no. 16)]	NA
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. health-care providers, users and policy-makers)	*Chapter 4*, *Summary*
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias) and at review level (e.g. incomplete retrieval of identified research, reporting bias)	*Chapter 5*, *Statement of principal findings* and *Strengths and limitations of assessment*
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	*Chapter 5*, *Uncertainties*
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review	*Executive summary*

NA, not applicable.

Appendix 9

Protocol

Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Protocol

1. Title of project

Computed tomography (CT) scanners for cardiac imaging – Somatom Definition Flash, Aquilion One, Brilliance iCT and Discovery CT750 HD.

2. Name of External Assessment Group (EAG) and project lead

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3. Plain English Summary

Medical imaging, including computed tomography (CT) scanning, is important in diagnosing and planning treatment for a wide range of conditions. It can also be used to follow patients' progress and to assess whether or not a treatment is working. However, there are some risks and potential disadvantages associated with particular imaging techniques; for example CT imaging uses x-rays and is therefore associated with exposure to potentially harmful radiation, and invasive coronary angiography (a technique used specifically to visualise the coronary arteries) is associated with an increased risk of stroke, heart attack and death).

Imaging technology has developed very rapidly in recent years and new generation high definition CT scanners may offer some advantages over CT scanners and other imaging methods currently in use (e.g. shorter imaging times, reduced radiation dose, better quality images in specific patient groups). The development of these scanners has particularly focussed on the assessment of patients with heart disease, specifically those with coronary artery disease (narrowing of the coronary arteries that may lead to angina or heart attack) and congenital heart disease (abnormalities of the heart present from birth).

The CT scanners currently in use can already diagnose very accurately coronary artery disease that needs treatment (either using stents to push open the affected artery, or one or more coronary artery bypass grafts) in most patients. Therefore, it is thought that new generation high definition CT scanners are most likely to be useful in patients who are difficult to image using current technologies (obese patients, patients with high or irregular heart rates, patients who cannot hold their breath during imaging, and patients who have high levels of coronary calcium or a stent).

High definition CT scanners may also be useful in assessing patients (babies, children and adults) who were born with heart disease. These patients can be diagnosed using existing imaging technologies (ultrasound and magnetic resonance imaging). However, it is thought that CT scanning may provide additional information to help with planning surgery in some patients who have complex abnormalities.

The purpose of this project is to assess the benefits, risks and cost-effectiveness of new generation high definition CT scanners in assessing patients with coronary artery disease who are otherwise difficult or impossible to image accurately, and in planning the treatment of patients with complex congenital heart conditions.

4. Decision problem

4.1.   Objectives

- To determine the clinical and cost effectiveness of high definition CT imaging for the diagnosis of clinically significant coronary artery disease (CAD) in patients with suspected CAD (defined as those who have chest pain or have other symptoms suggestive of CAD) or known CAD (defined as those who have previously been diagnosed with CAD and whose symptoms are no longer controlled by drug treatment and/or are being considered for revascularisation), who are difficult or impossible to image accurately using 64-slice CT technology.

- To determine the clinical and cost effectiveness of high definition CT imaging for treatment planning in babies, infants, children and adults diagnosed with complex congenital heart defects.

4.2.   Intervention technologies

High definition CT scanners can be used for all routine imaging procedures where earlier generations of CT technology are currently applied; this assessment focuses upon specialised cardiac applications, where high definition CT is claimed to offer potential advantages over current imaging modalities, e.g. decreased failure rates in difficult to image patients.[1-4]

The section below describes the relevant technical characteristics of the high definition CT devices included in this assessment.

Somatom Definition Flash

The Somatom Definition Flash is a second generation dual source 128-slice CT scanner designed to provide high resolution images at a fast scanning speed with low dose radiation. The scanner has two X-ray tubes and two detector arrays mounted at 95° to each other. There are 64 x 0.6 mm detector rows (total z-axis coverage 33.4 mm) and each detector row is double sampled to give 128 data channels. The maximum scan speed is 458 mm/s. Fast acquisition times may benefit uncooperative patients, such as young children, and patients for whom a breath hold is difficult.

Somatom Definition Flash also utilises a number of strategies to reduce the radiation load associated with imaging: 'Flash' mode scanning (is recommended for heart rates up to 65 beats per minute (bpm)) in which data projections of the entire heart can be captured in approximately 250 ms with a radiation dose of less than 1 mSv; selective photon shield which filters the high kilo voltage X-rays; Iterative Reconstruction in Image Space (IRIS) to reconstruct an image from raw data, which allows reduction in radiation dose with maintenance of image quality.

For heart patients with heart rates above 65 bpm, different scan modes are recommended which result in slightly higher acquisition times and radiation doses. These scan modes

provide the option of scanning patients with high heart rates without the need to use beta blockers to regulate the heart rate.

Aquilion One

The Toshiba Aquilion ONE is a 640-slice CT scanner with 320 x 0.5 mm detector rows giving z-axis coverage of 160 mm, or 80 mm from 160 x 0.5 mm detector rows in helical scanning mode. This technology offers reduced imaging time and reduced radiation and contrast doses.

Brilliance iCT

The Philips Brilliance iCT is a new generation 256-slice multi detector CT scanner. It has 128 x 0.625 mm detector rows providing a total z-axis coverage of 80 mm. Each detector row is double sampled which increases spatial resolution. It is claimed it can capture an image of the heart in two heart beats. Additional benefits claimed for the Brilliance iCT scanner are: A powerful X-ray tube for improved durability, image quality and spatial resolution, particularly in patients with high BMIs; Innovative NanoPanel detectors to reduce electronic noise, enabling fast, low-dose scans with better definition of small structures; Intelligent RapidView reconstruction to enable high resolution images with a high throughput.

Discovery CT750

The Discovery CT750 from GE Healthcare is a 2 x 64-slice dual energy CT scanner. It has a single X-ray source which switches between two energy levels, allowing two data sets – high energy and low energy – to be acquired simultaneously. It uses a GemstoneTM detector that contributes to high image quality, and an Adaptive Statistical Iterative Reconstruction algorithm to enhance low contrast detection at a reduced level of radiation.

4.3. Population

This assessment will consider two distinct populations, patients with CAD who are difficult or impossible to image using current 64-slice CT technology, and patients with complex congenital heart disease requiring additional information for treatment planning.

CAD is a major cause of cardiovascular disability and death in the UK. It is caused by narrowing of the coronary arteries, most commonly by atherosclerotic deposits of fibrous and fatty tissue, leading to a reduction in the flow of blood to the heart, angina, and ultimately myocardial infarction.
The NICE clinical guideline CG95 (Chest pain of recent onset) defines significant CAD as ≥ 70% diameter stenosis of at least one major epicardial artery segment or ≥ 50% diameter stenosis in the left main coronary artery. [5] Some factors intensify ischaemia and allow less severe lesions (for example ≥ 50% diameter stenosis of one major epicardial artery segment) to produce angina, for example, reduced oxygen delivery, increased oxygen

demand, large mass of ischaemic myocardium, or longer lesion length. Similarly, some factors reduce ischaemia and may render lesions (≥ 70% diameter stenosis of one major epicardial artery segment) asymptomatic, for example a well developed collateral supply or small mass of ischaemic myocardium.

Coronary angiography (CA) or CT coronary angiography (CTCA) is used to assess the state of the arteries and to identify significant narrowing (stenosis) as recommended by NICE clinical guideline CG95. [5] The guideline recommends use of a 64-slice (or above) CT scanner and the diagnostic performance of 64-slice CT is well established; recent systematic reviews have estimated the sensitivity and specificity of 64-slice CT, for the detection of ≥50% coronary artery stenosis, to be 92-99% and 89-92% respectively. [6-8] For most patients, it is therefore unlikely that the use of a high definition CT scanner would offer significant benefit over the use of a 64-slice CT scanner. However, high definition CT scanners may be beneficial in difficult to image groups of patients, for example, those who cannot hold their breath, have an irregular or fast heartbeat, are obese, or in whom artefacts produced by high levels of coronary calcium or existing stents may reduce image quality.[3, 4] These patients are not currently candidates for CT imaging in routine practice, though some may be imaged in specialist centres. The impact of reducing the radiation exposure associated with scanning may be limited in this population as patients with known or suspected CAD tend to be older adults. However, consideration of radiation exposure outcomes may provide some insight into the potential benefits of high definition CT scanners.

High definition CT scanners may also be used to aid treatment planning in a small group of patients with complex congenital heart disease. Though there is some evidence that high definition CT may provide accurate diagnoses for a range of congenital heart conditions,[9, 10] diagnostic accuracy is not considered a relevant outcome for this assessment, as existing imaging strategies provide accurate initial diagnoses, without the need for radiation exposure.

Congenital heart disease is a general term which describes birth defects that affect the heart. There are over 30 different types of heart defect, the most common being ventricular or atrial septal defects, pulmonary or aortic stenosis, patent ductus ateriosus, tetralogy of Fallot, and transposition of the great arteries. The incidence rate for congenital heart disease in the UK is estimated to be one in every 150 babies born and approximately 85% of children born with congenital heart disease respond well to treatment and will survive into adulthood.[11] It is likely that high definition CT would be applicable in only a small proportion of these patients, those with complex conditions. Expert input has indicated that these will primarily involve lesions with a major extra cardiac component that is not well imaged by echocardiography, e.g. Pulmonary atresia with Major Aorta Pulmonary Collaterals (MAPCA), variants of Anomalous Pulmonary Venous Drainage (TAPVD, Scimitar syndrome etc), aortic arch abnormalities (double aortic arch, vascular ring, etc), and lesions with both a vascular and an airway component (pulmonary artery sling, tracheal stenosis, right aortic arch with

aberrant subclavian artery, etc). Additionally, previously treated lesions where stents or pacemakers make MRI unsuitable will be of interest.

The potential advantage of high definition CT scanners over current CT technologies, in these patients, is the fast image acquisition time, which may allow babies and infants to be scanned without the need for a general anaesthetic. Reduced radiation dose also has the potential to decrease rates of radiation-induced cancer and infertility in later life. However, as CT scanning is likely to be used as a single instance for treatment planning, rather than for ongoing monitoring, this impact may be reduced.

4.4.   Relevant comparators

Evaluation of known or suspected CAD in patients who are difficult or impossible to image using 64-slice CT

In these patients, where 64-slice CT is not a viable option, high definition CT may be used to rule out significant stenosis, or to confirm substantial stenosis requiring CABG and thus avoid invasive CA. The only relevant comparator is therefore:

- Invasive coronary angiography (CA) - an invasive imaging technique which uses a contrast dye and X-rays to provide anatomical information about the degree of stenosis in the coronary arteries. A catheter is generally inserted into an artery in the groin and is moved up the aorta and into the coronary arteries. Once in place, the dye is injected through the catheter, and a rapid series of X-ray images are taken to show how the dye moves through the branches of the coronary arteries. Any narrowing of the arteries will show up on the X-ray images. In babies and children a general anaesthetic would be required to perform the procedure.

  Invasive CA is considered the 'gold standard' for providing anatomical information and defining the site and severity of coronary artery lesions despite the significant inter- and intra-reader variation in interpretation. However, there are serious complications associated with the technique, including death, non fatal myocardial infarction and stroke. In addition, it only provides a 2D image as oppose to the 3D image produced by other imaging techniques.

  Invasive CA will be the reference standard for diagnostic accuracy evaluations

Evaluation of congenital heart disease

In these patients, CT scanning is likely to be used following initial diagnosis and as an add-on to imaging with echocardiography and magnetic resonance imaging (MRI). Therefore, 64-slice CT is the only relevant comparator; conventional imaging (echocardiography and/or MRI), without the addition of CT, may be included in the cost-effectiveness model, dependent upon the advice of paediatric cardiology experts.

- 64-slice CT - Multi-slice CT scanners combine the use of X-rays with computerised analysis of series of 2D X-ray images to create 3D images. The technology has been rapidly advancing, with 4-slice CT scanners first appearing in 1998, 16-slice scanners in

2001 and 64-slice scanners at the end of 2004. Multi-slice CTCA is a minimally-invasive investigation which uses a contrast dye injected through a cannula in the forearm and provides anatomical information about the degree of stenosis in the coronary arteries. Cardiac CT has particular challenges due to the continuous motion of the heart.

Studies which compare treatment plan and/or patient outcome, in the same group of patients, with and without CT (high definition or 64-slice), or studies which randomise patients to receive treatment based on assessment with or without CT are relevant to this assessment. Diagnostic accuracy data are not considered relevant.

5.   Report methods for assessing the outcomes arising from the use of the interventions

A systematic review of the evidence on the clinical effectiveness of Somatom Definition Flash and equivalent high definition CT technologies, for the assessment of coronary artery stenosis in difficult or impossible to image patient groups with known or suspected CAD, and for treatment planning in patients with complex congenital heart disease. Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[12] and NICE Diagnostic Assessment Programme interim methods statement. [13]

5.1.   Inclusion and exclusion criteria

Participants

Study populations eligible for inclusion will be:

- Adults (≥18 years) with known (previously diagnosed who have symptoms that are no longer controlled by drug treatment and/or who are being considered for revascularisation) or suspected (chest pain or other suggestive symptoms) CAD, who are difficult to image (not currently candidates for CT imaging). Difficult or impossible to image patients may include, but are not limited to those with:
    - o   Obesity
    - o   High levels of coronary calcium
    - o   Arrhythmias
    - o   High heart rates (>70 bpm)
    - o   Intolerance of beta-blockers
    - o   Stents
    - o   Bypass grafts

- Infants, children and adults diagnosed with complex congenital heart disease, including but not limited to:
    - o   Pulmonary atresia with Major Aorta Pulmonary Collaterals (MAPCA)

- o variants of Anomalous Pulmonary Venous Drainage (TAPVD, Scimitar syndrome, etc)
- o aortic arch abnormalities (double aortic arch, vascular ring, etc)
- o lesions with both a vascular and airway component (pulmonary artery sling, tracheal stenosis, right aortic arch with aberrant subclavian artery, etc)
- o previously treated lesions where stents or pacemakers make MRI unsuitable

This list may be expanded/refined with further expert paediatric cardiology input.

Setting

Relevant settings are secondary or tertiary care.

Interventions

Included interventions are high definition CT scanners:

- Somatom Definition Flash (Siemens AG, Healthcare)
- Aquilion One (Toshiba Medical systems)
- Brilliance iCT (Philips Healthcare)
- Discovery CT750 (GE Healthcare)

If any additional equivalent technologies are identified during the review process, these will also be considered for inclusion.

Comparators

Relevant comparators are 64-slice CT, or conventional imaging (without CT) for the assessment of complex congenital heart disease, and CA only for difficult to image CAD patients.

Reference standard

The reference standard, for diagnostic accuracy of CAD is invasive CA. Diagnostic accuracy is not a relevant outcome for congenital heart disease.

Outcomes

The following outcomes will be considered for both clinical applications:

- Impact of testing on treatment plan (e.g. surgical or medical management), where information on the appropriateness of the final treatment plan is also reported
- Impact of testing on clinical outcome, (e.g. angina, myocardial infarction, cardiovascular mortality)
- Radiation exposure

Radiation dose data will be taken from audit sources rather than literature to avoid bias which may arise from patient selection in published studies.

The following outcomes will be considered for CAD only:

- Test accuracy
- Indeterminacy (test failure rate)

For included studies reporting any of the above outcome measures, the following outcomes will also be considered if reported:

- Acceptability of tests to patients
- Adverse events associated with testing

Study design

The following types of studies will be included:

- Randomised or non-randomised controlled trials, where participants are assigned to the intervention or comparator tests, for treatment planning, and outcomes are compared at follow-up.
- Randomised or non-randomised controlled trials where participants are assigned to conventional imaging only, or conventional imaging plus high definition or 64-slice CT (congenital heart disease only).

Where there is insufficient evidence from trials, the following observational study types will be considered:

- Cross-sectional test accuracy studies, where the intervention is compared with the reference standard (CAD only).
- Observational studies reporting change to treatment plan or clinical outcome subsequent to high definition CT (CAD and congenital heart disease), or 64-slice CT (congenital heart disease only.

Where these 'secondary' study designs are considered, studies of comparator tests (64-slice CT) will only be sought separately for congenital heart disease once similar studies of intervention tests (high definition CT) have been identified. This approach will ensure that the number of studies to be screened remains manageable within the resources allocated to this assessment, and resources are focussed only upon those areas where evidence is available for the intervention technology.

Test accuracy studies, will be required to report the absolute numbers of true positive, false negative, false positive, and true negative test results, or sufficient information to allow their calculation. If data are incomplete, study authors will be contacted to seek clarification, where practical.

The following study/publication types will be excluded:

- Pre-clinical, animal and phantom studies
- Reviews, editorials, and opinion pieces
- Case reports
- Studies reporting only technical aspects of the test, or image quality
- Studies with <10 participants

5.2.　Search strategy

Search strategies will be based on target condition and intervention, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[12, 14]

Additional supplementary searches will be carried out as necessary. Searches for studies for cost and quality of life will also be included, see Section 6 for further detail.

The following databases will be searched for relevant studies from 2000 to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (CRD website)
- Health Technology Assessment Database (HTA) (CRD website)
- Science Citation Index (SCI) (Web of Science)

Completed and ongoing trials will be identified by searches of the following resources (2000-2010):

- ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- Current Controlled Trials (http://www.controlled-trials.com/)
- International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)

Key conference proceedings will be screened for the last five years. These may include Society of Cardiovascular Computed Tomography, British Institute of Radiology, Radiological Society of North America.

Identified references will be downloaded in Endnote X4 software for further assessment and handling.
References in retrieved articles and relevant systematic reviews will be checked.

Search strategies will be developed specifically for each database and the keywords associated with congenital heart defects shall be adapted according to the configuration of each database.

No restrictions on language or publication status will be applied. Limits will be applied to remove animal studies. Searches will take into account generic and other product names for the intervention. Examples of the search strategies to be used are presented in Appendix 1; terms for congenital heart disease will be refined following paediatric cardiology input. Separate search strategies will be constructed for 64-slice CT and congenital heart disease, as necessary.

5.3.   Data extraction strategy

Two reviewers will independently screen titles and abstracts of all reports identified by searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Data relating to study details, participants, intervention and comparator tests, reference standard, and outcome measures will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

5.4.   Quality assessment strategy

The methodological quality of included studies will be assessed using standard tools.[12] The QUADAS tool,[15] is recommended for assessing the methodological quality of test accuracy studies, [12, 16] but a revised version of QUADAS (QUADAS-2) is soon to be published (planned submission date March 2011). QUADAS-2 will more closely resemble the approach and structure of the Cochrane risk of bias tool. The QUADAS-2 tool will be used in this assessment, with the permission of the QUADAS steering group of which the DAR team lead is a member.

The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. In addition, if enough data are available from the included studies, quality components will be included as covariates in SROC models, to investigate their possible association with test performance. Based on the findings of the quality assessment, recommendations will be made for the conduct of future studies.

5.5.   Methods of analysis/synthesis

The results of initial scoping searches suggest that trial data are likely to be sparse or non-existent. This section therefore focuses on the synthesis of data from observational studies.

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by clinical application (CAD or congenital heart disease), relevant patient sub-groups (e.g. type of congenital heart disease, specific 'difficult to image' CAD group), and the outcomes assessed.

Any data included on the following outcome measures: test failure rates; effects of testing on treatment planning and/or clinical outcome; radiation dose; adverse events associated with testing will be summarized according to the size and range of the outcomes reported. For test accuracy data, absolute numbers of true positive, false negative, false positive and true negative test results, as well as sensitivity and specificity values, with 95% confidence intervals will be presented for each study and patient group reported.

Where appropriate, and where sufficient accuracy data are available, summary receiver operating characteristic (SROC) curves will be calculated to summarise test accuracy data. SROC modelling will use the bivariate approach. [17][18][19] Potential sources of heterogeneity will be investigated by extending SROC models to include study level covariates, (e.g. participant age, risk category, CT instrument type, type of congenital heart disease); the bivariate approach to modelling allows investigation of the effects of covariates on sensitivity and specificity separately.

Where data are insufficient to support meta-analyses, the following graphical representations will be presented: plots in ROC space (without summary curves) for test accuracy data; forest plots for any trial data.

A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

6. Report methods for synthesising evidence of cost-effectiveness

6.1   Identifying and reviewing published cost-effectiveness studies

Exploration of the literature regarding published economic evaluations will be performed in the literature databases listed above. In addition, specific health economic databases will be searched (e.g. NHSEED (NHS Economic Evaluation Database), PEDE (Paediatric Economic Database Evaluation), and HEED (Health Economic Evaluation Database); an example search strategy is included in Appendix 1. Searches will focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses, either studying the diagnostic phase, therapeutic phase or a combination, within both populations (CAD and congenital

heart disease). For our assessment only full economic evaluations, i.e. those that explicitly compare different decision options will be selected. Clinical trials as well as modelling studies and cohort studies will be relevant within the frame of our project. The intention is not to perform a systematic review, but to use the studies identified to support the development of an economic model that will aim to answer the research questions of this project.

The results and the methodological quality of the studies selected will be summarised. Assessment of methodological quality will follow the criteria for economic evaluations in health care as described in the NICE methodological guidance.[13] Data extraction will focus on technologies compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), analytical methods and robustness of the study findings.

6.2   Evaluation of costs, quality of life and cost-effectiveness

Since this project aims to assess the value of the diagnostic technologies studied in two different patient populations, two separate economics models will be defined, constructed, analysed, and reported independently. Both models will evaluate the cost-effectiveness of new generation, high definition CT technologies compared to the currently available imaging methods, as described in section 5.1. The perspective will be that of the NHS and the timeframe used will be life time. Consequences will be expressed as number of correct diagnoses or treatment plans for the diagnostic phase, and (quality adjusted) life years to also include the therapeutic phase and the effects of reduced radiation exposure. Any assumption used in the models and any parameter value will be based primarily on literature and supplemented by clinical expert opinion as appropriate.

Known or suspected CAD in patients who are difficult or impossible to image using 64-slice CT

The focus of the evaluation of high definition CT in this population will be in assessing the accuracy of imaging. As it is currently foreseen, the model for this patient group will be constructed to reflect the following assumptions: Without the option of high definition CT, patients are referred to invasive angiography without selection based on CT imaging. Estimates of the numbers of patients falling into this category will be provided by expert opinion/audit data from at least two centres, both specialist and more generalist (i.e. a range of estimates). The use of high definition CT will make it possible to assess the disease status of indicated patients and may allow clinically significant disease to be ruled out, in some patients, without the risks of invasive testing. The number of false negative imaging results is important in this scenario since, in principle, this will cause loss of benefit arising from missed treatment. Where imaging is positive the diagnosis will need to be confirmed by

angiography leading to a specific treatment decision. In addition, it may be possible to use high definition CT in some patients to confirm severe disease, requiring CABG, and thus avoid CA. The number of false positive imaging results is important in this scenario since these may result in unnecessarily aggressive treatment (CABG, where PCI may have been possible). As a short term result, the cost of the diagnostic phase will be related to the number of correct diagnoses. For a long term assessment of the cost-effectiveness of testing, the therapeutic benefits of treating a patient correctly (true positive diagnosis), unnecessary treatment of persons (false positive diagnosis), inappropriately withholding treatment in patients (false negative diagnosis), and preventing unnecessary treatment (true negative diagnosis) will be reflected within a cost per QALY framework.

For the diagnostic phase, we may use and adapt the model that was developed for the clinical guideline for stable chest pain. [5] We are not aware of any existing relevant diagnostic models which address the possibility that CA is not 100% accurate, but we will further investigate whether any methods have been published that would allow this issue to be addressed. If suitable methods cannot be identified, we will consider using sensitivity analyses, contingent upon availability of data. For the therapeutic phase we may use and adapt a model that was developed for treatment of stable coronary artery disease based on data from the EUROPA Study. [20] The EUROPA study included patients with previous MI, previous revascularisation or 70% narrowing of one or more major coronary arteries. Probability of a cardiovascular event was defined using a risk score formula that was derived from the trial data. This risk formula contains, for example, obesity, age, the presence of diabetes, the use of lipids lowering drugs as covariates. For our model, it is important to realize that those factors that cause patients to be difficult to image in the diagnostic phase may also impact the probability of a cardiovascular event. The EUROPA study shows this for obesity, but it is possible that also other factors such as high coronary calcium levels and irregular/fast heartbeat have similar impacts. Therefore, data need to be collected to adjust the relevant model input parameters for these factors. We will need to run the model separately for each factor listed in section 5.1, for which effectiveness/accuracy data are available, and combine the results into an overall ICER by weighting the separate costs and effects by the relative prevalence of these factors.

Additionally, because high definition CT is associated with lower radiation exposure than CA, the effects of decreasing radiation on the risk of cancer, mortality and adverse events and its associated costs will be assessed. For this, we will make use of a model that is currently being developed for the diagnostic assessment of the EOS 2D/3D X-ray Imaging System by the Centre for Health Economics, University of York.

Congenital heart disease
The focus of the evaluation of high definition CT scanners in infants, children and adults with known complex congenital heart defects will be on assessing its potential impact upon

treatment planning. The costs and effects of high definition CT will be compared to current practice, i.e. 64-slice CT, and may also be compared to MRI and echocardiography alone (this is to be discussed with clinical experts). Since high definition CT is associated with lower radiation exposure than 64-slice CT, the effects of decreasing radiation on the risk of cancer, mortality and adverse events and its associated costs will be assessed. For this, we will make use of a model that is currently being developed for the diagnostic assessment of the EOS 2D/3D X-ray Imaging System by the Centre for Health Economics in York.

Resource utilisation
Resource utilisation and costs will be estimated for high definition CT scanners, 64-slice CT and CA. For high definition CT, these costs will include the capital cost of the equipment, including installation of workstation and software, consumables, annual maintenance costs and patient throughput. Particular attention will be paid to how per patient costs vary with total patient throughput for high definition CT and 64-slice CT in the indications listed in Section 5. The implication of this variation is likely to be explored using sensitivity and threshold analyses. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of high definition CT scanners.

Modeling issues
Necessary choices and definitions regarding the structure of both models will depend on the findings from the literature review and consultation with clinical experts. In addition, the existence/availability of any other electronic models that reflect the cost-effectiveness of treatment pathways for these patients, and are representative of current care within the NHS, will be determined.

The objectives of modelling will be:
To assess the cost-effectiveness of high definition CT scanners in comparison to current diagnostic pathways. For CAD, the analysis will be done in terms of the consequences of diagnostic accuracy, treatment planning, and QALYs. For congenital heart disease, the analysis will be done in terms of treatment planning and, if available evidence allows, in terms of QALYs using a life expectancy time horizon.

Issues relevant to analyses:
- Longer term cost and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects.
- One way sensitivity analyses will be performed for all key parameters, especially for parameters in the models based on expert opinion.

- Probabilistic sensitivity analyses will be performed using parameter distributions instead of fixed values.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

7. Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 04/04/2011. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

8. Competing interests of authors

None

9. Timetable/milestones

Milestones	Completion data
Draft protocol	18/01/2011
Final protocol	09/02/2011
Progress report	w/c 04/04/2011
Draft assessment report	w/c 16/05/2011
Final assessment report	22/06/2011

10. References

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Appendix 1

Clinical effectiveness search (high definition CT only)

Medline: 2000-2011/1/wk 1
Searched 17.1.11

1   Somatom definition flash.ti,ab,ot,hw. (4)
2   DSCT.ti,ab,ot,hw. (237)
3   (Aquilion-1 or Aquilion-one).ti,ab,ot,hw. (7)
4   Brilliance ict.ti,ab,ot,hw. (1)
5   (Discovery ct750 or Discovery ct-750).ti,ab,ot,hw. (0)
6   (640slice$ or 640 slice$).ti,ab,ot,hw. (0)
7   (256slice$ or 256 slice$).ti,ab,ot,hw. (44)
8   (128slice$ or 128 slice$).ti,ab,ot,hw. (30)
9   ('2' adj2 (energy or source$)).ti,ab,ot,hw. (2361)
10   (Dual$ adj2 (energy or source$) adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computed or tomography$)).ti,ab,ot,hw. (1101)
11   (High definition adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computer or tomography$)).ti,ab,ot,hw. (156)
12   modern cone-beam dual-source spiral.ti,ab,ot,hw. (1)
13   (high pitch dual spiral adj3 (CT or scan$ or imag$ or technique$ or protocol$ or DSCT or multidetect$ or multi-detect$ or computer or tomography$)).ti,ab,ot,hw. (1)
14   or/1-13 (3790)
15   exp Heart Defects, Congenital/ (103198)
16   exp Coronary Disease/ or myocardial ischemia/ or exp myocardial infarction/ (285046)
17   ((pulmonary or mitral or aortic or aorta or Tricuspid or coronary or cardiac or valve) adj2 (stenosis or atresia)).ti,ab,ot,hw. (50167)
18   (congenital$ adj2 arter$ adj2 (defect$ or deform$ or malform$ or anomal$ or abnormal$ or disease$)).ti,ab,ot,hw. (449)
19   (congenital$ adj2 heart adj2 (defect$ or deform$ or malform$ or anomal$ or abnormal$ or disease$)).ti,ab,ot,hw. (42499)
20   (CAD or ASD or AVSD or CAVSD or HLHS or HLH or HRH or HRHS or IAA or PDA or VSD or CHD or LVOT or PVOD or TGA or UVH or TAPVD or TAPVR or PAPVD or PAPVR).ti,ab,ot. (45488)
21   (TOF or TAPVC or TGV or D-TGA or DTGA or ITGA or I-TGA or DILV or DORV or COA or IAA or SS or PAPVC).ti,ab,ot. (63488)
22   (Dextrocardia$ or Dextro-cardia$).ti,ab,ot,hw. (1335)
23   (dextro-Transpos$ adj3 great arteries).ti,ab,ot,hw. (33)
24   (dextroTranspos$ adj3 great arteries).ti,ab,ot,hw. (29)
25   ((cardium or cardio$ or cardiac$ or heart) adj3 (dextrover$ or dextro-ver$ or dextro-rotat$ or dextroposition$ or dextrorotat$ or dextro-position$)).ti,ab,ot,hw. (101)
26   ((interauricular or inter-auricular or inter-atrial or interatrial or atrial or atrium) adj2 (septal or septum) adj2 (shunt$ or defect$)).ti,ab,ot,hw. (11938)
27   (Lutembacher$ adj2 (syndrome or complex)).ti,ab,ot,hw. (152)
28   ((persisten$ or Patent$) adj2 ostium secundum).ti,ab,ot,hw. (5)
29   (trilogy adj2 fallot).ti,ab,ot,hw. (54)
30   ((ventricul$ or Atrioventricul$) adj2 (septal or septum) adj2 (shunt$ or defect$)).ti,ab,ot,hw. (13819)
31   ((Hypo-plastic or Hypoplastic) adj3 left heart).ti,ab,ot,hw. (1819)

32   ((Hypo-plastic or Hypoplastic) adj3 left heart).ti,ab,ot,hw. (1819)
33   (Interrupt$ adj3 aortic arch).ti,ab,ot,hw. (912)
34   ((persisten$ or Patent$ or closure or closed or ligation or ligated or obliterate$) adj2 ductus arteriosus).ti,ab,ot,hw. (8591)
35   ((persisten$ or Patent) adj2 truncus arteriosus).ti,ab,ot,hw. (762)
36   (tetralogy adj2 fallot).ti,ab,ot,hw. (8220)
37   total$ anomalous pulmonary venous connection$.ti,ab,ot,hw. (491)
38   (Transpos$ adj3 great vessels).ti,ab,ot,hw. (5823)
39   (Transpos$ adj3 great arteries).ti,ab,ot,hw. (3205)
40   (levoTranspos$ adj3 great arteries).ti,ab,ot,hw. (7)
41   Bicuspid aortic valve$.ti,ab,ot,hw. (1150)
42   Double inlet left ventricle$.ti,ab,ot,hw. (163)
43   (Ebstein$ adj1 anomal$).ti,ab,ot,hw. (1704)
44   (Coarctat$ adj3 aorta).ti,ab,ot,hw. (3506)
45   (Co-arctat$ adj3 aorta).ti,ab,ot,hw. (3)
46   Interrupt$ aort$.ti,ab,ot,hw. (611)
47   (Scimitar adj2 (syndrome or complex)).ti,ab,ot,hw. (445)
48   Partial$ anomalous pulmonary venous connect$.ti,ab,ot,hw. (224)
49   Total$ anomalous pulmonary venous connect$.ti,ab,ot,hw. (491)
50   (Shone$ adj2 (syndrome or complex or anomaly or defect$ or deform$ or malform$ or abnormal$)).ti,ab,ot,hw. (66)
51   (Marfan$ adj2 (syndrome or complex)).ti,ab,ot,hw. (5176)
52   Marfans.ti,ab,ot,hw. (1904)
53   (eisenmenger$ adj2 (syndrome or complex)).ti,ab,ot,hw. (971)
54   univentric$ heart$.ti,ab,ot,hw. (499)
55   uni-ventric$ heart$.ti,ab,ot,hw. (3)
56   ((coronary or heart) adj2 disease).ti,ab,ot,hw. (237067)
57   (MI or IHD).ti,ab,ot,ab. (25570)
58   (isch?emic heart disease$ or myocardi$ isch?em$ or angina$).ti,ab,ot,hw. (104587)
59   or/15-58 (590875)
60   animals/ not (animals/ and humans/) (3394409)
61   59 not 60 (530061)
62   14 and 61 (323)
63   limit 62 to yr="2000 -Current" (294)

Economic evaluations search (high definition CT only)
Medline: 2000-2011/1/wk 1
Econ filter + Somatom + CHD/CAD
Searched 17.1.11

1   economics/ (25782)
2   exp "costs and cost analysis"/ (151394)
3   economics, dental/ (1783)
4   exp "economics, hospital"/ (16667)
5   economics, medical/ (8226)
6   economics, nursing/ (3784)
7   economics, pharmaceutical/ (2150)
8   (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (319366)
9   (expenditure$ not energy).ti,ab. (13589)
10   (value adj1 money).ti,ab. (16)
11   budget$.ti,ab. (13872)
12   or/1-11 (428922)
13   ((energy or oxygen) adj cost).ti,ab. (2195)
14   (metabolic adj cost).ti,ab. (566)
15   ((energy or oxygen) adj expenditure).ti,ab. (12453)
16   or/13-15 (14627)
17   12 not 16 (425575)
18   letter.pt. (690072)
19   editorial.pt. (263844)
20   historical article.pt. (266040)
21   or/18-20 (1207825)
22   17 not 21 (402171)
23   Somatom definition flash.ti,ab,ot,hw. (4)
24   DSCT.ti,ab,ot,hw. (237)
25   (Aquilion-1 or Aquilion-one).ti,ab,ot,hw. (7)
26   Brilliance ict.ti,ab,ot,hw. (1)
27   (Discovery ct750 or Discovery ct-750).ti,ab,ot,hw. (0)
28   (640slice$ or 640 slice$).ti,ab,ot,hw. (0)
29   (256slice$ or 256 slice$).ti,ab,ot,hw. (44)
30   (128slice$ or 128 slice$).ti,ab,ot,hw. (30)
31   ('2' adj2 (energy or source$)).ti,ab,ot,hw. (2361)
32   (Dual$ adj2 (energy or source$) adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computed or tomography$)).ti,ab,ot,hw. (1101)
33   (High definition adj3 (CT or scan$ or DSCT or imag$ or multidetect$ or multi-detect$ or computer or tomography$)).ti,ab,ot,hw. (156)
34   modern cone-beam dual-source spiral.ti,ab,ot,hw. (1)
35   (high pitch dual spiral adj3 (CT or scan$ or imag$ or technique$ or protocol$ or DSCT or multidetect$ or multi-detect$ or computer or tomography$)).ti,ab,ot,hw. (1)
36   or/23-35 (3790)
37   exp Heart Defects, Congenital/ (103198)
38   exp Coronary Disease/ or myocardial ischemia/ or exp myocardial infarction/ (285046)
39   ((pulmonary or mitral or aortic or aorta or Tricuspid or coronary or cardiac or valve) adj2 (stenosis or atresia)).ti,ab,ot,hw. (50167)

40   (congenital$ adj2 arter$ adj2 (defect$ or deform$ or malform$ or anomal$ or abnormal$ or disease$)).ti,ab,ot,hw. (449)

41   (congenital$ adj2 heart adj2 (defect$ or deform$ or malform$ or anomal$ or abnormal$ or disease$)).ti,ab,ot,hw. (42499)

42   (CAD or ASD or AVSD or CAVSD or HLHS or HLH or HRH or HRHS or IAA or PDA or VSD or CHD or LVOT or PVOD or TGA or UVH or TAPVD or TAPVR or PAPVD or PAPVR).ti,ab,ot. (45488)

43   (TOF or TAPVC or TGV or D-TGA or DTGA or ITGA or I-TGA or DILV or DORV or COA or IAA or SS or PAPVC).ti,ab,ot. (63488)

44   (Dextrocardia$ or Dextro-cardia$).ti,ab,ot,hw. (1335)

45   (dextro-Transpos$ adj3 great arteries).ti,ab,ot,hw. (33)

46   (dextroTranspos$ adj3 great arteries).ti,ab,ot,hw. (29)

47   ((cardium or cardio$ or cardiac$ or heart) adj3 (dextrover$ or dextro-ver$ or dextro-rotat$ or dextroposition$ or dextrorotat$ or dextro-position$)).ti,ab,ot,hw. (101)

48   ((interauricular or inter-auricular or inter-atrial or interatrial or atrial or atrium) adj2 (septal or septum) adj2 (shunt$ or defect$)).ti,ab,ot,hw. (11938)

49   (Lutembacher$ adj2 (syndrome or complex)).ti,ab,ot,hw. (152)

50   ((persisten$ or Patent$) adj2 ostium secundum).ti,ab,ot,hw. (5)

51   (trilogy adj2 fallot).ti,ab,ot,hw. (54)

52   ((ventricul$ or Atrioventricul$) adj2 (septal or septum) adj2 (shunt$ or defect$)).ti,ab,ot,hw. (13819)

53   ((Hypo-plastic or Hypoplastic) adj3 left heart).ti,ab,ot,hw. (1819)

54   ((Hypo-plastic or Hypoplastic) adj3 left heart).ti,ab,ot,hw. (1819)

55   (Interrupt$ adj3 aortic arch).ti,ab,ot,hw. (912)

56   ((persisten$ or Patent$ or closure or closed or ligation or ligated or obliterate$) adj2 ductus arteriosus).ti,ab,ot,hw. (8591)

57   ((persisten$ or Patent) adj2 truncus arteriosus).ti,ab,ot,hw. (762)

58   (tetralogy adj2 fallot).ti,ab,ot,hw. (8220)

59   total$ anomalous pulmonary venous connection$.ti,ab,ot,hw. (491)

60   (Transpos$ adj3 great vessels).ti,ab,ot,hw. (5823)

61   (Transpos$ adj3 great arteries).ti,ab,ot,hw. (3205)

62   (levoTranspos$ adj3 great arteries).ti,ab,ot,hw. (7)

63   Bicuspid aortic valve$.ti,ab,ot,hw. (1150)

64   Double inlet left ventricle$.ti,ab,ot,hw. (163)

65   (Ebstein$ adj1 anomal$).ti,ab,ot,hw. (1704)

66   (Coarctat$ adj3 aorta).ti,ab,ot,hw. (3506)

67   (Co-arctat$ adj3 aorta).ti,ab,ot,hw. (3)

68   Interrupt$ aort$.ti,ab,ot,hw. (611)

69   (Scimitar adj2 (syndrome or complex)).ti,ab,ot,hw. (445)

70   Partial$ anomalous pulmonary venous connect$.ti,ab,ot,hw. (224)

71   Total$ anomalous pulmonary venous connect$.ti,ab,ot,hw. (491)

72   (Shone$ adj2 (syndrome or complex or anomaly or defect$ or deform$ or malform$ or abnormal$)).ti,ab,ot,hw. (66)

73   (Marfan$ adj2 (syndrome or complex)).ti,ab,ot,hw. (5176)

74   Marfans.ti,ab,ot,hw. (1904)

75   (eisenmenger$ adj2 (syndrome or complex)).ti,ab,ot,hw. (971)

76   univentric$ heart$.ti,ab,ot,hw. (499)

77   uni-ventric$ heart$.ti,ab,ot,hw. (3)

78   ((coronary or heart) adj2 disease).ti,ab,ot,hw. (237067)

79   (MI or IHD).ti,ab,ot,ab. (25570)
80   (isch?emic heart disease$ or myocardi$ isch?em$ or angina$).ti,ab,ot,hw. (104587)
81   or/37-80 (590875)
82   animals/ not (animals/ and humans/) (3394409)
83   81 not 82 (530061)
84   22 and 36 and 83 (7)
85   limit 84 to yr="2000 -Current" (7)

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