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Title: Computed tomography (CT) scanners for cardiac imaging – Somatom Definition Flash, Aquilion One, Brilliance iCT and Discovery CT750 HD.

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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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GLOSSARY

Acute chest pain	Chest pain / discomfort which has occurred recently and may still be present, is of suspected cardiac origin and which may be due to acute myocardial infarction or unstable angina.
Congenital heart defect	A defect in the structure of the heart and great vessels, which is present at birth.
Coronary angiography	An invasive diagnostic test which 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 X-rays. It is considered the reference standard for providing anatomical information and defining the site and severity of coronary artery lesions.
Coronary artery	An artery which 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 ischemia.
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.
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 healthcare 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 CT machines, a gantry rotates around a patient for cross-sectional views.
Incremental cost-effectiveness ratio (ICER)	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 whose performance is being evaluated.
Major aortopulmonary collateral arteries (MAPCA)	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.
Multi-slice CT coronary angiography	A non-invasive investigation which provides coronary calcium scoring and anatomical information about the degree of stenosis (narrowing) in the coronary arteries. The scanner has a special X-ray tube and rotation speed and as the technology has advanced the number of slices in each rotation has increased. A dual source scanner has two pairs of X-ray sources and multi-slice detectors mounted at 90 degrees to each other.
Myocardial perfusion scintigraphy with SPECT	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 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 ateriosus	A duct or passage in the heart that is meant to close shortly after birth. In cases of PDA, 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 their ability to perform the ordinary tasks of living.
Quality-adjusted life year (QALY)	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 (ROC) curve	A graph which illustrates the trade-offs between sensitivity and specificity which result from varying the diagnostic threshold.
Reference standard	The best currently available diagnostic test, against which the index test is compared.
Scimitar	A rare congenital heart defect characterised by anomalous venous

syndrome	return (partial or total) from the right lung. The name scimitar syndrome refers to the curvilinear pattern, seen on a chest radiograph, due to the pulmonary veins that drain into the inferior vena cava.
Sensitivity	Proportion of people with the target disorder who have a positive test result.
Specificity	Proportion of people without the target disorder who have a negative 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 can't circulate as it should and the heart has to compensate by working harder.
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.
Stable angina	There are no case definitions of stable angina that have been agreed internationally. Working definition angina is a symptom of myocardial ischemia 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
Stress echocardiograph	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 ischemia.
Stress magnetic resonance imaging (stress MRI)	MRI is a diagnostic procedure that uses radio waves in a strong magnetic field. The pattern of electromagnetic energy released is detected and analysed by a computer to generate detailed images of the heart. Stress MRI is a specific application in which a contrast agent is used to detect myocardial blood flow at stress and at rest. Pharmacological stress is used to induce cardiovascular stress.
Tetralogy of Fallot	A complex congenital heart defect condition comprising of: a ventricular septal defect; pulmonary obstruction; a displaced aorta; an enlarged right ventricle.
Total anomalous pulmonary venous drainage (TAPVD)	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 TAPVD they drain into the right atrium, usually via systemic venous circulation.
Transposition of	A congenital heart defect in which the aorta and pulmonary artery

great arteries	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).

1 LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

ACC	American College of Cardiology
AF	Atrial fibrillation
AHA	American Heart Association
BMI	Body mass index
Bpm	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
CT	Computed tomography
CTA	Computed tomography angiography
CTCA	Computed tomography coronary angiography
CV	cardiovascular
CVD	Cardiovascular death
DSCT	Dual-source computed tomography
FN	False negative
FP	False positive
HCS	High calcium score
HD	High definition
HDCT	High definition computed tomography
HHR	High heart rate
HR	Heart rate
HRF	Heart rate frequency
HRQoL	Health-related quality of life
HRV	Heart rate variability
ICA	Invasive coronary angiography
ICER	Incremental cost-effectiveness ratio
MI	Myocardial infarction
MSCT	Multi-slice computed tomography
NA	Not applicable
NFE	Non-fatal event
NFMI	Non-fatal myocardial infarction
NR	Not reported
NGCCT	New generation cardiac computed tomography
OR	odds ratio
PCI	Percutaneous coronary intervention
QALY	Quality-adjusted life year
ROC	Receiver operating characteristic
SROC	Summary receiver operating characteristic

TIA	Transient ischemic attack
TN	True negative
TP	True positive

2 EXECUTIVE SUMMARY

2.1 Background

Medical imaging, including computed tomography (CT) scanning, is important in diagnosing and planning treatment for a wide range of conditions. 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 (ICA) (a technique used specifically to visualise the coronary arteries) is associated with an increased risk of stroke, heart attack and death). Imaging technologies have developed very rapidly in recent years and new generation CT scanners may offer some advantages over CT scanners and other imaging methods currently in use (e.g. shorter imaging times, reduced radiation dose, more accurate diagnosis 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 coronary artery bypass grafts) in most patients. However, the use of new generation CT scanners may benefit patients who are difficult to image using current technologies (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 successfully diagnosed using existing imaging technologies (CT, ultrasound and magnetic resonance imaging), new generation CT scanners may provide additional information to help with planning surgery in some patients who have complex abnormalities.

2.2 Objectives

To assess the clinical and cost-effectiveness of new generation cardiac CT, using CT750 HD (GE Healthcare), Brilliance iCT (Phillips Healthcare), Somatom Definition Flash (Siemens healthcare), or Aquilion ONE (Toshiba Medical Systems) for:

- the diagnosis of clinically significant coronary artery disease (CAD) in patients who are difficult or impossible to image accurately using 64-slice CT technology.
- treatment planning in babies, infants, children and adults diagnosed with complex congenital heart defects.

2.3 Methods

A systematic review was conducted to summarise the evidence on the clinical-effectiveness of new generation cardiac CT, for the diagnosis of clinically significant coronary artery stenosis in difficult or impossible to image patient groups (obese patients, patients with high heart rates, arrhythmias, intolerance to β-blockers, patients with previous stent implantation(s) or bypass graft(s)) with known or suspected CAD, and for treatment planning in patients with complex congenital heart disease. Search strategies were 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.[1-3] The following databases were searched from 2000 to 2000 to February/March 2011: MEDLINE; MEDLINE In-Process; EMBASE; the Cochrane Databases; Database of Abstracts of Reviews of Effects (DARE); NHS Economic Evaluation Database (NHS EED); Health Technology Assessment Database (HTA); Science Citation Index (SCI). Research registers and conference proceedings were also searched. 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. [1, 4] The risk of bias in included studies was assessed using the QUADAS-2 tool. 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% CIs were calculated using the bivariate modelling approach.[5, 6] 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.[7]

In the health economic analysis, we assessed the cost-effectiveness of new generation cardiac CT (NGCCT) in two different populations. The first assessment compared NGCCT versus ICA in difficult to image CAD patients, and the second compared NGCCT versus 64-slice CT in patients with congenital heart disease.

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 .[8]
2. a life–death Markov model for “healthy” patients without CAD .[9]
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) .[10]
5. a model to assess the impact of radiation due to imaging on cancer morbidity and mortality[11]

The latter of these five models, the York Radiation Model, was also used to assess the cost-effectiveness of the use of NGCCT to lower imaging-associated radiation exposure in patients with congenital heart disease.

The population of difficult to image CAD patients was divided into two subgroups, the suspected CAD population and the known CAD population. 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 decide if a revascularisation is necessary.

Three strategies were evaluated in the health economic analysis: ICA only, the combination of NGCCT and ICA for patients with a positive NGCCT scan (NGCCT-ICA), and NGCCT only. ICA was assumed to have both 100% sensitivity and 100% specificity; however, ICA is accompanied by a risk of serious complications, including stroke, non-fatal 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 the diagnostic performance of the test or test strategy and the prior likelihood of the test outcome. Estimates of sensitivity and specificity of NGCCT differed for the different difficult to image patient groups, (obese patients, patients with high heart rates, arrhythmias, intolerance to β-blockers, patients with previous stent implantation(s) or bypass graft(s)), but were assumed to be equal for the suspected CAD and the known CAD populations.

Two versions of the diagnostic model were created because the known (treatment options CABG and PCI) and suspected CAD (treatment options as for known CAD, or drug treatment) populations are treated differently after a positive test outcome. 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 the initial ICA or revascularisation were modelled using a simple life-death 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 the initial ICA or revascularisation, enter the EUROPA model. The Markov based EUROPA model predicts the probability of cardio-vascular events (cardiac arrest, (non-) fatal myocardial infarction) that patients may suffer and the mortality, decrease in quality of life, and costs associated with those events. The impacts of radiation reduction on life-time risk of cancer incidence and subsequently related life expectancy, health related quality of life and costs were assessed based using the YRM model. Each CAD population, while going through the various models, accumulates costs and QALYs. The impact of uncertainty about the various input parameters on the outcomes was explored through sensitivity analyses.

For the population with congenital heart disease, the YRM model was used to compare the costs and QALYs of NGCCT and 64-slice CT. As previously noted, in this model only the effect of reduced radiation was assessed; other potential benefits of NGCCT of costs or QALYs were not explored, due to a lack of available data.

2.4 Results

Twenty four studies (26 publications) that reported data on the accuracy of new generation cardiac CT for the diagnosis of clinically significant CAD in difficult to image patients were included in the systematic review. 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). Risk of bias with respect to patient selection was frequently unclear due to uncertainty regarding the potential impact of inappropriate exclusions; specific 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 their analyses, the potential impact of these exclusions 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, patients with high heart rates 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 new generation cardiac CT could be used to reliably rule out significant stenosis and thus potentially avoid invasive investigations such as ICA in these patient groups. Further, though there were no data specifically for β-blocker intolerant patients, it should be noted that no study reporting per patient data for patients with high heart rates used additional β-blockers before scanning. It may therefore be inferred that new generation cardiac CT could reasonably be used to image patients who are intolerant to β-blockers who could not otherwise be reliably imaged by 64-slice CT. With the exception of one small study, data on the accuracy of new generation cardiac CT 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, i.e. those for whom testing will add no information. However, few of the studies in this assessment 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 in different populations; these were 5% for patients with arrhythmias, 6.8% for patients with high heart rates and 9% for patients with previous stent implantation. These results indicate that the proportions of otherwise difficult or impossible to image patients in whom imaging would remain non-diagnostic, even with the use of new generation cardiac CT, are likely to be low. However, further studies are needed to confirm this.

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; the clinical effectiveness of NGCCT could not be assessed in this patient group.

The health economic analysis of the use of NGCCT in difficult to image CAD patients 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 to NGCCT-only was so high (£71,000) that it is unacceptable given the conventional thresholds of

£20,000 and £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 to NGCCT-ICA is so high (£726,230) that it is unacceptable. When taking uncertainty into account, these findings were confirmed. In the suspected population, in the range of thresholds below £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 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 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 rates for ICA and revascularisation. Overall, in the population with suspected CAD, the strategy NGCCT-only 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, a scenario analysis was performed, increasing this cost price from £150 to £207 per scan; this did not alter our conclusions. 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 above £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 only is not cost-effective in this patient group.

2.5 Conclusions

The results of our systematic review suggest that new generation cardiac CT is likely to be sufficiently accurate to diagnose clinically 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 otherwise difficult or impossible 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.

The results of the economic evaluation of new generation cardiac CT suggest that it is cost-effective for difficult to image CAD patients. Though invasive coronary angiography 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 amount of quality-adjusted life years. Whether NGCCT should be used with or without ICA depends on the CAD population.

2.6 Suggested research priorities

More, 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 regarding the diagnostic performance of new generation cardiac CT in difficult to image patients with known or suspected CAD. Studies should include and fully report details of patients with more than one difficult to image criteria, so that the important issue of the potential cumulative impact on accuracy of multiple criteria can be fully assessed. Studies should also report the numbers of patients in whom imaging is non-diagnostic.

Test accuracy cannot provide information on the contribution of new generation CT to therapeutic decision making, or subsequent impact on patient outcomes. The ideal study to address these questions would be a large multi-centre RCT. However, recognising that the establishment of large-scale RCTs can be problematic in rapidly evolving fields such as vascular imaging, one possible compromise strategy might be to establish a multi-centre tracker study. Such a study should enable the collection of data comparing numbers of misdiagnoses, clinical outcomes, and health-related quality of life resulting from alternative imaging strategies. Such a study would also be the ideal setting to provide a more robust assessment of the cost-effectiveness of the various diagnostic strategies.

If new generation cardiac CT is introduced on the basis of evidence in CAD patients and is opportunistically used in congenital heart disease patients, 'before and after' population survey studies could be considered in order to provide some insight into the impact of this change 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 NICE clinical guideline 'Chest pain of recent onset' one of the recommendations was to establish a national registry for people who are undergoing initial assessment for stable angina.[12] 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 is 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 registry could increase robustness of the health economic findings.

3 BACKGROUND AND DEFINITION OF THE DECISION PROBLEM(S)

3.1 Conditions and aetiologies

This assessment concerns the clinical and cost-effectiveness of cardiac computed tomography (CT), using the instruments described in section 3.2 and hereafter to be referred to as 'new generation cardiac CT (NGCCT).' The assessment was conducted in two distinct populations. These populations were patients with known or suspected coronary artery disease (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.

3.1.1 Coronary artery disease (CAD)

CAD is a major cause of cardiovascular 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).[13] 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 narrowing (stenosis) of at least one major epicardial artery segment or ≥50% diameter stenosis in the left main coronary artery.[14] Some factors intensify ischemia 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 ischemic myocardium, or longer lesion length. Similarly, some factors reduce ischemia 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 ischemic myocardium.

Invasive coronary angiography (ICA) or CT coronary angiography (CTCA) are used to assess the state of the arteries and to identify significant stenosis as recommended by NICE clinical guideline CG95.[14] The guideline recommends use of a 64-slice (or above) CT scanner in patients with an estimated probability of CAD of 10-29% and calcium score <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.[15] [16] [17] 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 or impossible to image, 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. These patients are not currently candidates for CT imaging in routine practice, though some may be imaged in specialist centres.

In addition to enabling the assessment of otherwise difficult or impossible 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.

3.1.2 Congenital heart disease

Congenital heart disease is a general term which describes birth defects that affect the heart. There are over 30 different types of congenital 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.[18] Adequate visualization of the defect is important to surgical/treatment planning and diagnostic work-up currently comprises multiple imaging modalities including echocardiography, magnetic resonance imaging (MRI) and 64-slice 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 extra cardiac component that is not well imaged by echocardiography, e.g. pulmonary atresia with major aortopulmonary 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, as with CAD, patients who have previously treated lesions where stents or pacemakers make imaging with MRI or 64-slice CT difficult or impossible may benefit from NGCCT.

Though there is some evidence that NGCCT may provide accurate initial diagnoses for a range of congenital heart conditions, [19] [20] 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.

3.2 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, e.g. 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 where 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). [21] There follows a brief summary of the key features of each of these scanners, as well as Discovery CT750 HD, GE Healthcare (not included in the CEP report), as they relate to the applications considered in this assessment. Summaries are presented in alphabetical order, by manufacturer name.

3.2.1 Discovery CT750 HD, GE Healthcare

The Discovery CT750 HD is a 2 x 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 ±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/s. The maximum scan field is 50 cm.

The Discovery CT750 HD has advanced features which give a spatial resolution of 0.23 mm. It has a Gemstone^{TM} detector which uses a fast scintillator made of a complex rare earth based oxide with a chemical structure of garnet crystal. This contributes to high image quality and a low amount of afterglow. 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 has the ability to detect very small concentrations of contrast agent and can deliver non-contrast-like images by subtracting the detected agent from the images. It also gives a cardiac temporal resolution of 0.44 ms.

The SnapShot Pulse^{TM}, 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 to reduce radiation dose are:

- Dynamic z-axis tracking provides automatic and continuous correction of the X-ray beam position to block unused radiation at the beginning and end of a helical scan.
- Filters reduce noise providing dose reduction while maintaining image quality and spatial resolution.
- 3D Dose Modulation allows dose protocols to be easily personalised to each patient.

3.2.2 Brilliance iCT, Philips Healthcare

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 per rotation. Each detector row is double sampled which increases 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 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 optimise the dose for each patient based on the planned scan and also to increase or decrease the signal over different areas of the scan. It has a collimator that lowers patient exposure during helical scanning by removing radiation at the beginning and end which would not contribute to image formation.

Additional benefits of the Brilliance iCT scanner are:

- A powerful X-ray tube: for improved durability, image quality and spatial resolution, particularly in patients with high BMIs.
- 120 kW generator: provides instantaneous power to maximise the image quality of short scans.
- Innovative NanoPanel detectors: reduce electronic noise, enabling fast, low-dose scans with high spatial resolution (up to 24 lp/cm) which gives better definition of small structures.
- iDose iterative reconstruction technique: uses advanced reconstruction algorithms to enable diagnostic images at low dose without the problems noise and image artefacts. The faster reconstruction of data means higher throughput and less waiting for large volume datasets.

It is claimed that when using low dose Step and Shoot imaging, patients with heart rates of up to 75 bpm can be imaged successfully.

3.2.3 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 x 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. 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 facilitates 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 ms and allows scanning in a high pitch helical ‘Flash’ mode.

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.

3.2.4 Aquilion ONE, Toshiba Medical Systems

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. This specification allows the imaging of whole organs in a single non-helical rotation, for example an image of the heart can be captured within a single heart beat. In addition to reducing the exam time, the radiation and the contrast dose are also reduced. In helical scanning mode the z-axis coverage is 80 mm from 160 x 0.5 mm detector rows.

Advanced features include:

- Adaptive Iterative Dose Reduction: rapidly produces diagnostic images with low noise levels and minimal operator input.
- Automated parameter selection to ensure consistent image quality for all patients, regardless of size.
- PhaseXact: automatically selects the cardiac phase that displays the least amount of motion to improve temporal accuracy and reduce review time.
- ConeXact volume reconstruction: removes artefacts related to the wide cone angle to produce high quality images.
- Automatic arrhythmia rejection software: terminates radiation exposure if abnormal heart beat is detected and acquires the next normal beat for image reconstruction.
- Adaptive multi-segment reconstruction: improves 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.

3.3 Comparators

3.3.1 CAD patients difficult or impossible to image using 64-slice CT

In patients where 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 CAD patients is ICA.

ICA is 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.

Despite some limitations (see section 7.2.1), 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, hemodynamic complications, perforation of heart chamber), is <2%.[22, 23]

ICA was the reference standard in our assessment of diagnostic accuracy.

3.3.2 Congenital heart disease patients

In these patients, cardiac CT is likely to be used for treatment/surgical planning following, after diagnosis and as an add-on to imaging with echocardiography and magnetic resonance imaging (MRI). Therefore, 64-slice CT is the only relevant comparator.

Multi-slice CT scanners (64-slice CT) 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 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 which 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, since existing imaging strategies can provide accurate initial diagnosis.

3.4 Care pathways

3.4.1 Coronary artery disease

3.4.1.1 Diagnosis

NICE clinical guideline CG95 (Chest pain of recent onset) details the care pathway recommended to make a diagnosis of stable angina in people with chest pain.[14] The guideline suggests that a diagnosis of significant CAD can be made using anatomical

imaging and a diagnosis of reversible myocardial ischemia can be made using functional imaging. Both significant CAD and reversible myocardial ischemia 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 or impossible 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 greater than 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 ischemia.
- 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**
- magnetic resonance imaging 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. The management of stable angina is currently being evaluated by NICE and the draft clinical guideline has been released for stakeholder consultation (15 December 2010 to 9 February 2011).[24] It should be noted that the provisional recommendations presented do not constitute the NICE's formal guidance on this topic. The recommendations are provisional and may change after consultation. The finial clinical guideline is due for publication in July 2011.

Key provisional recommendations from the draft guideline state:

- Functional tests for myocardial ischemia or anatomical tests for obstructive CAD to stratify risk are not routinely recommended.
- 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 cardiovascular disease.
- Treatment with one or two anti-anginal 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 (only in combination with a dihydropyridine calcium channel blocker), nicorandil or ranolazine.
- A third drug can be considered when symptoms are not controlled with two anti-anginal drugs and the person is waiting for revascularisation or it is not considered appropriate or acceptable.

Management by revascularisation

The NICE draft clinical guideline on stable angina provisionally 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 71 (Guidance on the use of coronary artery stents)[25] and NICE technology appraisal 152 (Drug-eluting stents for the treatment of coronary artery disease)[26] provide recommendations on the use of stents for revascularisation in CAD.

The NICE draft clinical guideline on stable angina provisionally recommends that PCI should be considered in preference to CABG for people with single-vessel disease or multi-vessel disease, including left main stem disease, and continuing symptoms despite optimal medical treatment if the anatomy is suitable for PCI. The draft guideline also provisionally recommends that CABG should be considered for people with single-vessel disease or multi-vessel disease, including left main stem disease, and continuing symptoms despite optimal medical treatment if the anatomy is unsuitable for PCI, if the person is over 65 years and/or if they have diabetes.

NICE technology appraisal 71 recommends that for patients who are indicated for PCI, stents should be routinely used.[25] Further, NICE technology appraisal 152[26] states that drug-eluting stents are only recommended for use in PCI for the treatment of CAD if:

- the target artery to be treated has less than a 3 mm 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.

3.4.2 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 have been identified. Other sources of information such as NHS Choices and Patient UK provide limited information.[27, 28] They suggest that if congenital heart disease is suspected 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 ionizing radiation that can provide information on the anatomy and function of the heart. Other tests such as an electrocardiogram, chest X-rays and pulse oximetry may also be used, as clinically appropriate. CT imaging or magnetic resonance imaging (MRI) may be used, in some instances, to provide further anatomical information and to prepare for correction of the defect.

The main disadvantage of using MRI in this population is the procedure length, which 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, 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.

ICA, which would require a general anaesthetic, is avoided whenever possible. It may be used in children who have tetralogy of Fallot, in which coronary anomalies also occur, and for those with inflammatory problems.

As many babies born with congenital heart disease now survive into adulthood, long-term monitoring and care may be required. 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.[29] Recommendations are similar to those suggested for paediatric patients (above). That is, a clinical examination followed by an echocardiogram and pulse oximetry. Chest X-rays may be performed when indicated, but are 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. ICA is reserved for the resolution of specific anatomical and physiological questions, or for intervention.[29]

Treatment and monitoring

Once congenital heart disease is diagnosed, watchful waiting, medical management, non-invasive surgery, 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, thrombo-embolic 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.[29]

Due 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 under the age of 25 years do not require regular follow-up. Patients with more complicated defects or sequelae following interventional treatment may require regular follow-up, with frequencies ranging from yearly to once every five years.[29]

4 DEFINITION OF DECISION PROBLEM

4.1 Overall aim of the assessment

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

4.2 Objectives

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

5 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 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 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. [1, 4]

5.1 Inclusion and exclusion criteria

Participants

Study populations eligible for inclusion were:

- 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 patient groups defined *a priori* were:
    - Obesity (body mass index (BMI)≥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 bpm)
    - Intolerance of beta-blockers
    - Previous stent implantation
    - Previous bypass graft(s)

Difficult or impossible 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 bpm) specified in the protocol was broadened to avoid potential loss of relevant data, as identified studies frequently defined HHR as >65 bpm.

- Infants, children and adults diagnosed with complex congenital heart disease, including but not limited to:
    - Pulmonary atresia with major aortopulmonary collaterals (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 AG, 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 CAD patients was ICA.

Relevant comparators, for the assessment of complex congenital heart disease, were 64-slice CT, or 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, myocardial infarction, cardiovascular mortality)

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

- Test accuracy
- Indeterminacy (test failure rate)

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, where 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 where 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, false negative, false positive, and true negative 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

5.2 Search strategy

Search strategies were 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.[1-3]

The following databases were searched for relevant studies from 2000 to February/March 2011:

- MEDLINE (2000-2011/02/wk 2) (OvidSP)
- MEDLINE In-Process Citations and Daily Update (2000-2011/02/16) (OvidSP)
- EMBASE (2000-2011/wk 6) (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library Issue 1:2011) (Wiley)

- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library Issue 1:2011) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (2000-2011/03/09) (CRD website)
- NHS Economic Evaluation Database (NHS EED) (2000-2011/03/09) (CRD website)
- Health Technology Assessment Database (HTA) (2000-2011/03/09) (CRD website)
- Science Citation Index (SCI) (2000-2011/03/05) (Web of Science)

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

- NIH Clinicaltrials.gov (2000-2011/03/09) (Internet) http://www.clinicaltrials.gov/
- Current Controlled Trials (2000-2011/03/09) (Internet) http://www.controlled-trials.com/
- WHO International Clinical Trials Registry Platform (ICTRP) (2000-2011/03/09) (Internet) http://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) (2006-2010) (Internet) http://www.cardiosource.org/Meetings/Previous-Meetings-OLD.aspx
- Society of Cardiovascular Computed Tomography (SCCT) (2006-2010) (Internet) http://www.scct.org/annualmeeting/2010/index.cfm
- European Society of Cardiology (ESC) (2006-2010) (Internet) http://www.escardio.org/congresses/past_congresses/Pages/past-ESC-congresses.aspx
- American Heart Association (AHA) (2007-2010) (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 for further assessment and handling.

References in retrieved articles were checked for additional studies.

5.3 Inclusion screening and data extraction

Two reviewers 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 cardiovascular risk for the relevant participant groups or the whole study population); assessed technology and reference standard (technical details of the test, any use of β-blockers prior to scanning, details of who interpreted tests and how, threshold used to define a positive test); 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 true positive (TP), false negative (FN), false positive (FP) and true negative (TN) test results; numbers of patients, arteries, or segments classified as non-diagnostic by NGCCT; 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.

5.4 Quality assessment

All studies included in the systematic review were test accuracy studies. The QUADAS tool,{#10} is recommended for assessing the methodological quality of test accuracy studies.[1, 2] However, a revised version of QUADAS (QUADAS-2) is soon to be published (to be submitted to Annals of Internal Medicine June 2011). 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 only assess 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 will be available at the QUADAS website: www.quadas.org (currently under development).

The QUADAS-2 tool has been used in this assessment, with the permission of the QUADAS steering group of which the DAR team lead is a member. 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 (section 5.6) 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.

5.5 Methods of analysis/synthesis

All studies included in the systematic review were test accuracy studies in difficult to image CAD patients. Results were summarised by patient group (e.g. obese, high heart rate, 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 true positive, false negative, false positive and true negative 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;[5, 6] four data sets are the minimum requirement to fit models of this type. Analyses were conducted in STATA 10, using the 'metandi' function.[30] In two cases, a bivariate model could not be fitted because the number of studies was small (four), 2 x 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 MetaDiSc 1.4,[31] 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.[7] There were no data sets of sufficient size (minimum ten) 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. due to 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.

5.6 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 [32-36] could not be obtained within the time scale of this assessment; these were held in British Library stacks which are currently closed for asbestos removal, or 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, twenty three 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.[37-39] A total of 24 studies in 26 publications were, therefore, included in the review.

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.

Twenty of the 24 included studies reported using Somatom Definition; three studies did not specify the instrument used,[39-41] though the authors of one of these[40] had used Somatom Definition in an earlier study which was also included in this review,[42] and the remaining study used Aquilion ONE.[43] This study assessed patients who had previous stent implantation for in-stent re-stenosis.[43]

All included studies were published 2006 or later.

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.

Figure 1: Flow of studies through the review process

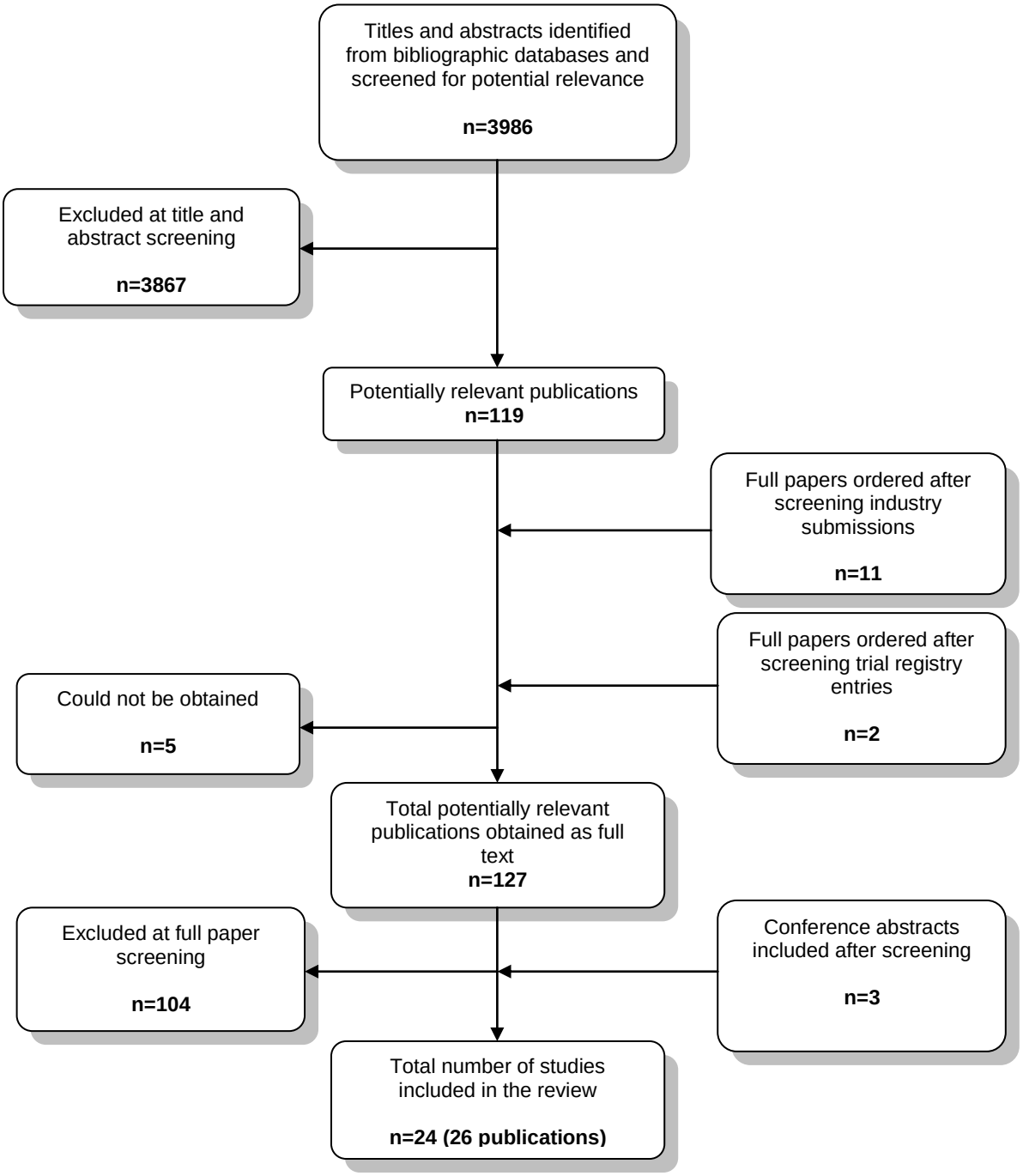


Table 1: Included studies

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Alkadhi 2010 [44]	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.'				✓			

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Brodoefel 2008b [45]	Prospective diagnostic cohort Recruitment not described (September 2006 to July 2007) Single-centre Germany Funding not reported	'To prospectively evaluate the effect of body mass index (BMI) on DSCT image quality and to assess diagnostic accuracy for coronary artery stenosis, using invasive coronary angiography (ICA) as the reference standard.'	✓						
Brodoefel 2008a [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 invasive coronary angiography as the reference standard.'		✓		✓			

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
de Graaf 2010[43]	Prospective? diagnostic cohort	'To evaluate the diagnostic accuracy of 320-row computed tomography angiography (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 versus stent characteristics and heart rate during CTA image acquisition.'					✓		
	Recruitment not described (dates not reported) Multi-centre The 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.								

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
LaBounty 2010[41]	Prospective diagnostic cohort, abstract only Consecutive recruitment (dates not reported) Multi-centre U.S.A. and Canada Funding not reported	To evaluate the diagnostic accuracy of high definition (HD)-CCTA in an intent-to-diagnose analysis.					✓		
Leber 2007 [47]	Prospective? diagnostic cohort Consecutive recruitment (July 2006 to January 2007) Single-centre Germany Not reported	'To assess the clinical performance of a dual x-ray source multi-slice CT (MSCT) with high temporal resolution to assess coronary status in patients with an intermediate pre-test likelihood for significant coronary artery disease without using negative chronotropic pre-treatment.'			✓[a]	✓[a]			

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Lin 2010[48]	Retrospective diagnostic cohort Selected patients from a consecutive series (October 2006 to June 2007) Multi-centre 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.				✓			

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Marwan 2010[49]	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 invasive coronary angiography.'			✓				

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Meng 2009[50]	Prospective? diagnostic cohort Consecutive recruitment (November 2006 to November 2007) Multi-centre 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[51]	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.'			✓				

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Oncel 2008[52]	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 improved temporal resolution aid in visualization of coronary stents.'					✓		

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Pflederer 2009[53]	Prospective? diagnostic cohort Consecutive recruitment (dates not reported) Multi-centre Germany and U.S.A. Work supported by the Bundesministerium für Bildung und Forschung, Berlin Germany. One author supported by research grants from Siemens Healthcare, Erlangen, Germany 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 >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Pflederer 2010[37]	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 invasive coronary angiography.					✓	✓	
Pugliese 2008[54] and Pugliese 2007[55]	Prospective diagnostic cohort Recruitment not described (April 2006 – January 2007) Single-centre Netherlands Funding not reported	'To evaluate the diagnostic performance of dual source computed tomography coronary angiography (DSCT-CA) for the detection of in-stent re-stenosis in patients with angina symptoms after stent implantation.'				✓[b]	✓		

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Rist 2009 [56]	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 [38]	Prospective? Diagnostic cohort, abstract only Consecutive recruitment (dates not reported) Single-centre Germany Funding not reported	'To investigate the feasibility of dual-source CT (DSCT) with a temporal resolution of 83 ms for the detection of coronary artery disease in patients with atrial fibrillation compared to conventional quantitative coronary angiography.			✓				

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Ropers 2007[42]	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 β-blocker pre-medication.'				✓			
Ropers 2008[40]	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.'						✓	

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Scheffel 2006[57]	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[58] and Drosch[59]	Prospective? diagnostic cohort Recruitment not described (July 2006 to January 2008) Multi-centre 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.'			✓				

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Van Mieghem 2007[39]	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.					✓		
Weustink 2009b[60]	Prospective? diagnostic cohort Consecutive recruitment (dates not reported) Single-centre Netherlands Funding not reported	'To evaluate the contribution of non-invasive dual-source computed tomography angiography (CTA) in the comprehensive assessment of symptomatic patients after coronary artery bypass grafting (CABG).'				✓[b]		✓	

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
Weustink 2009a[61]	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 heart rate frequency (HRF) and heart rate variability (HRV) on radiation exposure and image quality in a large cohort of patients undergoing DSCT coronary angiography with adaptive ECG pulsing, and to evaluate the impact of HRF and HRV on the diagnostic performance of DS CT coronary angiography to help detect or rule out significant stenoses in a subgroup of patients who underwent additionally conventional coronary angiography.'				✓			
Zhang 2010[62]	Prospective diagnostic cohort Consecutive recruitment (December 2006 to September 2008) Multi-centre China and USA Funding not reported	'To prospectively evaluate the accuracy of dual-source CTCA in diagnosing coronary artery stenosis according to conventional coronary angiography (CAG), and the effect of average heart rate, heart rate variability, and calcium score on the accuracy of CTCA.'		✓		✓			

Study ID	Study design	Objective	Obesity	HCS	Arrhythmias	HR >70 bmp	Stent(s)	Bypass	B-blocker intolerance
[a] Combined data (patients with HHR or arrhythmia); [b] Combined data (patients with HHR and previous bypass) ✓Difficult to image patient group for which the study reports data HCS high calcium score HR heart rate HHR high heart rate									

5.6.1 Accuracy of NGCCT for the detection of CAD in obese patients

One study 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 ≥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.

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 2008b[45]	?	↑	↓	↓
↑: 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 def[n]	Patient or segment data (n)	Index test	Ref.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
Brodoefel 2008b [45]	≥30 kg/m^2	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
a: calculated values, b: unclear how non-diagnostic segments were classified												

5.6.2 Accuracy of NGCCT for detection of CAD in HCS patients

For the purpose of this assessment levels of coronary calcium, likely to result in a patient being difficult to image, was classified as a high calcium score (HCS) >400. Four studies reported ten data sets describing the accuracy of NGCCT for the detection of CAD in patients with HCS.[46, 50, 57, 62] Three of the four studies[46, 50, 57] only reported 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), previous stent implantation (3 studies)). 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[50] 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 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; there was 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 SROC curve for per segment data in patients with HCS.

Two studies also reported accuracy data on a per artery basis; these results are summarised in Table 5.[50, 62]

Only one study reported per patient estimates of accuracy and these were of limited values as all 12 included patients were classified as true positive using ≥50% vessel narrowing as the threshold to define significant stenosis.[62] This same study[62] also reported 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 ≥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 confidence intervals reflect the very small number of patients included in the analysis.

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

Study ID	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**	**FLOW AND TIMING**
	Risk of Bias	**Risk of Bias**	**Risk of Bias**	**Risk of Bias**
Brodoefel 2008a[46]	?	↑	↓	↓
Meng 2009[50]	?	↑	↓	?
Scheffel 2006[57]	?	↑	↓	↓
Zhang 2010[62]	?	↓	↓	?
↑: high risk of bias, ↓: low risk of bias, ?: unclear risk of bias				

Figure 2: SROC curve for per segment data in studies of patients with HCS

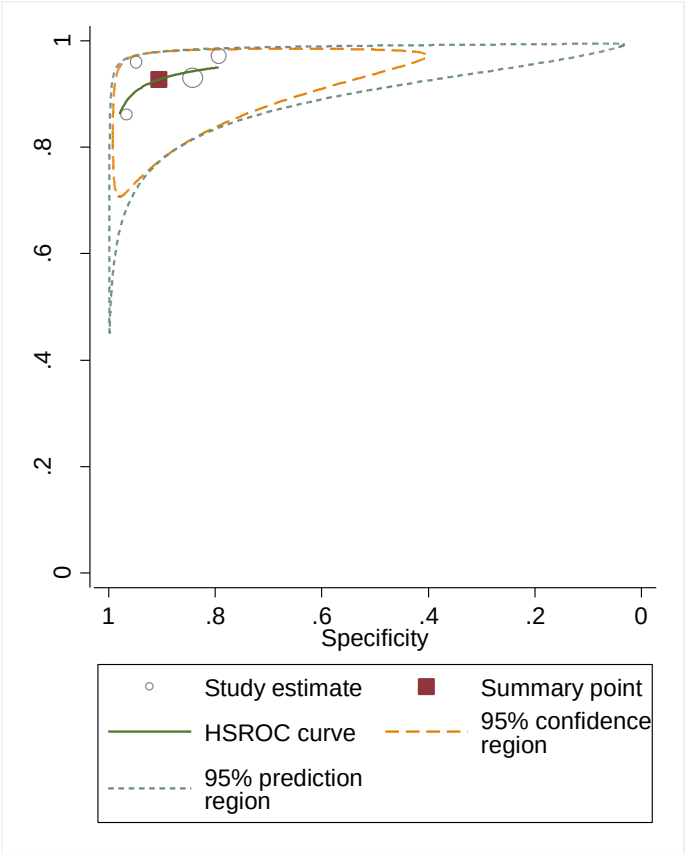


Table 5: Accuracy of NGCCT for the detection of CAD in patients with HCS

Study ID	HCS threshold	Patient or segment data (n)	Index test	Ref. Stand.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
Brodoefel 2008a[46]	Calcium score >400	segment (576)	Somatom Definition (+ve test ≥ 1 stenosis ≥50%)[b]	ICA (+ve test ≥ 1 stenosis ≥50%)	187	14	59	316	93.0 (95% CI 88.6 to 96.1)[a]	84.3 (95% CI 80.2 to 87.8)[a]	92 (16.0%)	NR
Meng 2009[50]	Calcium score >400	artery (135)	Somatom Definition (+ve test ≥ 1 stenosis >50%)[c]	ICA (+ve test ≥ 1 stenosis >50%)	43	1	19	72	97.7 (95% CI 88.0 to 99.9)[a]	79.1 (95% CI 69.3 to 86.9)[a]	NR	For total population, CT dose index 30-42 mGy
		segment (342)			69	2	56	215	97.2 (95% CI 90.2 to 99.7)[a]	79.3 (95% CI 74.0 to 84.0)[a]	Total population 25/1558 (NR for the HCS group)	
Scheffel 2006 [57]	≥400	segment (206)	Somatom Definition (+ve test >50%)[b]	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[62]	> 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) 61.38±11.64 mGy, 16.51±3.75 mSv
		artery (36)			29	0	0	7	100 (95% CI 88.1-100%)[a]	100 (95% CI 59.0-100%)[a]	NR	
		segment (180)			50	8	4	118	86.2 (95% CI 74.6 to 93.9)[a]	96.7 (95% CI 91.8 to 99.1)[a]	Total (all patients) 134/1661 (8.1%)	
		patients (12)	(+ve test ≥1 stenosis	(+ve test ≥1 stenosis >75%)	10	1	0	1	90.9 (95% CI 58.7 to 99.8)[a]	100 (95% CI 25.0 to 100)[a]	NR	

Study ID	HCS threshold	Patient or segment data (n)	Index test	Ref. Stand.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
		artery (36)	>75%)		17	3	1	15	85.0 (95% CI 62.1 to 96.8)[a]	93.8 (95% CI 69.8 to 99.8)[a]	NR	
		segment (180)			28	10	6	136	73.7 (95% CI 56.9 to 86.6)[a]	95.8 (95% CI 91.0 to 98.4)[a]	Total (all patients) 193/1661 (11.6%)	
a: calculated values, b: unclear how non-diagnostic segments were classified, 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												

5.6.3 Accuracy of NGCCT for detection of CAD in arrhythmia patients

Five studies reported ten data sets describing the accuracy of NGCCT for the detection of CAD in patients with arrhythmias.[38, 49, 51, 56, 58] Three[38, 51, 56] of the five studies reported using no additional (extra to the patient's normal medication) β-blockers prior to scanning, and β-blocker use was unclear in a fourth study.[58] The fifth study[49] used β-blockers prior to scanning in 40% of patients, and excluded 14% of otherwise eligible patients because they were un-responsive to β-blockers and had rapid AF (>100 bpm) at the time of scanning; this study was judged to be at high risk of bias with respect to participant selection. In one study[56] 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 of patients with AF reported per patient data. The pooled estimates of sensitivity and specificity, derived from these data using a Der Simonian-Laird random effects model where 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. One study reported the proportion of patients with AF who had non-diagnostic images (5%).[49]

One study also reported per artery data and these results are described in Table 7.[49]

Four studies reported per segment data.[38, 51, 56, 58] 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 SROC curve for per segment data in patients with arrhythmias.

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

Study ID	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**	**FLOW AND TIMING**
	Risk of Bias	**Risk of Bias**	**Risk of Bias**	**Risk of Bias**
Marwan 2010[49]	↑	?	?	↓
Oncel 2007[51]	↓	↓	↓	↓
Rist 2009 [56]	?	↓	↓	↑
Rixe 2009[38]	↓	?	?	?

Study ID	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
	Risk of Bias	Risk of Bias	Risk of Bias	Risk of Bias
Tsiflikas 2010[58] and Drosch 2008[59]	?	↑	↓	?
↑: 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

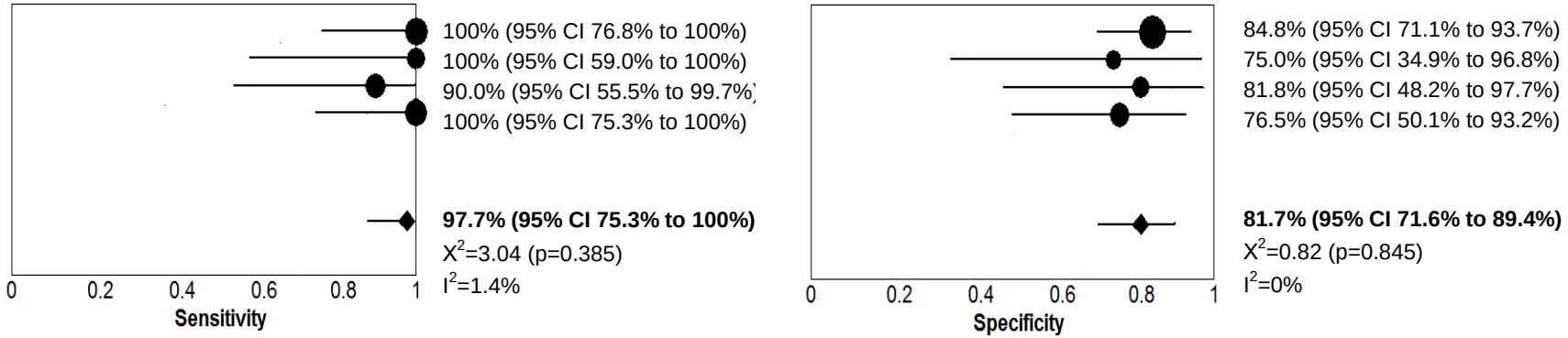


Figure 4: SROC curve for per segment data in studies of patients with arrhythmias

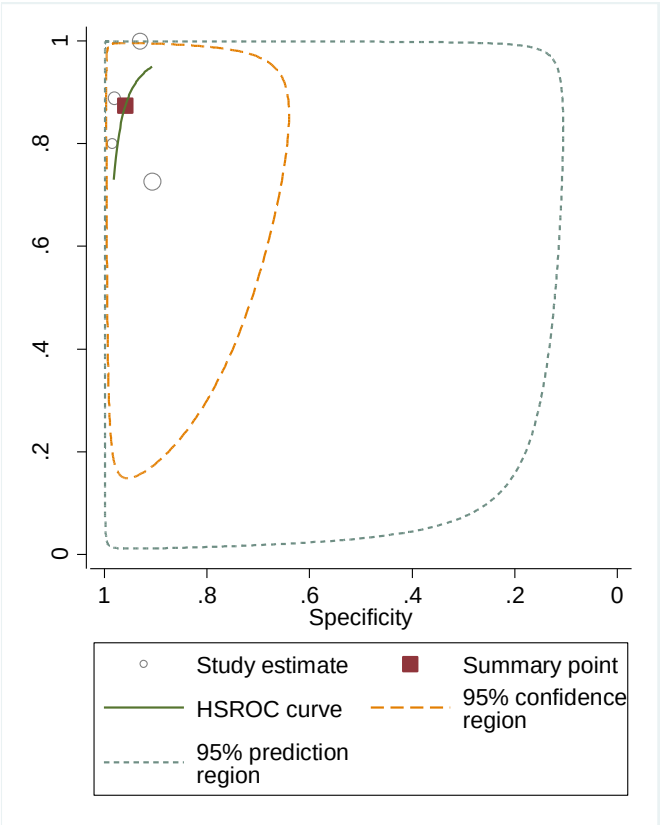


Table 7: Accuracy of NGCCT for the detection of CAD in patients with arrhythmias

Study ID	Arrhythmia def[n]	Patient or segment data (n)	Index test	Ref. Stand.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
Marwan 2010[49]	All patients in AF at scan (39 permanent, 21 persistent)	patient (60)	Somatom Definition (+ve test ≥1 stenosis ≥50)[d]	ICA (+ve test ≥1 stenosis >50%)	14	0	7	39	100 (95% CI 76.8 to 100) [a]	84.8 (95% CI 71.1 to 93.7) [a]	3 patients (5%)	Mean DLP 1186±375 mGy*cm(Range 630-2038mGy*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) [a]	93.6 (95% CI 89.5 to 96.4) [a]	3 vessels (1.3%)	
Oncel 2007[51]	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) [a]	75.0 (95% CI 34.9 to 96.8) [a]	NR	13.8 ±1.37 mSv
		artery (60)			12	3	2	43	80.0 (95% CI 51.9 to 95.7) [a]	95.6 (95% CI 84.9 to 99.5) [a]	NR	
		segment (212)			12	3	3	194	80.0 (95% CI 51.9 to 95.7) [a]	98.5 (95% CI 95.6 to 99.7) [a]	13 (5.8%)	
Rist 2009 [56]	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) [a]	81.8 (95% CI 48.2 to 97.7) [a]	Total population 4/68 (5.9%)	For all 68 participants, mean DLP 942.9±442 mGy x cm, mean effective dose 13.28 mSv.
		segment (283)			16	2	5	260	88.9 (95% CI 65.3 to 98.6) [a]	98.1 (95% CI 95.7 to 99.4) [a]	Total population 81/979 (8.3%)[e]	

Study ID	Arrhythmia def[n]	Patient or segment data (n)	Index test	Ref. Stand.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
Rixe 2009[38]	AF (no further details)	patient (30)	Somatom Definition (+ve test ≥ 1 stenosis >50%)[d]	ICA (+ve test ≥1 stenosis ≥50%)	13	0	4	13	100 (95% CI 75.3 to 100) [a]	76.5 (95% CI 50.1 to 93.2) [a]	NR	13.5±4.2 mSv
		segment (459)			24	0	30	405	100 (95% CI 85.8 to 100) [a]	93.1 (95% CI 90.3 to 95.3) [a]	32 (7.0%)	
Tsiflikas 2010[58] and Drosch 2008[59]	Patients without stable sinus rhythm during CT-scan	segment (572)[f]	Somatom Definition (+ve test ≥1 stenosis ≥50%)[b]	I ICA (+ve test ≥1 stenosis ≥50%)	69	26	41	400	72.6 (95% CI 62.5 to 81.3) [a]	90.7 (95% CI 87.6 to 93.2) [a]	28 (5%)	NR

a: calculated values, b: unclear how non-diagnostic segments, c: non-diagnostic segments were excluded, d: non-diagnostic segments were classified as positive, e: found in 19 patients, f: total segments reported in text inconsistent with number of segments for which results are reported.

5.6.4 Accuracy of NGCCT for detection of CAD in HHR patients

Eight studies reported 24 data sets describing the accuracy of NGCCT for the detection of CAD in patients with high heart rates.[42, 44, 46, 48, 50, 57, 61, 62] Three studies[46, 50, 57] only reported 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. With the exception of one study[63], all studies in this group excluded patients with previous revascularisations (previous stent implantation and/or previous bypass graft; one study[48] 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[42, 61] also excluded patients with AF. The first of these[42] 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[61] 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, due 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 bpm, ≥65 bpm or ≥70 bpm; for the purposes of meta-analysis, these studies were treated as a single group assessing the accuracy of NGCCT in patients with HR ≥65 bpm. The baseline use of β-blockers by study participants varied (see Appendix 4), but all studies in this section reported that no additional β-blockers were given prior to CT scanning.

Five studies reported per patient data, using a threshold of ≥50% or >50% vessel narrowing to define significant stenosis.[42, 44, 48, 61, 62] 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 reported per patient accuracy data for multiple definitions of HHR; these results are summarised in Table 9.[61] One study reported the proportion of patients with HHR who had non-diagnostic images (6.8%).[42]

Four studies reported per artery data, using a threshold of ≥50% or >50% vessel narrowing to define significant stenosis.[42, 48, 50, 62] 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 ≥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 patient data in patients with HHR. One study reported per segment accuracy data for multiple definitions of HHR; these results are summarised in Table 9.[61]

One study[62] 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 ≥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	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**	**FLOW AND TIMING**
	Risk of Bias	**Risk of Bias**	**Risk of Bias**	**Risk of Bias**
Alkadhi 2008[63]	↓	↓	↓	↓
Brodoefel 2008a[46]	?	↑	↓	↓
Lin 2010[48]	↑	?	↓	↓
Meng 2009[50]	?	↑	↓	?
Ropers 2007[42]	?	↓	?	↓
Scheffel 2006[57]	?	↑	↓	↓
Weustink 2009a[61]	↑	↓	↓	↑
Zhang 2010[62]	?	↓	↓	?
↑: high risk of bias, ↓: low risk of bias, ?: unclear risk of bias				

Figure 5: SROC curve for per patient data in studies of patients with HHR

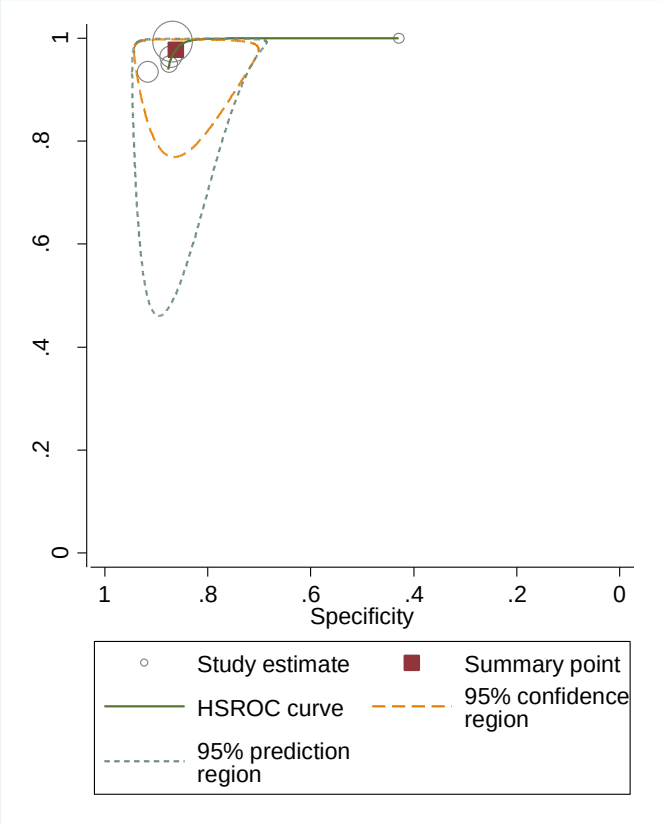


Figure 6: SROC curve for per artery data in studies of patients with HHR

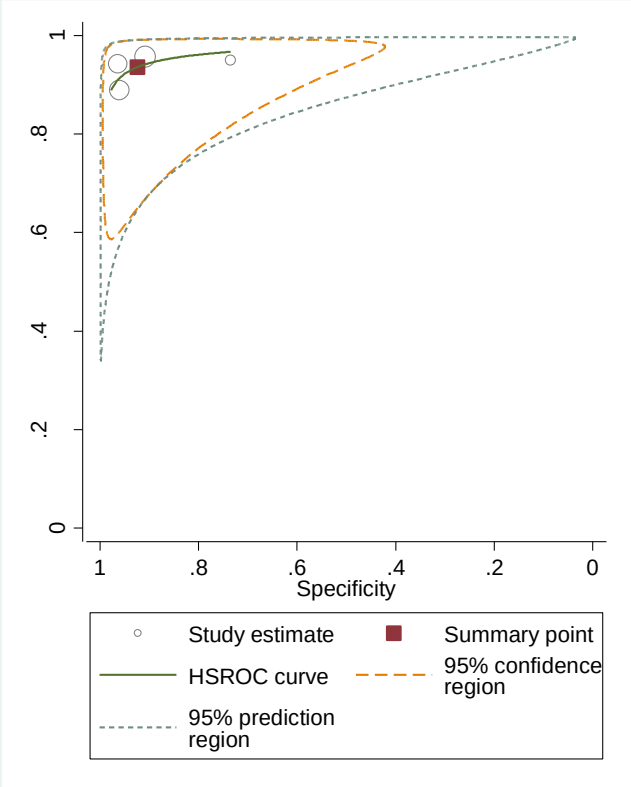


Figure 7: SROC curve for per segment data in studies of patients with HHR

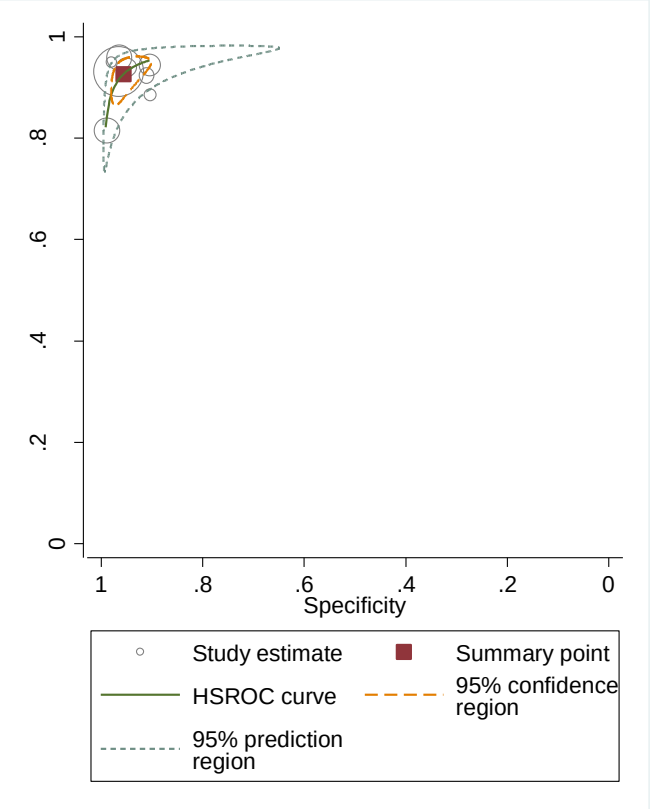


Table 9: Accuracy of NGCCT for the detection of CAD in patients with high heart rates

Study ID	HR	Patient or segment data (n)	Index test	Ref. Stand.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
Alkadhi 2010[44]	>66 bpm	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 to 9 mSv[?]
		segment (1018)	Somatom Definition (+ve test ≥1 stenosis >50%)[d]		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 2008a[46]	>70 bpm	segment (370)	Somatom Definition (+ve test ≥1 stenosis ≥50%)[b]	ICA (+ve test ≥1 stenosis ≥50%)	73	6	26	265	92.4 (95% CI 84.2 to 97.2) [a]	91.1(95% CI 87.2 to 94.1) [a]	7 (1.9%)	NR
Lin 2010[48]	≥70 bpm	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) [a]	42.9 (95% CI 9.9 to 81.6) [a]	NR	NR
		artery (54)			19	1	9	25	95 (95% CI 75.1 to 99.9) [a]	73.5 (95% CI 55.6 to 87.1) [a]	NR	
		segment (223)			31	4	18	170	88.6 (95% CI 73.3 to 96.8) [a]	90.4 (95% CI 85.3 to 94.2) [a]	NR	
Meng 2009[50]	≥70 bpm	artery (225)	Somatom Definition (+ve test	ICA (+ve test ≥1 stenosis	68	3	14	140	95.8 (95% CI 88.1 to 99.1) [a]	90.9 (95% CI 85.2 to 94.9) [a]	NR	For total population, CT dose

Study ID	HR	Patient or segment data (n)	Index test	Ref. Stand.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
		segment (756)	≥1 stenosis >50%)[c]	>50%)	103	6	62	585	94.5 (95% CI 88.4 to 98.0) [a]	90.4 (95% CI 87.9 to 92.6) [a]	Total population 25/1558 (NR for the HHR group)	index 30-42 mGy
Ropers 2007[42]	≥65 bpm	patient (44)	Somatom Definition (+ve test ≥1 stenosis >50%)[d]	ICA (+ve test ≥1 stenosis >50%)	19	1	3	21	95 (95% CI 75.1 to 99.9) [a]	87.5 (95% CI 67.6 to 97.3) [a]	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) [a]	96.5 (95% CI 91.9 to 98.8) [a]	9 (5.1%)	
		segment (616)			62	4	27	523	93.9 (95% CI 85.2 to 98.3) [a]	95.1 (95% CI 92.9 to 96.7) [a]	50 (8.1%)	
Scheffel 2006[57]	≥70 bpm	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) [a]	98.1 (95% CI 94.4 to 99.6) [a]	4/175 (2.2%)	NR
Weustink 2009a[61]	66-79 bpm	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) [a]	86.8 (95% CI 74.7 to 94.5) [a]	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	Ref. Stand.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
	≥80 bpm	patients (171, 85 underwent ICA and were included in the analysis)			47	0	5	33	100 (95% CI 92.5 to 100) [a]	86.8 (95% CI 71.9 to 95.6) [a]	NR	Optimal ECG pulsing: Pitch: 0.3 ±0.04 $CTDI_{vol}$(mGy): 42.7 ±16.9 $CTDI_{w}$ (mGy): 14.9 ±1
	≥66 bpm	patients (504, 255 underwent ICA and were included in the analysis)			163	1	12	79	99.4 (95% CI 96.6 to 100) [a]	86.8 (95% CI 78.1 to 93.0) [a]	NR	NR
	66-79 bpm	segment (2613)			240	21	71	2281	92.0 (95% Ci 88.0 to 95.0) [a]	97.0 (95% CI 96.2 to 97.6) [a]	NR	NA
	≥80 bpm	segment (1327)			102	4	49	1172	96.2 (95% CI 90.6 to 99.0) [a]	96.0 (95% CI 94.7 to 97.0) [a]	NR	NA
	≥66 bpm	segment (3940)			342	25	120	3453	93.2 (95% CI 90.1 to 95.5) [a]	96.6 (95% CI 96.0 to 97.2) [a]	NR	NA
Zhang 2010[62]	>70 bpm	patients (70)	Somatom Definition (+ve test ≥1 stenosis ≥50%	ICA (+ve test ≥1 stenosis >50%)	43	3	2	22	93.5 (95% 82.1 to 98.6) [a]	91.7 (95% CI 73.0 to 99.0) [a]	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) [a]	96.1 (95% CI 91.1 98.7) [a]		
		segment (1035)			110	25	10	890	81.5 (95% CI 73.9 to 87.6) [a]	98.9 (95% CI 98.0 to 99.5) [a]		

Study ID	HR	Patient or segment data (n)	Index test	Ref. Stand.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
		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) [a]	97.1 (95% CI 84.7 to 99.9) [a]		
		artery (209)			41	8	4	156	83.7 (95% CI 70.3 to 92.7) [a]	97.5 (95% CI 93.7 to 99.3) [a]		
		segment (1035)			59	16	8	952	78.7 (95% CI 67.7 to 87.3) [a]	99.2 (95% CI 98.4 to 99.6) [a]		
a: calculated values, b: unclear how non-diagnostic segments were classified, c: non-diagnostic segments were excluded, d: non-diagnostic segments were classified as positive												

5.6.5 Accuracy of NGCCT for detection of CAD in β-blocker intolerance

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

5.6.6 Accuracy of NGCCT for detection of CAD in stented patients

Seven studies reported ten data sets describing the accuracy of NGCCT for the detection of CAD in patients with previous stent(s) implantation.[37, 39, 41, 43, 52-54] Three studies[37, 41, 54] only reported 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 which may contribute to difficulty in imaging. These included HHR and intolerance to β-blockers[43], previous bypass graft[39] and irregular heart rhythm/AF[53, 54]. The last of these studies[53] 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[53] 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 of the seven studies considered only in-stent re-stenosis and the seventh[39] considered both in-stent re-stenosis and stenosis of native vessels.

Four studies reported per patient data, using a threshold of ≥50% or >50% vessel narrowing to define significant stenosis.[39, 43, 52, 53] The pooled estimates of sensitivity and specificity, derived from these data using a Der Simonian-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 reported the proportion of patients with previous stent implantation who had non-diagnostic images (9%).[43]

Six studies reported accuracy data by stent or stented lesion.[37, 41, 43, 52-54] 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 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[41] reported additional data, using a threshold of ≥70% narrowing to define significant in-stent re-stenosis; sensitivity and specificity estimates were broadly similar to those obtained using the ≥50% narrowing threshold and are reported in Table 11.

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	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**	**FLOW AND TIMING**
	Risk of Bias	**Risk of Bias**	**Risk of Bias**	**Risk of Bias**
de Graaf 2010[43]	?	↓	↓	↓
LaBounty 2010[41]	?	↑	↓	?
Oncel 2008[52]	?	↓	↓	↓
Pflederer 2009[53]	↑	?	↓	?
Pflederer 2010[37]	?	↑	?	?
Pugliese 2008[54] and Pugliese 2007[55]	?	↑	↓	?
Van Mieghem 2007[39]	?	?	?	?
↑: high risk of bias, ↓: low risk of bias, ?: unclear risk of bias				

Figure 8: Forest plot of per patient sensitivity and specificity of NGCCT for the detection of CAD in patients with previous stent(s)

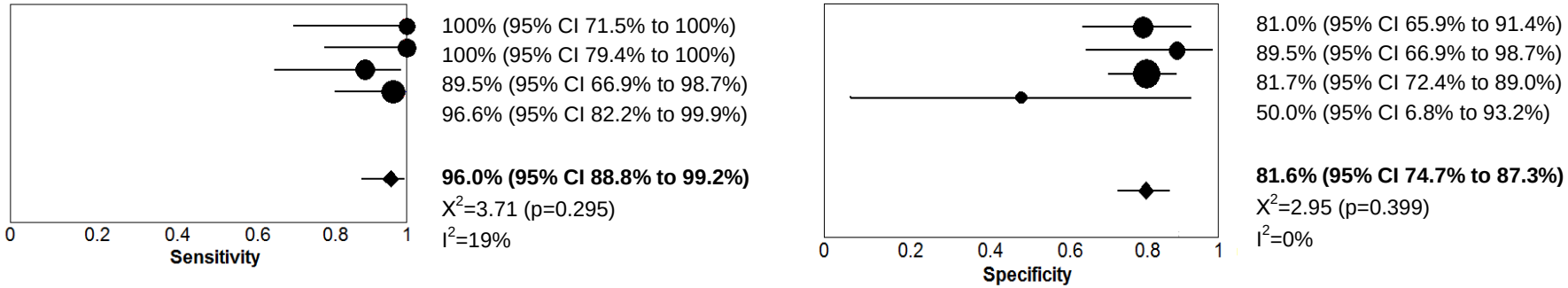


Figure 9: SROC curve for per stent/stented lesion data in studies of patients with previous stent(s)

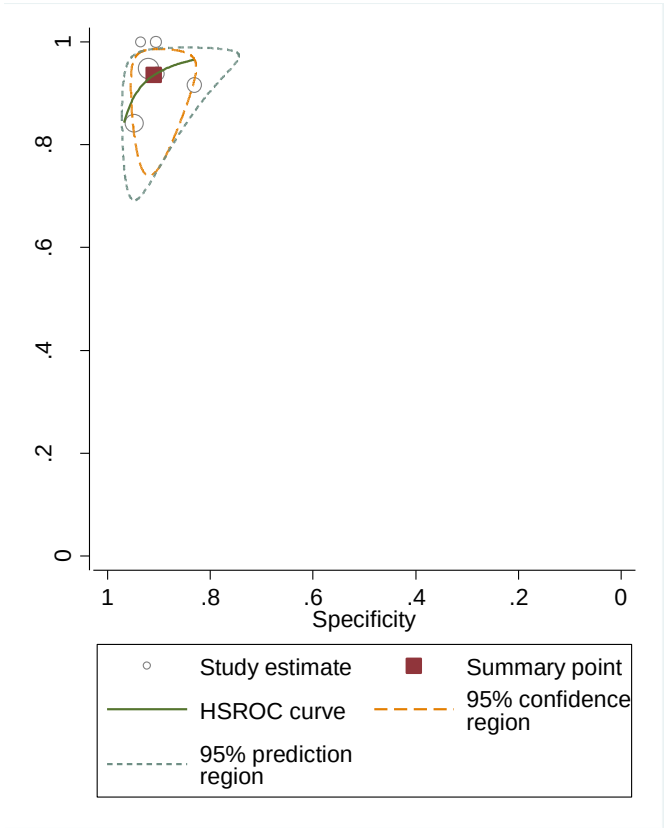


Table 11: Accuracy of NGCCT for the detection of CAD in patients with previous stent(s)

Study ID	Patient or segment data (n)	Index test	Ref. Stand.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
de Graaf 2010[43]	patient (53) [d]	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) [a]	81.0 (95% CI 65.9 to 91.4) [a]	patients 5 (9%)	Unclear, reported for different imaging protocols. Mean dose ranged from 3.2±1.1 to 16.7±6.3 mSv
	stent (89, overlapping stents treated as a single stent)			11	1	13	64	91.7 (95% CI 61.5 to 99.8) [a]	83.1 (95% CI 72.9 to 90.7) [a]	stents 7 (7.9%)	
LaBounty 2010[41]	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) [a]	90.6 (95% CI 79.3 to 96.9) [a]	NR	For total population, median = 3.9 mSv (IQR 1.9 to 9.1), not reported for stented patients.
		(+ve test stenosis ≥70%)	(+ve test stenosis ≥70%)	1	0	2	51	100 (95% CI 2.5 to 100) [a]	96.2 (95% CI 87.0 to 99.5) [a]		
Oncel 2008[52]	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) [a]	89.5 (95% CI 66.9 to 97.8) [a]	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) [a]	93.5 (95% CI 78.6 to 99.2) [a]		
Pflederer 2009[53]	patient (112) [c,d]	Somatom Definition (+ve test ≥1 stenosis ≥50)[b]	ICA (+ve test ≥1 stenosis ≥50%)	17	2	17	76	89.5 (95% CI 66.9 to 98.7) [a]	81.7 (95% CI 72.4 to 89.0) [a]	NR	14.8±4.8 mSv
	stent (135)			16	3	6	110	84.2 (95% CI 60.4 to 96.6) [a]	94.8 (95% CI 89.1 to 98.1) [a]	15(11%)	

Study ID	Patient or segment data (n)	Index test	Ref. Stand.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
Pflederer 2010[37]	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) [a]	90.3 (95% CI 80.1 to 96.4) [a]	NR	NR
Pugliese 2008[54] Pugliese 2007[55]	stented lesions (178)[f]	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) [a]	86.5 (95% CI 79.9 to 91.5)	9 (5.1%)	NR
Van Mieghem 2007[39]	patient (33)[e]	DSCT (unspecified), (+ve test >50% stenosis)	ICA (+ve test >50% stenosis)	28	1	2	2	96.6 (95% CI 82.2 to 99.9) [a]	50.0 (95% CI 6.8 to 93.2) [a]	NR	NR
a: calculated values, b: non-diagnostic stents/lesions were classified as positive, c: non-diagnostic stents/lesions were excluded, d: in-stent re-stenosis only, e: in-stent re-stenosis and stenosis of native vessels, f: multiple stents per lesion were treated as a single unit											

5.6.7 Accuracy of NGCCT for detection of CAD in CABG patients

Three studies reported six data sets describing the accuracy of NGCCT for the detection of CAD in patients with previous bypass graft(s).[37, 40, 60] Two of the three studies included in this section were only published as conference abstracts.[37, 40] 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 which was reported as a full paper[60] only reported 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 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.[40] 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%).

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**	**INDEX TEST**	**REFERENCE STANDARD**	**FLOW AND TIMING**
	Risk of Bias	**Risk of Bias**	**Risk of Bias**	**Risk of Bias**
Pflederer 2010[37]	?	↑	?	?
Ropers 2008[40]	?	?	?	?
Weustink 2009b[60]	↓	↑	↓	↓
↑: 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	Ref. Stand.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
Pflederer 2010 [37]	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 [40]	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 2009b [60]	bypass graft, segment (152)	Somatom Definition (+ve stenosis ≥50%) [c]	ICA (+ve stenosis ≥50%)	29	0	0	123	100 (95% CI88.1 to100) [a]	100 (95% CI 97.0 to 100) [a]	NR	DLP (mGy*cm) 1.726±596 Effective dose (mSv) 22.1±2.8
	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	
	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	

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 <1.5 mm were excluded from analyses

5.6.8 Accuracy of NGCCT for detection of CAD (multiple criteria)

Three studies reported the accuracy of NGCCT in patients with different combinations of difficult to image criteria.[47, 54, 60] Two studies[54, 60] only reported per segment or per lesion accuracy data. The only study to report per patient data[60] 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 reported per patient data.[47] 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 >65 bpm and/or AF.

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	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**	**FLOW AND TIMING**
	Risk of Bias	**Risk of Bias**	**Risk of Bias**	**Risk of Bias**
Leber 2007[47]	↓	?	?	?
Pugliese 2008[54] and Pugliese 2007[55]	?	↑	↓	?
Weustink 2009b[60]	↓	↑	↓	↓
↑: 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	Ref. Stand.	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	ND (n)	Radiation (mean±sd)
Leber 2007[47]	HR >65 bpm and/or AF	patient (46)	Somatom Definition (+ve test stenosis >50%)[b]	ICA (+ve test stenosis >50%)	11	1	4	30	91.7 (95% CI 61.5 to 99.8) [a]	88.2 (95% CI 72.5 to 96.7) [a]	1 Patient	For total population, mean dose 9.6 mSv (range 7.1 to 12.3). No separate data reported for HHR/AF participants.
		segment (637)			21	3	5	608	87.5 (95% CI 67.6 to 97.3) [a]	99.2 (95% CI 98.1 to 99.7) [a]	NR	
Pugliese 2008[54] Pugliese 2007[55]	previous stent implantation, and HHR (≥70 bpm)	lesions (54)	Somatom Definition	CA	9	1	4	40	90.0 (95% CI 55.5 to 99.7) [a]	90.9(95% CI 78.3 to 97.5) [a]	NR	NR
Weustink 2009b[60]	previous bypass graft and HHR (>65 bpm)	native coronary arteries (grafted), segment (289)[d]	Somatom Definition (+ve stenosis ≥50%)[c]	ICA (+ve stenosis ≥50%)	90	0	1	63	100 (95% CI 96.0 to 100) [a]	98.4 (95% CI 91.6 to 100) [a]	NR	DLP (mGy*cm): 1.726 +/- 596 Effective dose (mSv): 22.1 +/-2.8
a: calculated values, b: non-diagnostic segments were excluded, c: segments distal to an occlusion or with lumen diameter <1.5 mm were excluded, d: 154 segments in patients with HR >65 bpm included in analysis												

5.7 Summary

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. 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 as to whether 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. Further, though there were no data specifically for β-blocker intolerant patients, it should be noted that no study reporting per patient data for patients with HHR used additional β-blockers prior to scanning. It may therefore be inferred that NGCCT could reasonably be used to image patients who are intolerant to β-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).

Data on the numbers 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 sub-group. Three studies did report subgroup specific non-diagnostic image rates in different populations; these were 5% for patients with arrhythmias,[49] 6.8% for patients with HHR[42] and 9% for patients with previous stent implantation.[43]

Figure 10: Summary of QUADAS-2 assessments

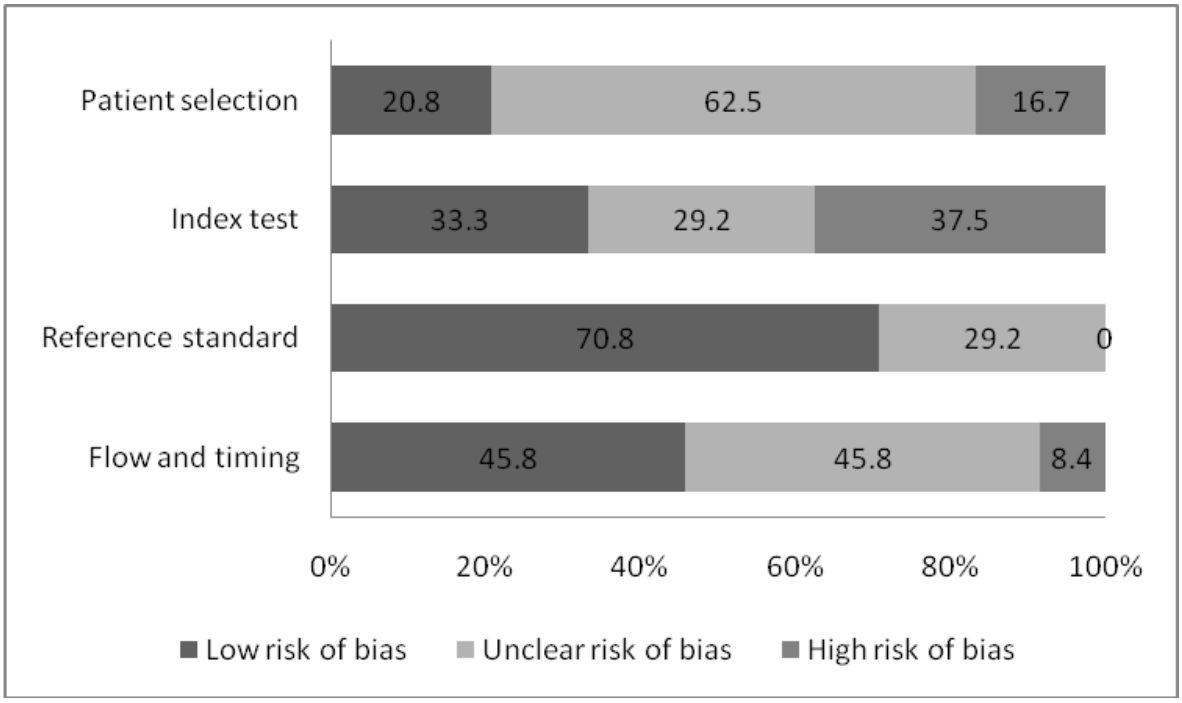


Table 16: Summary of test accuracy results

Patient group	Unit of analysis	Number of studies	N	Sensitivity	I^2	Specificity	I^2
obesity (BMI ≥30 kg/m^2)	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 bpm)	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%

6 ASSESSMENT OF COST-EFFECTIVENESS

6.1 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 2000 to present:

- MEDLINE (2000-2011/03/wk 2) (OvidSP)
- MEDLINE In-Process Citations and Daily Update (2000-2011/03/17) (OvidSP)
- EMBASE (2000-2011/wk 11) (OvidSP)
- NHS Economic Evaluation Database (NHS EED) (2000-2011/03/09) (CRD website)
- Health Economic Evaluation Database (HEED) (2000-2011/03/09) (Wiley) http://onlinelibrary.wiley.com/book/10.1002/9780470510933
- Paediatric Economic Database Evaluation (PEDE) (2000-2011/03/05) (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 Guidelines Clearinghouse (NGC) (2005-2011/03/16) (Internet) http://www.guideline.gov/
- GIN: International Guidelines Library (GIN) (2005-2011/03/16) http://www.g-i-n.net
- National Institute for Health and Clinical Excellence (NICE) Guidance (up to 2011/03/16) (Internet) http://guidance.nice.org.uk/
- TRIP database (2005-2011/03/16) (Internet) http://www.tripdatabase.com/
- Health Technology Assessment Database (HTA) (2005-2011/03/16) (CRD website)

Identified references were downloaded in Endnote X4 software for further assessment and handling.

References in retrieved articles were checked for additional studies.

6.2 Cost-effectiveness of NGCCT in CAD

6.2.1 Model structure and methodology

The cost-effectiveness of new generation cardiac computed tomography (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 decide if a revascularisation is necessary.

Five models were combined to estimate the cost-effectiveness of the NGCCT:

6. a decision tree that models the diagnostic pathway (Diagnostic model, section 6.2.1.1)
7. a life–death Markov model for "healthy" patients without CAD (Healthy population Markov model, section 6.2.1.2)
8. a simple stroke model to estimate the impact of test and treatment related stroke (stroke model, section 6.2.1.3).
9. a model for the prognosis of patients with CAD (EUROPA, section 6.2.1.4)
10. 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)[11] (YRM, section 6.2.1.5)

The comparator used for the evaluation of suspected or known CAD in difficult or impossible to image patients was ICA (section 3.3.1). Three strategies were evaluated in this assessment. The first strategy (ICA-only) is a strategy where patients with suspected or known CAD only undergo an ICA. While 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 myocardial infarction 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.[15] 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.[15] 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 micro-simulations were run.

6.2.1.1 Diagnostic model

The diagnostic pathway was modelled using a modified version of the CEmarc model, developed by Walker et al. 2011.[8] The model identifies patients as true positive (TP), true negative (TN), false positive (FP) and false negative (FN) depending on the diagnostic performance of the test or test strategy and the prior likelihood of the test outcome. Figures 11-13 (suspected) and Figures 16-19 (known) show decision trees for this process, in patients with suspected and known CAD. Two versions of the diagnostic model were created because the known (2-treatment

model) and suspected CAD (3 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 (section 6.2.1.4). Modification of the original CEmarc model was necessary because the test strategies considered in this assessment did not correspond with the test strategies used in the original model. The CEmarc study [redacted]. Furthermore, they did not include the treatment medication-only option required for our suspected CAD population. We assumed that the tests were performed immediately after each other without any time delay.

Figure 11: CAD suspected population – ICA-only

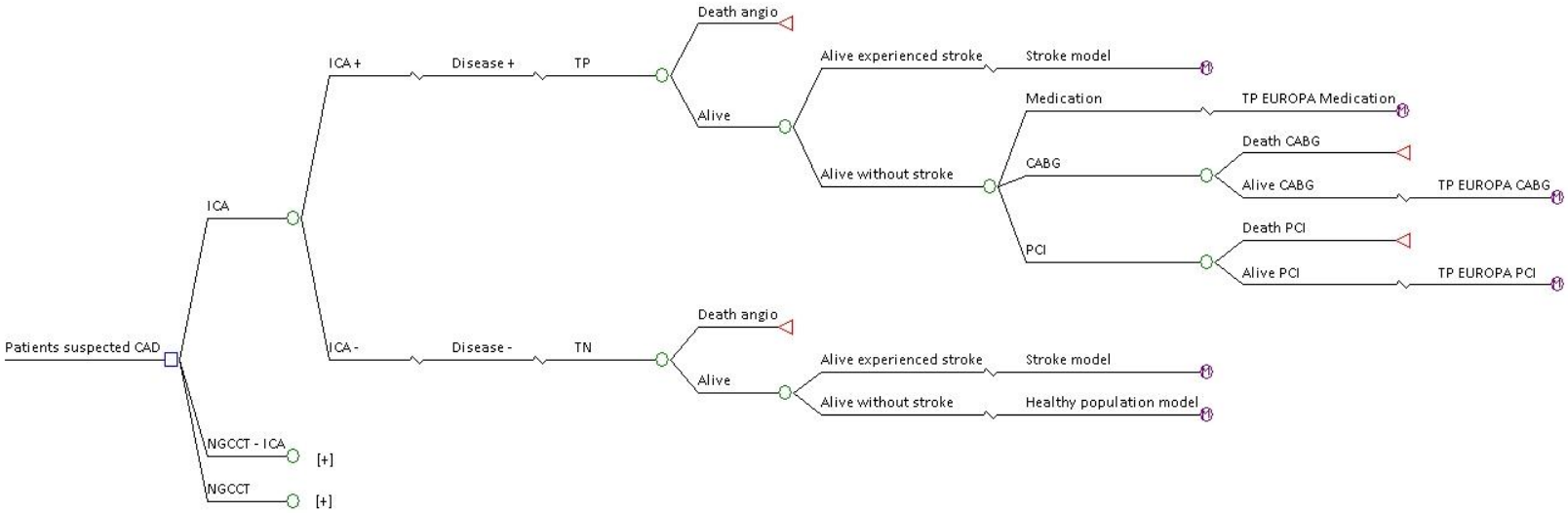


Figure 12: CAD suspected population – NGCCT – ICA

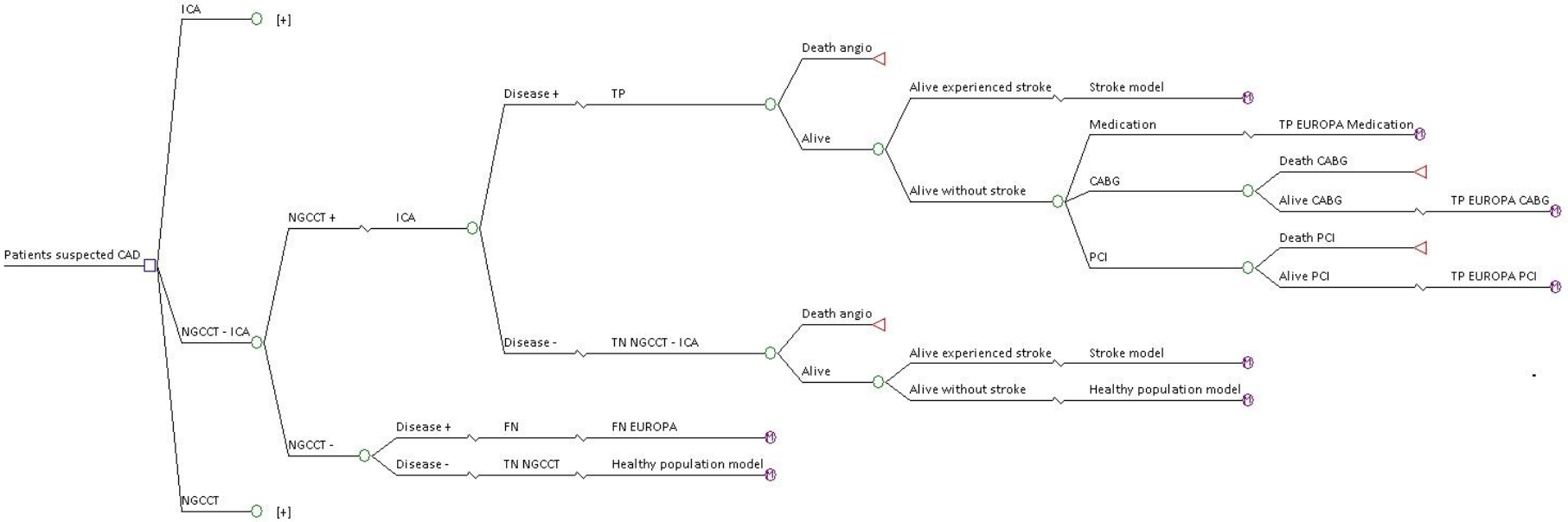
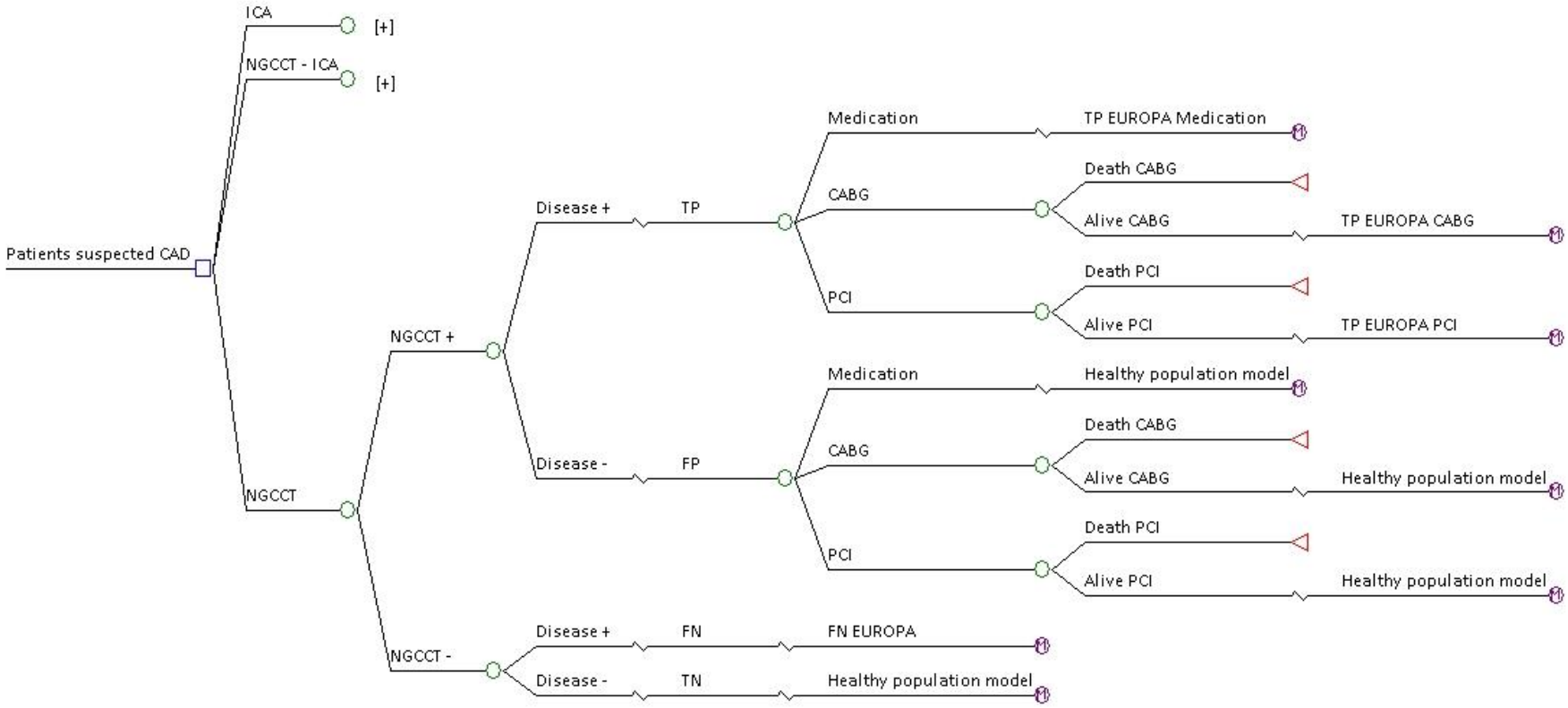


Figure 13: CAD suspected population – NGCCT



Diagnostic model for patients with suspected CAD

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 bet 10 to 29%, based on the clinical guideline "Chest pain of recent onset".[12] 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.

Table 17: Prevalence CAD populations

	Mean	**Source**
Prevalence suspected CAD:	0.200	CG95[12]
Prevalence known CAD:	[redacted]	Walker et al. 2011[65]

The sensitivity and specificity of ICA was assumed to be 100%, as in Mowatt et al. 2008.[15] The systematic review performed for this assessment provided the estimates of the sensitivity and specificity for the NGCCT. As described in section 5, estimates of sensitivity and specificity differed for the different difficult to image patient groups. The sensitivity and specificity of the NGCCT in the β-blocker intolerant patient group were assumed to be the same as the sensitivity and specificity in patients with a high heart rate. Since β -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 patient may have a heart rate that is too high during the scan; studies reporting per patient sensitivity and specificity in patients with a high heart rate did not use β-blockers prior to scanning. Table 18 shows the sensitivity and specificity estimates for the NGCCT in the different difficult to image patient groups.

Table 18: NGCCT 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 - 0.949	0.921	0.891 - 0.945	Review
NGCCT: High coronary calcium score	0.927	0.883 - 0.956	0.906	0.806 - 0.958	Review
NGCCT: Arrhythmias	0.977	0.881 - 0.999	0.817	0.716 - 0.894	Review
NGCCT: High heart rate	0.977	0.932 - 0.993	0.863	0.802 - 0.907	Review
NGCCT: β-blocker intolerance	0.977	0.932 - 0.993	0.863	0.802 - 0.907	Assumption

NGCCT: Previous stented	0.960	0.822 - 0.999	0.816	0.747 - 0.873	Review
NGCCT: Previous CABG	0.964	0.875 - 0.996	0.87	0.664 - 0.972	Review

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.

Figure 14: Illustration of a 2 x 2 table for patients with suspected CAD

	Disease positive	**Disease negative**
Test positive	true positive (TP)	false positive (FP)
Test negative	false negative (FN)	true negative (TN)

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.
- 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. myocardial infarction (MI) or cardiac arrest) before the correct diagnosis is established. The false positives 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 true negatives. As a result, these patients will not receive any unnecessary treatment. In the model, all of these patients are subsequently considered as true negatives for the NGCCT-ICA strategy since the ICA correctly reclassified them. However, an ICA is not performed in patients with a negative NGCCT result. Since 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 known CAD population

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 determine whether or not revascularisation is necessary.

The prior likelihood of performing a revascularisation in patients with known CAD is [redacted] based on the CEmarc study (Table 17).[65] The CEmarc study [redacted]. The purpose of diagnostic testing assessed in the CEmarc study captures the aim of this economic evaluation for the known CAD population and therefore the prior likelihood of the CEmarc 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.

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 strategy ICA only will define only TP and TN because ICA is assumed to be 100% accurate. The strategy NGCCT-only gives four possible outcomes: TP, FP, TN, FN. The combined strategy (NGCCT –ICA) defines three outcomes: TP, TN, FN.

Figure 15: Illustration of a 2 x 2 table for patients with known CAD

	Revascularisation needed	**Revascularisation not needed**
Test positive	true positive (TP)	false positive (FP)
Test negative	false negative (FN)	true negative (TN)

Figure 16: Known CAD – ICA-only

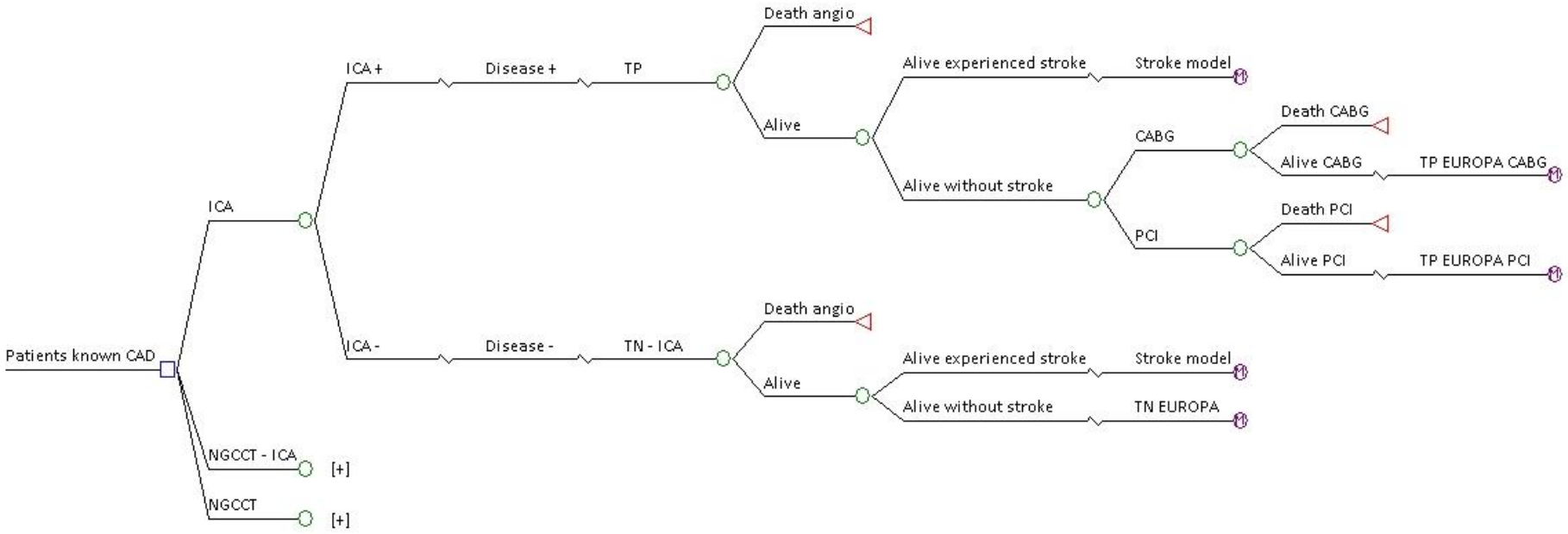


Figure 17: Known CAD – NGCCT-ICA

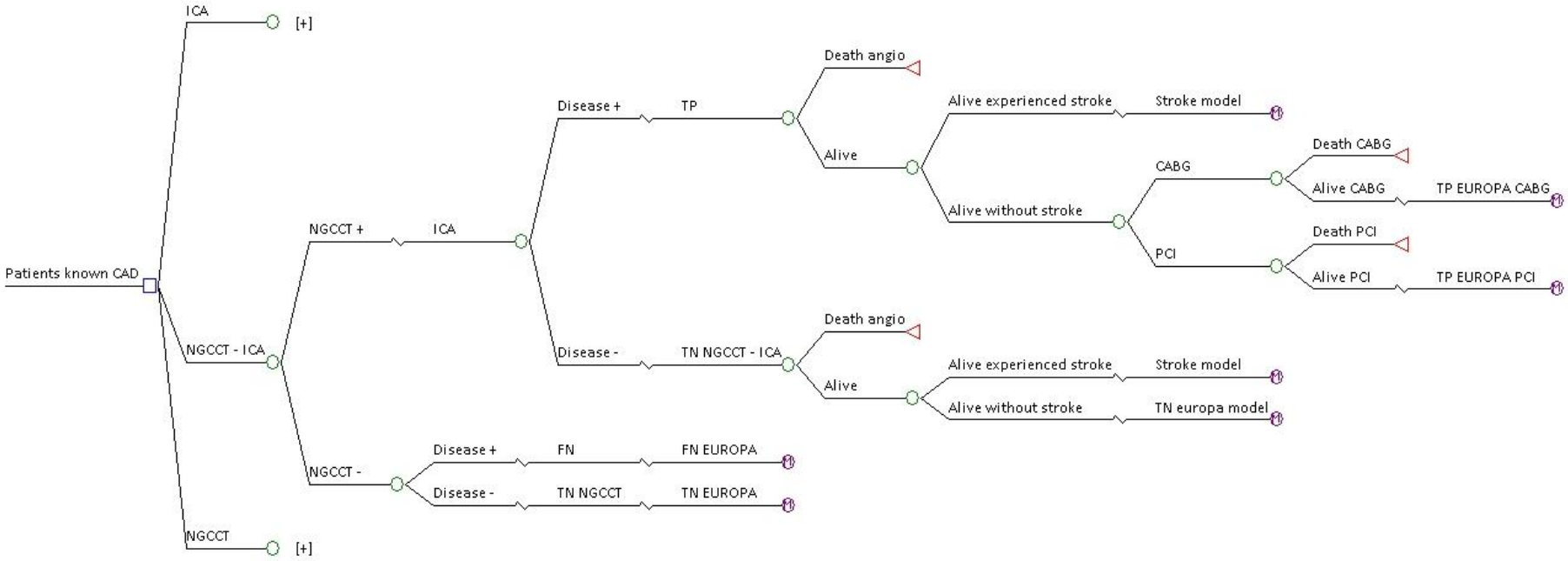
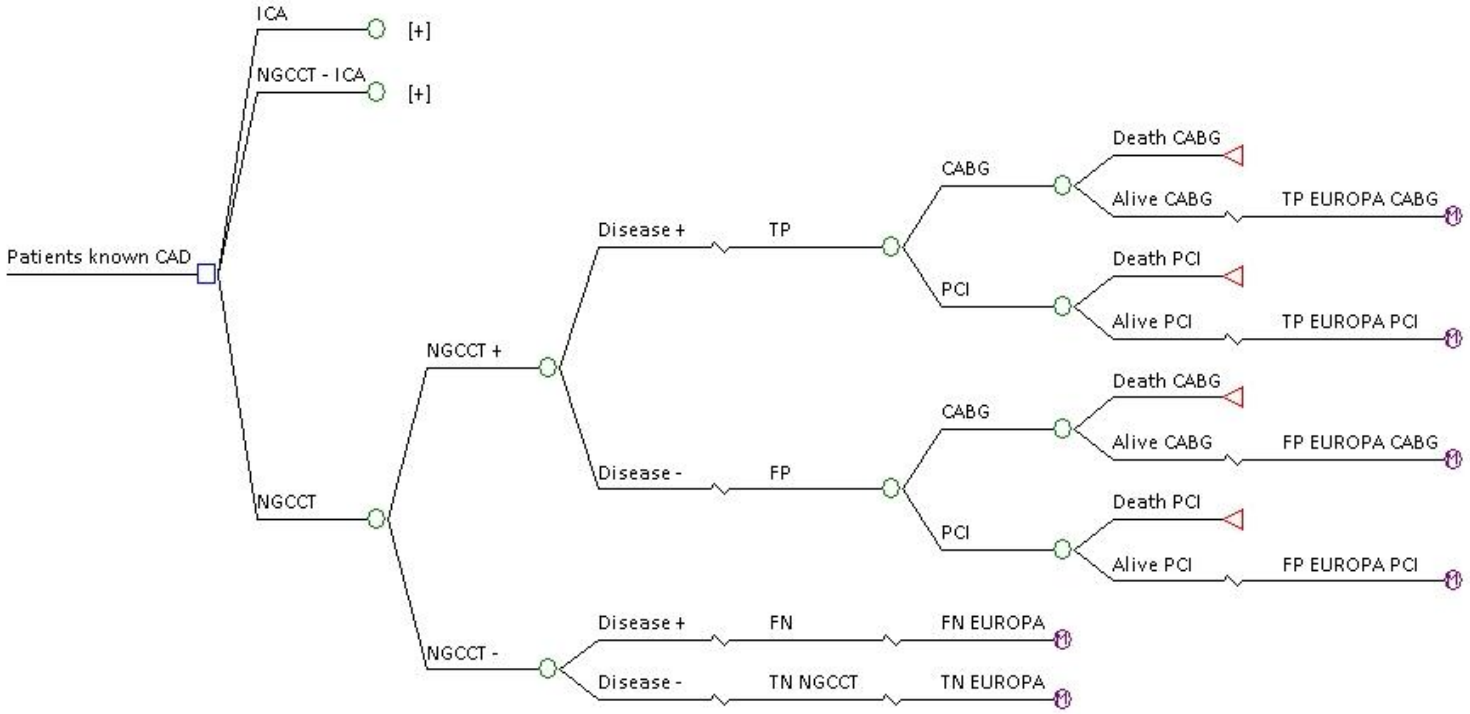


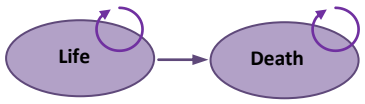
Figure 18: Known CAD – NGCCT-only



6.2.1.2 Healthy population Markov model

Patients without the disease (TN and FP from the suspected CAD population): Table 19, were modelled with a simple alive – death Markov model (Figure 19) based on UK life tables.[9] Based on UK life tables, patients could either die of all causes (including cardiovascular, because a negative test result does not mean that patients will never develop CAD) or stay in the 'alive' state. Only quality-adjusted life years (QALYs) but no costs were calculated with this model.

Figure 19: Simple alive-death Markov model



6.2.1.3 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 life-death 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 ischemic stroke compared with standard care for the NHS perspective. In particular, we assumed that stroke patients would receive thrombolytic treatment.[67]

6.2.1.4 EUROPA

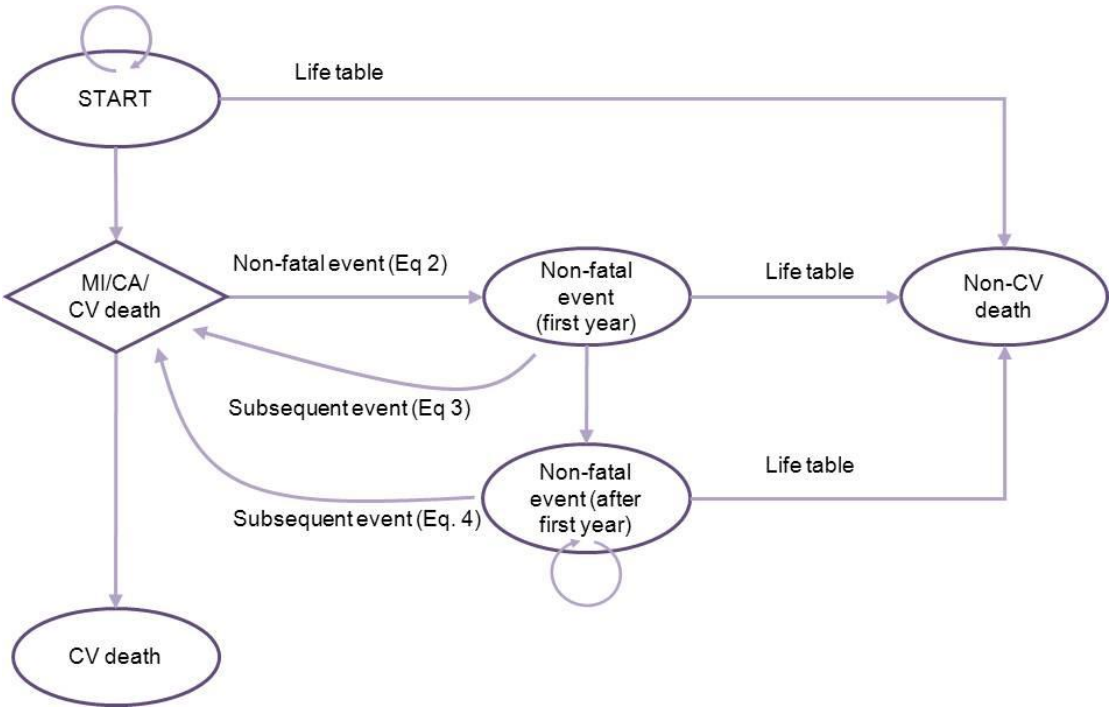
The EUROPA trial assessed the ability of the ACE-inhibitor perindopril to reduce cardiovascular death, myocardial infarction, and cardiac arrest in a broad population of patients with stable coronary heart disease and without heart failure or substantial hypertension.[68] Based on the patients in this trial Briggs et al. built a Markov model.[10]

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 (cardiac arrest, (non-) fatal myocardial infarction) that patients could suffer and the mortality associated with those events.

EUROPA model structure

The EUROPA Markov model (Figure 20) consisted of five health states which were defined as absence of primary event in the EUROPA trial: "trial entry", "cardiovascular death (CV death)", "non-fatal primary event in current year", "history of non-fatal event (NFE)" and "non cardiovascular death".[10] The 3-monthly transition probabilities between the different states were based on risk equations and on UK life tables on non-cardiovascular 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.

Figure 20: NFE: non fatal event; CV: cardiovascular; CA: cardiac arrest; MI: myocardial infarction (based on Briggs et al. 2007)



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-cardiovascular cause (and move to the 'Non-CV death' state), or experience a cardiovascular 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' state 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 can remain in this state for maximum of one year without experiencing a subsequent event. After that, a patient can move to: the 'Non fatal event (after first year)' state if the patient 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-cardiovascular 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 'Nnon 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-cardiovascular cause. The risks of events and the mortality associated with events are predicted by the risk equations. Non-cardiovascular mortality was based on UK life tables.

EUROPA model entry for suspected CAD population

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 true negative 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 life-death Markov model (healthy population model) based on life tables, as described in section 6.2.1.2.

EUROPA model entry for known CAD population

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.

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 which are still not identified have a higher change of experiencing an event.

Table 19: EUROPA model entry & Healthy population model entry for Suspected CAD population

Suspected CAD	Without angiographic and revascularization mortality				With angiographic and revascularization mortality							
Strategy	TP	FP	TN	FN	TP	FP	TN	FN	Mortality ICA	Morbidity ICA	Mortality Revascularization	Morbidity revascularization
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	0.72517	0.0145	-	-	0.0004	0.001
High heart rate												
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

TP: True Positive; FP: False Positive; TN: True Negative; FN: False Negative

Table 20: EUROPA entry for known CAD patients**Error! Not a valid link.**

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.

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 three months as a function of the following covariates: age, years older than 65, perindopril usage, smoking, previous MI, existing vascular disease (stroke, transient ischemic attack (TIA) or peripheral vascular disease), family history of CAD, symptomatic angina or history of heart failure, systolic blood pressure, total cholesterol, obese (BMI >30 kg/m^2), gender, nitrates usage, calcium channel blockers usage, lipid lowering treatment, units creatinine clearance below 80ml/min, 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 non-fatal event 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 one 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 since we used a cohort model. The accuracy of the NGCCT was based on the systematic review reported in section 5, 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 (Table 21).

Suspected CAD population

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 β-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 (Table 21)

was taken. “Perindopril usage” was assumed to be 0.23 for the whole suspected CAD population.[69] We will assume that the effect of perindopril does apply for any ACE-inhibitor. The covariates “age”, “age over 65”, “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. Table 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 strategy 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 [64], 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 a β-blockers.[64]

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

	Mean values EUROPA population	**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 non-fatal event**	
Covariates	Mean or %	Coefficient	HR	Coefficient	OR	Coefficient	HR
Perindopril usage	100%	-0.2148	0.8067				
Age	60			0.0396	1.0403		
Age over 65	0	0.0592	1.0610			0.6139	1.8476
Gender	85.0%	0.4349	1.5448				
Smoking	15.0%	0.3959	1.4858				
Previous Myocardial Infarction	65.0%	0.3675	1.4441	0.4673	1.5956		
Previous revascularisation	55.0%	-0.1332	0.8753				
Existing vascular disease	9.8%	0.5233	1.6876				
Diabetes mellitus	12.0%	0.4005	1.4926				
Family history	27.0%	0.1873	1.2060				
Symptomatic angina	25.0%	0.2801	1.3232				
Systolic blood pressure	137	0.0045	1.0045				
Creatinine clearance below 80 ml/min	6.9	0.0114	1.0115				
Obesity	21.0%	0.3455	1.4127				
Total cholesterol	5.4	0.1248	1.1329	0.1870	1.2056		
Use of nitrates at baseline	44.0%	0.3537	1.4243				
Use calcium channel blockers at baseline	32.0%	0.1815	1.1990				
Use lipid-lowering treatment at baseline	55.9%	-0.1566	0.8551				
Constant (log scale)	1		-12.2737		-4.3725		-6.459
Ancillary parameter							0.7
HR: hazard ratio; OR: odds ratio							

Table 22: Input for the EUROPA risk equations for the Suspected CAD population

	Strategy 1: ICA - only		**Strategy 2: HDCT - ICA**			**Strategy 3: HDCT - only**		
	TP revascularisation	**TP medication**	**TP revascularisation**	**TP medication**	**False negative**	**TP revascularisation**	**TP medication**	**False negative**
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**	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23
Previous myocardial infarction	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*	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

* Stroke, TIA & peripheral vascular disease
** Daly et al. 2005
TP: True Positive; FP: False Positive; TN: True Negative; FN: False Negative

Table 23: Subgroup specific input for the EUROPA risk equations Suspected CAD population

	Obese	Arrhythmias	Beta-blockers	High coronary calcium	High heart rate
Age	63	66.11	NA	63.93	61.91
Gender	0.659	0.69	NA	0.75	0.68
Positive family history	NA	0.17	NA	NA	0.16
Smoking	0.28	0.08	NA	NA	0.37
Diabetes mellitus	0.341	0.27	NA	NA	0.19
Obesity	1	0.42	NA	0.37	0.18
Symptomatic angina	NA	NA	NA	NA	0.85
NA: not available - EUROPA proportions are used: Table 21					

Known CAD population

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 β-blocker intolerance and high coronary calcium score groups. For the other groups these data were collected from the accuracy studies included in the systemic review. The covariates "age", "age over 65", "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.[69] 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 (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 cardiovascular event.

In the obese patient group, the increased risk of events was already captured in the risk equation since 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.[70] 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 to the EUROPA population, was used to adjust the risk of events. For the HCS patient group, data from an unpublished study[71] were used to estimate the relative risk without correcting for other factors of experiencing primary events in patients with a coronary calcium score >400 vs. patients without a coronary calcium score >400. The proportion with a coronary calcium score higher than 400 in the EUROPA population was not reported and therefore the study of Shemesh et al. 1998 was used to estimate a proportion assuming that the populations are comparable.[72] We assumed that this relative risk also applies for the risk of having a subsequent event.

A relative risk, compared to 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 atrial fibrillation 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 atrial fibrillation against patients without atrial fibrillation.[73] The proportion of the patients with atrial fibrillation was not reported by the EUROPA study and therefore we assumed that the proportion atrial fibrillation in patients with CAD is 19% based on Banasiak et al. 2007.[74]

No adjustments to the risk equations were necessary for the intolerant to β-blockers patient group because it was assumed that intolerance of β-blockers does not lead to an increased risk of experiencing events; patients undergoing a cardiac CT receive β-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 β-blockers but these can be replaced with calcium channel blockers and/or ACE inhibitors and therefore intolerance to β-blockers will probably not affect prognosis.

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

Table 24: Relative risks of cardiovascular events compared to EUROPA population for Arrhythmias and High coronary calcium level subgroups for the known and suspected CAD population

	RR Female	RR Men	Source	Proportion condition stable angina population	Source	Adjusted RR female	Adjusted RR Men
Arrhythmias	3.06	2.04	Hippisley-Cox et al. 2008	19%	Banasiak et al. 2007	2.2	1.7
HCS	4.58	4.58	Joosen et al. 2011	49%	Shemesh et al. 1998	1.66	1.66

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

	Obese	Arrhythmias	Beta-blockers	High coronary calcium	High heart rate	Revascularisation
Age	63	68	NA	NA	56.2	65.12
Gender	0.659	0.71	NA	NA	0.52	0.69
Positive family history	NA	0.7	NA	NA	NA	0.39
Smoking	0.28	NA	NA	NA	NA	0.2858
Diabetes mellitus	0.341	0.2	NA	NA	NA	0.3
Obesity	1	0.59	NA	NA	NA	0.264
Symptomatic angina	NA	NA	NA	NA	NA	NA
NA: not available - EUROPA proportions are used: Table 21						

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

	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 **	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23
Previous myocardial infarction	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

	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**
Existing vascular disease*	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
*Stroke, TIA & peripheral vascular disease									
** Daly et al. 2005 TP: True Positive; FP: False Positive; TN: True Negative; FN: False Negative									

6.2.1.5 YRM model

The impact of imaging-associated radiation on cancer rates and outcomes was not estimated with the EUROPA model, but with the YRM model.[11] The EUROPA model only takes into account mortality and not the QALYs and costs of treatment of radiation induced cancer. The YRM model 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.[11]

Biological Effects of Radiation

The dose of ionized radiation absorbed by a body is measured in gray (G). However, the health-relevant (and harmful) energy absorbed depends on the tissue and type of radiation and is expressed in sievert (Sv). Because of the small doses of imaging radiation, more often milli-sievert are used (1000mSv = 1Sv). One Sv equals one G times a weighting factor (e.g. for a breast scan the weighting factor is .05).

Exposure to ionized radiation has mainly three biological adverse effects.[75] 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 a 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 life-time risk of cancer incidence. For low doses, sparse clinical evidence exists. A prominent source is a cohort study of Japanese A-Bomb survivors that were exposed to radiation. This data provides strong evidence of an increased cancer mortality risk at equivalent doses greater than 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.[76]

The standard epidemiological risk models use a linear relationship between radiation exposure and life-time probability of solid cancer without assuming a threshold, i.e. even a minimal exposure is assumed to increase the life-time risk of cancer incidence. The younger the age at exposure the higher is the life-time 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 life-time risk of an individual for repeated exposure to radiation is calculated by summing over the respective probabilities for life-time cancer incidence over each exposure.

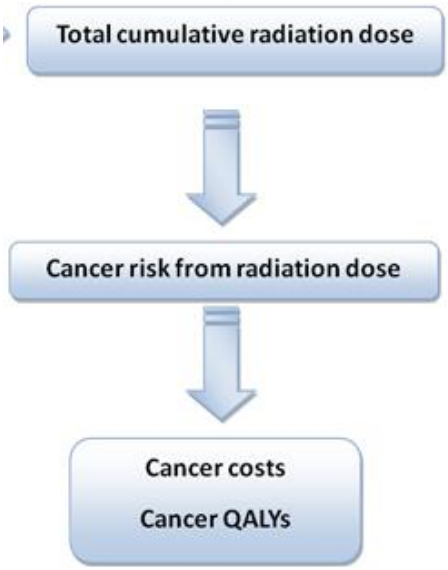
In a recent report, the Centre for Radiation, Chemical and Environmental Hazards (CRCE), formerly the National Radiological Protection Board (NRPB), of the Health Protection Agency (HPA) has calculated life-time risks for cancer incidence by age and sex for different levels of radiation.[77] Those calculations are based on a 2007 publication of the International Commission on Radiological Protection (ICRP).[78]

Structure of YRM Model

The calculations for health consequences of radiation exposure are based on an adjusted version of the York Radiation Model (YRM). The YRM consist mainly of four

elements: a radiation module, a cancer module, a utility module, and a main module combining all intermediate calculations.

Figure 21: Stylised Overview of YRM model



In the radiation module, the YRM estimates the life-time probability of an individual given the timing and the amount of radiation exposure. To translate the cumulative radiation dose into the probability of life-time cancer incidence the HPA model is used (Table 47).[78]

The cancer module is based on prior research.[11] In 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 cancer patients at the average age of diagnosis (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, while for females the weights are 16% colorectal, 50% lung and 34% breast.

The utility module is based on data for the general UK population (Table 49).[11] For patients that do not get cancer, the remaining life-time QALYs from the age of first radiation exposure are calculated. For patients that do get cancer, the utility module calculates the QALYs until the age of diagnosis of cancer, i.e. the time span without cancer.

The main module combines the outcome of the three prior modules. So for a given age of first exposure, the share of patients is calculated that get radiation induced cancer during their life-time. For those, their QALYs until age of cancer diagnosis equal the general UK population and after that the remaining QALYs and the (additional) disease costs due 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 of 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 life-time radiation induced cancer. The YRM allows to conduct a probabilistic sensitivity analysis (PSA) accounting for the uncertainties in age of 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 where the radiation doses vary with CT generation and by manufacturer. Moreover, scanning protocols themselves change over time. In particular multi-slice 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, e.g. head or full chest, only roughly differentiating by CT type (mostly single-slice vs. multi-slice). 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 coronary artery disease patients) and Table 66(for congenital heart disease patients).

The results of our expert surveys are in line with the literature that focuses on general chest CTs (see 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,[79] 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, [80] and a review article focusing on children's exposure and based on German data[81] support the overall lower radiation dose for CT64 indicated by our expert survey.

The York radiation model was used for the two patient populations under assessment, the coronary artery disease patients (this section) and the congenital heart disease patients (section 6.3). 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 of exposure, radiation dose (dependent on type and number of scans), and sex are used. In the case of the CAD patients the YRM output was used for further analysis. Table 52 and Table 66 give an overview of the radiation doses in the patient populations for the different strategies under assessment.

Table 27: Comparative Radiations Dose by age at exposure from diagnostic examination of “chest” with a CT (in mSv)

Source	**Age**			
	1	**5**	**10**	**Adult**
UNSEAR Report[80] **(lowest and highest reported values)**	[1.8-6.3]	[2.1-3.6]	[3.0-3.9]	[3.5-12.9]
NRPB report[79] **(mean and 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 et al 2008[81]	2.2	2.5	3.0	5.9

6.2.1.6 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 model 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 & FP). The known and suspected CAD populations with CAD were modelled separately using two versions of the EUROPA model. The Suspected CAD population with CAD had three treatment options (PCI, CABG and medication), the known CAD population could only undergo 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. 2006 and Briggs et al. 2007 use only one coefficient in the risk equation namely previous revascularisation.[10, 70] 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. 2004.[66] Subgroup specific costs and QALYs obtained in the stroke model were calculated by using subgroup specific age and proportion men.

Table 28: Overview model runs for subpopulations

	Diagnostic model	YRM	Healthy population model	EUROPA model		Stroke
				2 treatment model	3 treatment model	
Suspected CAD population						
Obese	X	X	X		X	X
Arrhythmias	X	X	X		X	X
High Coronary Calcium level	X	X	X		X	X
High heart rate	X	X	X		X	X
Beta blocker intolerant	X	X	X		X	X
Known CAD population						
Obese	X	X		X		X
Arrhythmias	X	X		X		X
High Coronary Calcium level	X	X		X		X
High heart rate	X	X		X		X
Beta blocker intolerant	X	X		X		X
Previous stent implantation	X	X		X		X
Previous CABG	X	X				X

6.2.2 Model parameters

This section describes the parameters used in the diagnostic model, the EUROPA model, the healthy population model, the YRM model and the stroke model. Distributions of the parameters are presented in Table 61 and described in section 6.2.3.5. The last section 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).

6.2.2.1 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 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. Medication induced costs were modelled as part of the background costs in the disease progression model. Table 31 presents an overview of the costs used in the original CEmarc model[65] and the costs used in the adjusted diagnostic model. The average costs prices for the revascularisation procedures and the ICA were calculated based on the NHS reference prices 2009-2010.[82] An average cost price is calculated by multiplying the number of admissions with the costs for each different specific procedure. An invasive coronary angiography was estimated as costing on average £1003. A CABG would cost £8280 per procedure and in combination with an ICA £9242. 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 invasive coronary angiography (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 was for any CT i.e. not specifically for CTCA (Table 29).

Table 29: Costs for any CT

Currency Code	Currency Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	No. Data Submissions
RA08Z	Computerised Tomography Scan, one area, no contrast	535,388	£101	£69	£108	159
RA09Z	Computerised Tomography Scan, one area with post contrast only	200,500	£116	£88	£126	144
RA10Z	Computerised Tomography Scan, one area, pre and post contrast	48,604	£112	£73	£128	102

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):

Table 30: Estimated costs for any cardiac CT

Category	64-slice	NGCT	Source
Capital	£500000	£1000000	The ImPACT Group, 2009[83]
Maintenance per year	£73624	£137941	Expert opinion
Scanner life (years)	10	10	National Audit Office, 2011[84]
Capital per year plus maintenance per year	£123624	£237941	Calculated
Number of scans per year	3120	3120	Calculated*
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	PRSSU, 2010[85]
Radiologist cost per hour (includes overheads)	£146	£146	PRSSU, 2010[85]
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

*assuming a maximum of 12 scans per day (expert opinion, personal communication from Simon Padley), 5 days per week and 52 weeks per year.

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 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 (personal

communication from Valerie Fone). 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).

Table 31: Costs of diagnostic tests and treatment

Diagnostic test	[redacted]	**HDCT model**	
	[redacted]	**Cost per diagnostic test (£)**	**Source**
Coronary angiography	[redacted]	1003	NHS Ref costs**
NGCCT	[redacted]	169	Calculated (see table 30)
Coronary artery bypass graft	[redacted]	8280	NHS Ref costs**
Percutaneous coronary intervention	[redacted]	3633	NHS Ref costs**
Coronary artery bypass graft + ICA		9242	NHS Ref costs**
Percutaneous coronary intervention + ICA		4196	NHS Ref costs**
* 2008 – 2009 ** 2009-2010			

Prior likelihood

The prior likelihood for the suspected and known CAD populations is presented in section 6.2.1.1

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 CAD 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 revascularisation or medication after a positive test result were based on expert opinion[86] in combination with an un-published study conducted in the Netherlands.[71]

[redacted]

[redacted]. UK procedure figures also show a 70% - 30% proportion for PCI vs. CABG.[87]

The rest of the patients with significant CAD (81.9%) are assumed to be treated with medication only. Patients treated with medication only are treated with beta-blockers or calcium channel blockers.[24] When the symptoms are not controlled with one of the two drugs 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 to a previously published article based on the Euro Heart survey which reported a revascularisation rate of 13%.[69] Furthermore, expert opinion indicated that the results of this study were also appropriate for the difficult to image patient groups considered in this assessment.

Known CAD population
Given a positive CT or ICA test for patients with known CAD two treatment options are considered; that is 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
ICA 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 where 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.[88] 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[88-91] were identified after checking the references of the initial 17 studies and performing a citation search. Two studies[89, 90] did not present a complication rate based on the UK population, but were conducted in Turkey and Canada, respectively. One study reported a complication rate for a UK population, but was based on a single centre.[91] A multi-centre study on diagnostic angiography in the UK and, (the most recently performed study,) was considered the most appropriate study to inform the model.[88] 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 1000 patients, based on 219,227 procedures 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.[89] 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 a coronary angiography presented by the selected study is applicable regardless of the underlying risk of cardiovascular 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. 2007.[92] CABG related stroke was taken from the study.[93] Since there were no studies that reported CABG related MI we used the study by Serruys et al. 2001 to give an estimate of CABG related MI.[94] A survival curve (patients without MI and stroke) presented in the Serruys study was used: at 30 days the survival was 96%, thus 4% experienced a stroke or a MI. Since we found a stroke rate of 1.6%[93] 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. is not related to the procedure per se. [94]

The complication rates induced by PCI were based on the study of Rajani et al.; mortality due to a PCI is 0.0029; a MI 0.0005 and stroke due to PCI 0.0005.[95]

Table 32: Complications of ICA and revascularisations

Complications invasive coronary angiography	Batyraliev et al.[89] 2005	Chandrasekar et al. 2001[90]	West et al. 2006[88]	Smith et al. 1999[91]
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
Myocardial infarction rate	0.0008	0.0010	0.00003	
Other complications	0.0182	0.0383	0.0060	
Complications PCI				
Mortality rate	0.0029	Rajani et al. 2011[95]		
Cerebrovascular accident rate	0.0005	Rajani et al. 2011[95]		
Myocardial infarction rate	0.0005	Rajani et al. 2011[95]		
Complications CABG				
Mortality rate	0.018	Bridgewater et al. 2007[92]		
Cerebrovascular accident rate	0.016	Tarakji et al. 2011[93]		
Myocardial infarction rate	0.024	Serruys et al. 2001[94] & Tarakji et al. 2011[93]		

6.2.2.2 Healthy population model

The healthy population model only applies 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-depended 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).[9] All cause mortality life tables were used, since these patients can still develop and die from CAD in the future.

Table 33: Mortality rates all causes

Age	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

Utility for patients without CAD

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).[96] 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 appropriate treatment. Additionally, it should be realized 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 34: Population norm by EQ5D (Kind et al. 1999)

Age	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

6.2.2.3 EUROPA model

The EUROPA model models the progression of stable CAD by predicting cardiovascular events and mortality. Healthcare costs were evaluated by Briggs et al. 2007[10] from resource items collected as part of the EUROPA study[68] and these are grouped, for our analysis, into three categories: background costs, non-fatal event costs and fatal event costs. More details can be found in the technical appendix of Briggs et al. 2007.[10] 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.[10]. Table 35 shows the results of the cost regression.

The original cost prices of the EUROPA trial 2003/2004 were updated with a price correction based on PSSRU Health 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%.[97]

Table 35: EUROPA costs

Covariate	**Coefficient £**
Proportion of the year remaining following death/censoring	-1,224
Non-fatal event	11,805
Non fatal event history	986
Cardiovascular fatal event	3,641
Non-cardiovascular fatal event	12,421
Age	13
Existing vascular diseases	392
Diabetes mellitus	253
Symptomatic disease	283
Creatinine clearance below 80ml/min	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

Background costs

Background costs are costs which are applied to the trial entry state and the non-fatal event states. The background costs are based on age, the existence of vascular diseases, diabetes mellitus, medication usage, 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 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 true positive in strategy ICA-only.

The age of a obese patient with known CAD and a TP test outcome is 63, 34% has diabetes mellitus, 25% is symptomatic, creatinine clearance below 80 ml/min is on average 6.9, nitrates usage at baseline is 44%, 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 three months as a background cost (Table 36).

Table 36: Example background cost calculation

	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 clearence below 80 ml/min	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

Non-fatal event costs

For the year in which a non-fatal event occurs, £11805 was added to the background cost. For subsequent years, the additional cost was estimated as £986. In the year that a fatal cardiovascular event occurs, the additional cost was estimated as £3641. When a fatal non-cardiovascular event occurred, an additional cost of £12421 was added.

Table 37: Monthly background costs EUROPA – Suspected CAD population (£)

			Obese	HHC	HHR	Intolerance B-Blocker	Arrhythmias
Strategy ICA-only	True positive	Revascularization	298.0	287	328.2	288.3	303.6
	True positive	Medication	329.6	319	359.8	319.8	335.1
Strategy NGCCT-ICA	True positive	Revascularization	298.0	287	328.2	274.6	303.6
	True positive	Medication	329.6	319	359.8	319.8	335.1
	False negative		0	0	0	0	0
Strategy NGCCT-only	True positive	Revascularization	298.0	287.3	328.2	288.3	303.6
	True positive	Medication	329.5	318.8	359.7	319.8	335.1
	False negative		0	0	0	0	0

Table 38: Monthly background costs EUROPA - Known CAD population (£)

		Obese	HHC	HHR	Intolerance B-Blocker	Arrhythmias	Revascularization
Strategy ICA-only	True positive	298.0	274.6	262.2	274.6	305.4	302.6
	True negative	297.6	274.1	261.8	274.1	304.9	302.1
Strategy NGCCT-ICA	True positive	298.0	274.6	262.2	274.6	305.4	302.6
	True negative	297.5	274.0	261.7	274.0	304.8	302.1
	False negative	297.5	274.0	261.7	274.0	304.8	302.1
Strategy NGCCT-only	True positive	298.0	274.5	262.2	274.5	305.3	302.6
	True negative	297.5	274.0	261.7	274.0	304.8	302.1
	False negative	297.5	274.0	261.7	274.0	304.8	302.1
	False positive	298.0	274.5	262.2	274.5	305.3	302.6

Utilities for patients with CAD

HRQoL estimates were assigned to the states in the Markov model based on age, gender, baseline CCS classification and whether the patient had undergone treatment. Patients modelled through the disease progression model are assumed to have a CCS class (Campeau et al. 1976) of 2. The HRQoL estimates were based on three sources including population norm for the EQ5D,[96] EQ5D scores per CCS class[98] and treatment effect on QoL based on the RITA2 trial.[65]

Baseline EQ5D: Untreated patients with CAD:

Combining the population norm values with the EQ5D scores per CCS class (0-4) (Tables 39 and 40) generates relative HRQoL by CCS class and gender. Longworth's scores[98] were based on a median age of 61 and these were divided by population norms for the age group 55-64. 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.,[96] assuming that the relative HRQoL by CCS class compared to the general population would hold across all ages. This multiplication was taken for the patients with CAD at baseline (without treatment).

Table 39: Baseline HRQoL male

	CCS class				
Age	**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

	CCS class				
Age	**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

Treatment EQ5D: Patients with CAD, 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 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 was estimated by combining the changes in CCS after treatment with association seen between baseline CCS and baseline HRQoL. 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[99] was assigned to the non–fatal event states because an event has occurred. We assumed that the disutility due to a MI is the same as for a cardiac arrest.

Table 41: HRQoL following treatment male

	Before-treatment CCS class				
Age	**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: HRQoL following treatment female

	Before-treatment CCS class				
Age	**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

Suspected CAD population
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).

Known CAD population
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 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 (Table 43).

Table 43: HRQoL 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

Transition probabilities

Tables 44 and 45 present the three 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 section 6.2.4.1.

Table 44: Transition probabilities CAD suspected population

	Obese	Arrhythmias	HCC	HHR	B-blocker
Probability first trial event- TP revascularization strategy 1- three monthly	0.0078	0.0113	0.0095	0.0067	0.0056
Probability first trial event- TP revascularization strategy 2 -three monthly	0.0078	0.0113	0.0095	0.0067	0.0056
Probability first trial event- TP revascularization strategy 3 -three monthly	0.0078	0.0113	0.0095	0.0067	0.0056
Probability first trial event- TP medication strategy 1- three monthly	0.0100	0.0145	0.0121	0.0087	0.0073
Probability first trial event- TP medication strategy 2 -three monthly	0.0100	0.0145	0.0121	0.0087	0.0073
Probability first trial event- TP medication strategy 3 -three monthly	0.0100	0.0145	0.0121	0.0087	0.0073
Probability first trial event- False negative strategy 2- three monthly	0.0089	0.0129	0.0107	0.0077	0.0064
Probability first trial event- False negative strategy 3- three 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 revascularization	0.2958	0.3220	0.3035	0.2869	0.2750
Probability subsequent event is fatal - TP Strategy 1 revascularization	0.4004	0.4303	0.4093	0.3901	0.3723
Probability event is fatal - TP Strategy 2 revascularization	0.2958	0.3220	0.3035	0.2869	0.2750
Probability subsequent event is fatal - TP Strategy 2 revascularization	0.4004	0.4303	0.4093	0.3901	0.3723
Probability event is fatal - TP Strategy 3 revascularization	0.2958	0.3220	0.3035	0.2869	0.2750
Probability subsequent event is fatal - TP Strategy 3 revascularization	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- three monthly	0.0144	0.0210	0.0175	0.0125	0.0105
Probability subsequent event after first year- TP Strategy 1 revascularization - three monthly	0.0112	0.0163	0.0136	0.0097	0.0081

Probability subsequent event after first year- TP Strategy 2 medication - three monthly	0.0144	0.0210	0.0175	0.0125	0.0105
Probability subsequent event after first year- TP Strategy 2 revascularization - three monthly	0.0112	0.0163	0.0136	0.0097	0.0081
Probability subsequent event after first year- TP Strategy 3 medication - three monthly	0.0144	0.0210	0.0175	0.0125	0.0105
Probability subsequent event after first year- TP Strategy 3 revascularization - three monthly	0.0112	0.0163	0.0136	0.0097	0.0081
Probability subsequent event after first year- False negative strategy 2- three monthly	0.0128	0.0185	0.0155	0.0110	0.0092
Probability subsequent event after first year- False negative strategy 3- three 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
TP: True Positive; FP: False Positive; TN: True Negative; FN: False Negative					

Table 45: Transition probabilities known CAD population

	Obese	Arrhythmias	HCC	HHR	B-blocker	Revascularization
Probability first trial event- TP Strategy 1 known- three monthly	0.01212	0.0231	0.0145	0.0076	0.0088	0.0097
Probability first trial event- TN Strategy 1 known- three monthly	0.01286	0.0245	0.0154	0.0080	0.0093	0.0097
Probability first trial event- TP Strategy 2 known- three monthly	0.01212	0.0231	0.0145	0.0076	0.0088	0.0097
Probability first trial event- TN Strategy 2 known- three monthly	0.01286	0.0245	0.0154	0.0080	0.0093	0.0097
Probability first trial event- FN Strategy 2 known- three monthly	0.01286	0.0245	0.0154	0.0080	0.0093	0.0097
Probability first trial event- FP Strategy 2 known- three monthly	0.01286	0.0245	0.0154	0.0080	0.0093	0.0097
Probability first trial event- TP Strategy 3 known- three monthly	0.01212	0.0231	0.0145	0.0076	0.0088	0.0097
Probability first trial event- TN Strategy 3 known- three monthly	0.01286	0.0245	0.0154	0.0080	0.0093	0.0097
Probability first trial event- FN Strategy 3 known- three monthly	0.01286	0.0245	0.0154	0.0080	0.0093	0.0097
Probability first trial event- FP Strategy 3 known- three 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 - three monthly	0.01378	0.0262	0.0165	0.0086	0.0100	0.0110
Probability subsequent event after first year- TN Strategy 1 - three monthly	0.01463	0.0278	0.0176	0.0091	0.0106	0.0110
Probability subsequent event after first year- TP Strategy 2 - three monthly	0.01378	0.0262	0.0165	0.0086	0.0100	0.0110
Probability subsequent event after first year- TN Strategy 2 - three monthly	0.01463	0.0278	0.0176	0.0091	0.0106	0.0110
Probability subsequent event after first year- FN Strategy 2 - three monthly	0.01463	0.0278	0.0176	0.0091	0.0106	0.0110
Probability subsequent event after first year- FP Strategy 2 - three monthly	0.01463	0.0278	0.0176	0.0091	0.0106	0.0110
Probability subsequent event after first year- TP Strategy 3 - three monthly	0.01378	0.0262	0.0165	0.0086	0.0100	0.0110
Probability subsequent event after first year- TN Strategy 3 - three monthly	0.01463	0.0278	0.0176	0.0091	0.0106	0.0110
Probability subsequent event after first year- FN Strategy 3 - three monthly	0.01463	0.0278	0.0176	0.0091	0.0106	0.0110
Probability subsequent event after first year- FP Strategy 3 - three 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
TP: True Positive; FP: False Positive; TN: True Negative; FN: False Negative						

6.2.2.4 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 life-death model based on estimates by Sandercock et al. 2004 for thrombolytic therapy of stroke.

Survival

Mortality rates were based on UK life tables[9] and a relative risk of 2.5 to reflect the increased risk of mortality following a stroke.[100] 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. 2004 estimated a cost of approximately £6260 in the first year after a stroke.[66] Since Sandercock et al. 2004 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 2010 and then discounted at a rate of 3.5%.

QALYs

Calibration of the model to fit with the results by Sandercock et al. 2004 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%.

6.2.2.5 YRM 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 of first exposure to radiation is below 40, the average age of incidence for breast-cancer is assumed to be 40, for higher ages the average is assumed to be 60. In the CAD patient population all patients are above age 40. This can be clearly seen in Table 51, with demographic characteristics of the patient population. The life time risk of cancer incidence by age and sex for a one time exposure to 10mSv 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 that do not get cancer, based on the 2007 England and Wales life table.

Table 52 presents the radiation doses for each of the analysed scanning strategies for CAD patients. The value for NGCCT is based on an expert survey (response: n=2) for this particular patient group, whereas the average radiation dose for ICA and PCI are taken from literature.[11]

For all the scanning strategies, the uncertainty in the costs 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 46: Total costs and QALYs lost due to cancer, discounted at 3.5% per annum to age of cancer diagnosis[11] (SD in parentheses)

Cancer	**Age of diagnosis**	**Costs of cancer**	**QALYs lost due to cancer**
Breast	40 (0)	£14990 (£940)	5.6988 (.4533)
Breast	60 (0)	£13927 (£848.11)	3.4219 (.311)
Lung	72.2684 (.0395)	£22712 (£440,60)	6.8011 (.056)
Colorectal	73.72 (0.139)	£14075 (£356.00)	3.4493 (.1386)
Prostate	74 years (NA)	£12,389 (NA)	4.6226 (NA)

Table 47: Lifetime risks of cancer incidence for all cancers by age and sex at exposure based on HPA data[11]

Age at exposure (years)	Risk of all cancers (for exposure to 10mSv)	
	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	**Costs per scan**
CT64	£132.62
NGCCT	£169.26

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

	Mean	**SD**
Under 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

Table 50: Overview of age-specific remaining life expectancy

Age	**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**	
	Mean age	**% Male**	**Mean age**	**% 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	x	x
Previous CABG	66	0.788	x	x
High heart rate	61.91	0.52	56.2	0.68
High coronary calcium score	63.93	0.854	60	0.7503

Table 52: Radiation dose (in mSv) of scanning strategies for coronary artery disease (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

6.2.2.6 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 who completed and returned it. Means are calculated from the proportions that the experts filled in. 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.

Table 53: Mean proportion difficult to image subgroups

	Suspected CAD population	Known CAD population
Obese	16.25%	10.00%
High level coronary calcium	27.50%	25.67%
Arrhythmias	11.75%	7.33%
High heart rate	29.25%	27.33%
Intolerance beta blocker	15.25%	9.33%
Previous PCI		11.00%
Previous CABG		9.33%
	100%	100%

6.2.2.7 Assumptions

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

Table 54: Assumptions

	General assumptions	Reference
-	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 high heart rate	
-	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 - 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 receives medication	Hofstra{#4871
-	Prior likelihood of patients suspected of CAD is 10 - 29%	NICE CG95[12]

	Diagnostic model known population	
-	Patients with known CAD with a positive test outcome have two treatment options: CABG/PCI	CEmarc[65]
-	[redacted]	
	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	British Heart Foundation[13]
-	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 myocardial infarction and death	
-	The input values for the risk equations are if available based on the systematic review	
-	The input values for the risk equations are if not available based on the EUROPA population	
-	Relative risks are used to update the risk equations of the EUROPA model for the subgroups: high coronary calcium, high heart rate 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	
-	Atrial fibrillation is taken as an proxy for the difficult to image subgroup arrhythmias because atrial fibrillation is the most common type of arrhythmias	
-	Proportion AF in EUROPA population is assumed to be the same as in study…..	
-	It is assumed that the conditions of the subgroups high heart rate and beta blockers intolerant do not have an impact on the transition probabilities	

-	Age and CCS specific HRQoL values based on Longworth et al. 2005, Kind et al. 1999 & the RITA2 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 B blocker. The clinical effectiveness of these two drugs are 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 will be modelled with the EUROPA model irrespective of the test outcome will be modelled with the EUROPA model - ACE inhibitor usage at baseline 23% - 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 false positives and true negatives	Daly et al. 2005[69]
	Life-death model	
-	TN and FP modelled with the life death model with all cause mortality probabilities	

	Stroke model	
-	Patients are treated with thrombolytic agents	

6.2.3 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.

6.2.3.1 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, FN) are also important. Tables 55 and 56 show, for both CAD populations and for each difficult to image group, these three intermediate outcomes.

Suspected CAD population

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 only uses the NGCCT to diagnose patients has test-induced mortality and morbidity rates of zero. Conversely, revascularisation-induced mortality and morbidity rates were highest in the NGCCT-only strategy due to the FPs who undergo unnecessary revascularisations with the associated complications. The strategy NGCCT-ICA 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 strategy NGCCT-only has the lowest overall mortality rate in the suspected population. The NGCCT-only strategy, as expected, had the lowest correct classification proportion.

Known CAD population

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, the strategy NGCCT-only 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

Suspected CAD	Proportion correct classification	Misclassification		Mortality tests	Morbidity tests	Mortality revascularisation	Morbidity revascularisation
Strategy		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
High heart rate							
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

Table 56. Intermediate outcomes known CAD population

Known CAD Strategy	Proportion correct classification	Misclassification FPs	Misclassification FNs	Mortality tests	Morbidity tests	Mortality revascularization	Morbidity revascularization
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
High heart rate							
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 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

6.2.3.2 Costs per model

Table 57 shows the costs assigned to the patients in the diagnostic model, the EUROPA model, the York Radiation model 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.

Suspected CAD population

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. Strategy ICA-only has the highest costs in the diagnostic model because the test itself is much more expensive than NGCCT. The impact of treating false positives 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.

Known CAD population

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 than in 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 population only 18% of the FPs receives a revascularisation and since medication costs are modelled in the EUROPA model it will lead to less costs for the FPs.

The same applies for the stroke model because the non-fatal complication rate of the strategy NGGCT-only in the known group is higher than 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 in the known population this is 100%, therefore the proportion that experience a stroke due to the revascularisation is higher in the known population.

Table 57: Costs per model (£)

	Diagnostic model		EUROPA model		YRM model *		Stroke model		Total	Total
	Suspected	Known	Suspected	Known	Suspected	Known	Suspected	Known	Suspected	Known
Obese										
ICA - only	1174	2867	5747	26676	2.6	3.9	44	147	6968	29694
NGCCT - ICA	568	2252	5709	26806	2.3	3.8	18	116	6297	29177
NGCCT - only	405	2360	5686	26776	1.7	3.0	13	116	6106	29254
Arrhythmias										
ICA - only	1175	2869	5569	24436	2.8	4.4	39	119	6785	27428
NGCCT - ICA	675	2450	5530	24529	2.7	4.7	19	101	6227	27084
NGCCT - only	536	3115	5524	24493	1.9	3.8	16	114	6077	27726
High heart rate										
ICA - only	1172	2866	6111	27405	2.8	4.0	56	159	7342	30434
NGCCT - ICA	640	2455	6089	27484	2.7	4.3	26	136	6758	30080
NGCCT - only	484	2864	6089	27463	1.9	3.4	20	146	6595	30477
High coronary calcium score										
ICA - only	1172	2867	5577	28126	2.2	3.5	49	148	6801	31145
NGCCT - ICA	591	2321	5528	28216	2.0	3.6	21	120	6142	30661
NGCCT - only	430	2525	5515	28188	1.5	2.8	15	123	5962	30839
Intolerance beta-blockers										
ICA - only	1173	2869	5791	26303	2.0	3.1	49	164	7016	29339
NGCCT - ICA	643	2457	5763	26371	1.9	3.3	23	141	6430	28972
NGCCT - only	485	2862	5775	26339	1.4	2.6	18	150	6279	29354

Previous stents									
ICA - only	-	2868	-	25443	-	4.1	-	136	-	28450
NGCCT - ICA	-	2378	-	25562	-	4.3	-	112	-	28056
NGCCT - only	-	3020	-	25522	-	3.5	-	127	-	28672
Previous CABG										
ICA - only	-	2867	-	25465	-	4.0	-	130	-	28466
NGCCT - ICA	-	2405	-	25570	-	4.1	-	109	-	28088
NGCCT - only	-	2892	-	25540	-	3.3	-	118	-	28554

*Incremental costs compared with no exposure to radiation

6.2.3.3 QALYs per model

Table 58 shows QALYs for every strategy, subgroup and population. The presented QALYs are after including the probabilities; adding the QALYs of the different models together leads to the total QALYs per strategy.

Suspected CAD population

In the EUROPA model the ICA-only strategy obtains, in every difficult to image patient group, the highest amount of QALYs. This is because of the lower HRQoL FNs experienced in the NGCCT-only and in the NGCCT-ICA strategy. FN 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 TNs is the lowest for this strategy. The strategies NGCCT-ICA and NGCCT-only have larger proportion in the TNs because less ICA related mortality occurs. 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.

CAD-known population

In the known population there is little difference between the three strategies since all test outcomes are modelled with the EUROPA model. In all cases the ICA-only has the lowest QALYs in the EUROPA model. This could be due to the fact that ICA-only has the largest overall mortality rate and therefore less people are modelled with the EUROPA model. The morbidity rate was for the ICA-only strategy the highest and therefore it accumulates the highest amount of QALYs in the stroke model. The NGCCT-ICA strategy has the lowest morbidity rate and therefore it obtains less 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; since 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 for the ICA-only strategy due to the higher radiation dose of the ICA compared with the NGCCT.

Table 58: QALYs per model

	EUROPA model		Healthy population model	YRM model *		Stroke model		Total	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
High heart rate									
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 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
*Incremental QALYs compared with no exposure to radiation									

6.2.3.4 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. Incremental cost-effectiveness ratio's (ICERs) are presented in Table 59 for the suspected CAD population and in Table 60 for the known CAD population. The cost-effectiveness is based on probabilistic modelling since 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 standard error), 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 in section 6.2.2.6 (Table 53).

Suspected CAD population

Table 59 presents very small differences in QALYs, however the ICA-only strategy is in general more effective than the other two strategies. Strategy NGCCT-ICA achieves in most subgroups less QALYs than the other strategies. The strategy ICA-only is the most expensive strategy, the NGCCT-only is cost-saving compared to 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.

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

Suspected	Costs		QALYs				
	Mean	**se**	**Mean**	**se**	**iCosts**	**iQALYs**	**ICER**
Obese							
NGCCT – ICA	6297	1237	10.508	0.167			
							Dominates
NGCCT – only	6106	1202	10.508	0.167	-191	0.000	NGCCT - ICA
ICA – only	6968	1217	10.519	0.163	862	0.011	81318
Arrhythmias							
NGCCT – ICA	6227	1190	9.419	0.171			
							Dominates
NGCCT – only	6077	1161	9.420	0.171	-150	0.000	NGCCT - ICA
ICA – only	6785	1205	9.448	0.166	708	0.029	24645
High heart rate							
NGCCT – only	6595	1256	10.967	0.156			
NGCCT – ICA	6758	1289	10.968	0.157	162	0.001	312047
ICA – only	7342	1263	10.969	0.155	584	0.001	440057
HCC							
NGCCT – only	5962	1168	10.201	0.169			
NGCCT – ICA	6142	1248	10.202	0.169	180	0.001	205536
ICA – only	6801	1189	10.210	0.167	659	0.008	80446
Intol. BB							
NGCCT – ICA	6430	1320	11.540	0.151			
ICA – only	7016	1242	11.541	0.148	586	0.001	972803
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	71000
ICA – only	6534	572	10.597	0.107	584	0.007	83429

Known CAD population

In the known CAD population the cost-effectiveness differed by subgroup. The NGCCT-ICA strategy 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, it provided more effects and costs less than the other two strategies. In all subgroups the strategy NGCCT-ICA was less expensive than the other strategies.

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

Known	Costs		QALYs				
	Mean	**se**	**Mean**	**se**	**iCosts**	**iQALYs**	**ICER**
Obese							
ICA - only	29694	928	8.857	0.464			
NGCCT – only	29254	924	8.869	0.477	-439	0.012	Doninates ICA only
NGCCT – ICA	29177	920	8.872	0.460	-77	0.003	Dominant
Arrhythmias							
ICA - only	27428	908	6.545	0.504			
NGCCT – ICA	27084	916	6.588	0.503	-344	0.043	Dominates ICA only
NGCCT – only	27726	971	6.595	0.499	642	0.007	90683
High heart rate							
ICA - only	30434	1169	11.223	0.381			
NGCCT - only	30477	1190	11.233	0.377	43	0.011	4021
NGCCT - ICA	30080	1184	11.242	0.378	-397	0.009	Dominant
HCS							
ICA - only	31145	1079	9.271	0.538			
NGCCT - only	30839	1103	9.301	0.533	-306	0.030	Dominates ICA-only
NGCCT - ICA	30661	1075	9.306	0.539	-178	0.005	Dominant
Intolerance beta-blockers							
ICA - only	29339	986	10.016	0.392			
NGCCT - only	29354	1004	10.039	0.392	14	0.024	610
NGCCT - ICA	28972	988	10.042	0.394	-381	0.003	Dominant
Previous stents							
ICA - only	28450	842	8.724	0.364			
NGCCT - ICA	28056	855	8.737	0.358	-394	0.013	Dominates ICA only
NGCCT - only	28672	888	8.744	0.354	617	0.007	93526
Previous CABG							
ICA - only	28466	844	8.719	0.363			
NGCCT - ICA	28088	859	8.725	0.360	-378	0.006	Dominates ICA only

NGCCT - only	28554	1028	8.725	0.359	466	0.000	2943850
Known overall							
ICA - only	28234	502	9.516	0.288			
NGCCT - ICA	27785	531	9.537	0.283	-449	0.022	Dominates ICA only
NGCCT - only	28228	498	9.538	0.286	443	0.001	726230

6.2.3.5 Sensitivity analyses

Probabilistic sensitivity analyses were performed to explore the robustness of the outcomes. 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 only presented for the obese subgroup of the population suspected CAD.

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 CAD Suspected	BETA	0.2		20	80
Prior likelihood Known CAD	BETA	0.395		296	454
Proportion of patients receiving revascularization (CAD-suspected population)	BETA	0.181		50	227
ICA mortality	BETA	0.0007		155	211490
PCI mortality	BETA	0.0029		11	3849
CABG mortality	BETA	0.018		47	2552
ICA non-fatal complications	BETA	0.00064		136	211509
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			
Riks equation 3: Risk of subsequent event in first year after intial non-fatal event	Weibull regression: cholesky decomposition	0.0272			
Riks 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	Normal	0.0409	0.0002		

cardiac arrest					
TP: True Positive					

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 below £70,000, the NGCCT-only strategy has the higest probability of being cost-effective. For thresholds above £70,000, the three different strategies are more or less 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.

Figure 22: Suspected CAD population CEAC

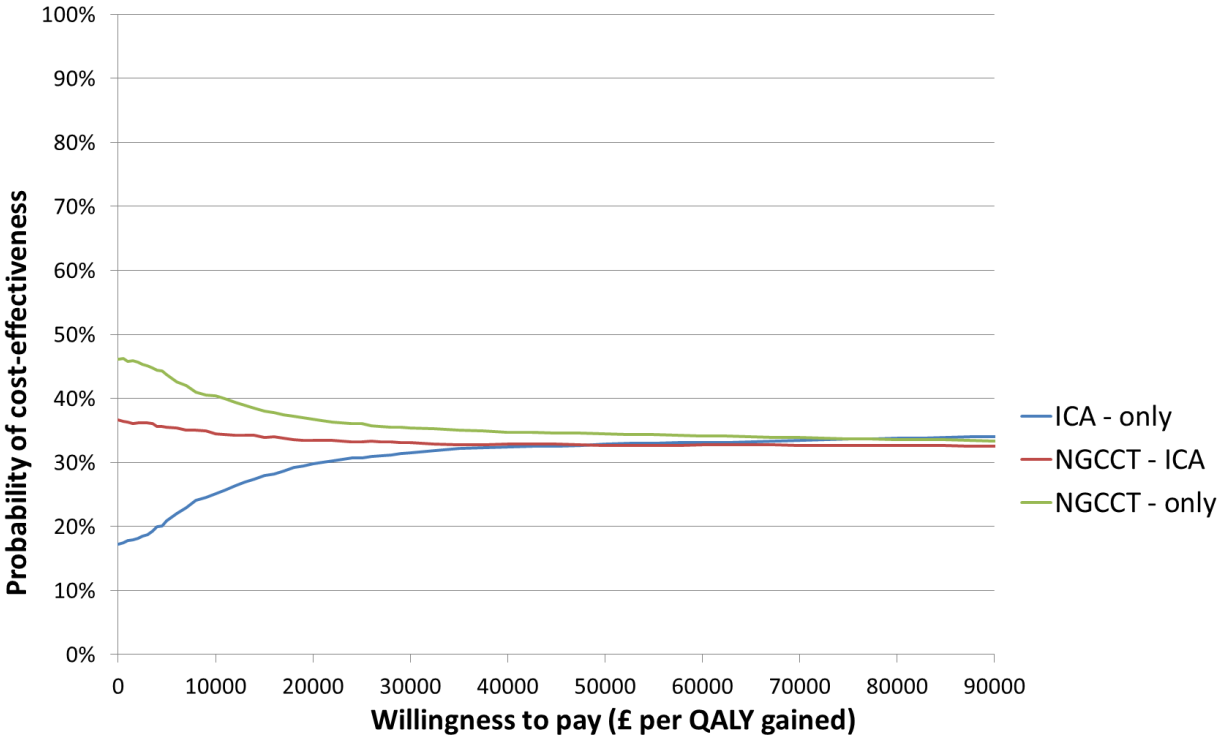
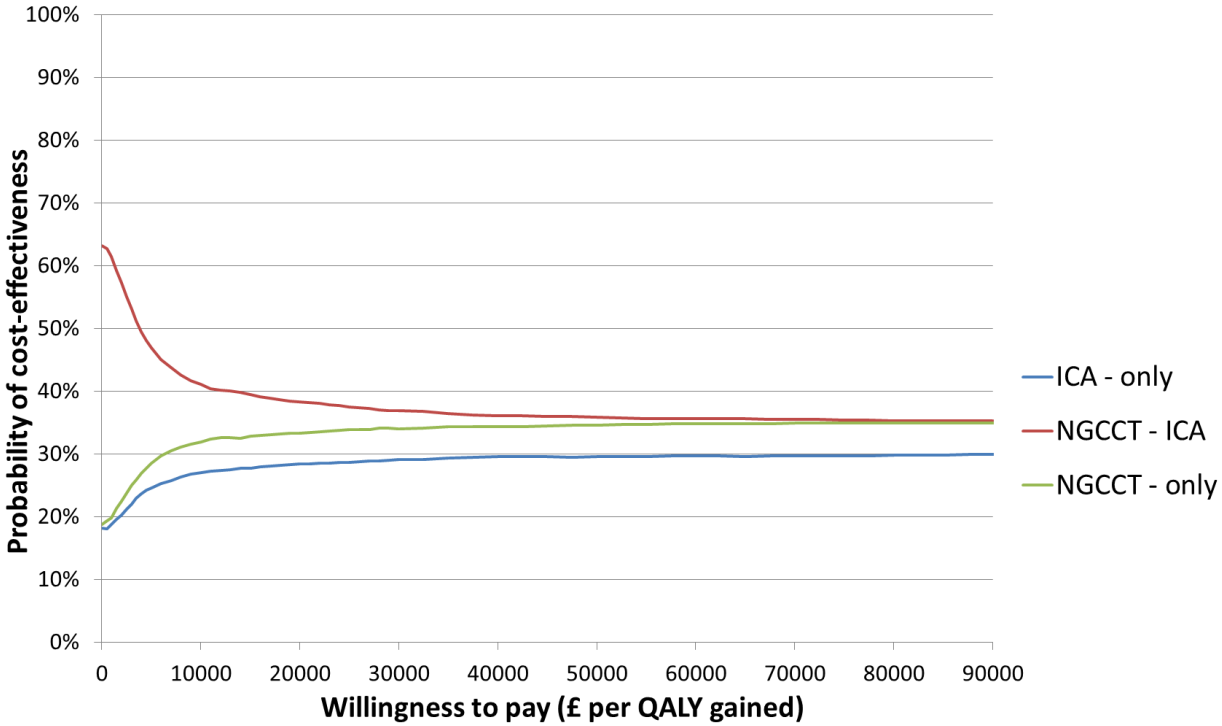


Figure 23: Known CAD population CEAC



6.2.3.6 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 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.

A worst case and best case scenario analysis was performed to show the influence of the revascularization and test complications on the cost-effectiveness. Table 67 and 68 show the influence of the rates on the cost-effectiveness in the suspected CAD population.

Scenario NGCCT £150 CAD

A lower cost price means that the strategies NGCCT-ICA and the NGCCT-only become less expensive. The overall results do not change.

Table 62: Scenario analysis NGCCT £150 CAD suspected population

Suspected	**Costs**		**QALYs**				
	Mean	**se**	**Mean**	**se**	**iCosts**	**iQALYs**	**ICER**
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	145092
Arrhythmias							
NGCCT – only	6023	1160	9.421	0.172			
NGCCT – ICA	6172	1189	9.423	0.172	148	0.001	144492
ICA – only	6741	1205	9.449	0.168	569	0.027	21258
High heart rate							
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	5182062
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	123267
Intolerance beta-blockers							
ICA – only	6997	1203	11.544	0.150			
NGCCT – ICA	6374	1282	11.545	0.153	-624	0.001	Domiates 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	125500

Table 63: Scenario analysis NGCCT £150 Known CAD population

Known	Costs		QALYs				
	Mean	**se**	**Mean**	**se**	**iCosts**	**iQALYs**	**ICER**
Obese							
ICA – only	29705	930	8.853	0.463			
NGCCT - ICA	29163	918	8.871	0.463	-542	0.019	Dominates ICA - only
NGCCT - only	29241	920	8.877	0.459	78	0.006	13597
Arrhythmias							
ICA – only	27453	888	6.560	0.505			
NGCCT - only	27085	899	6.591	0.507	-368	0.031	Dominates ICA - only
NGCCT - ICA	27729	947	6.603	0.488	644	0.012	52655
High heart rate							
ICA – only	30458	1194	11.229	0.383			
NGCCT - only	30451	1181	11.251	0.372	-6	0.022	Dominates ICA - only
NGCCT - ICA	30056	1175	11.262	0.379	-395	0.010	Dominant
HCS							
ICA – only	31133	1073	9.276	0.531			
NGCCT - ICA	30629	1074	9.308	0.539	-504	0.032	Dominates ICA - only
NGCCT - only	30809	1081	9.314	0.530	179	0.006	29531
Intolerance beta-blockers							
ICA – only	29333	981	10.025	0.390			
NGCCT - only	29347	998	10.033	0.394	14	0.008	1640
NGCCT - ICA	28972	982	10.034	0.394	-375	0.001	Dominant
Previous Stent							
ICA – only	28454	843	8.725	0.364			
NGCCT - only	28664	875	8.727	0.361	210	0.001	147862
NGCCT - ICA	28043	845	8.729	0.357	-620	0.002	Dominant
Previous CABG							
ICA – only	28452	839	8.722	0.365			
NGCCT - ICA	28051	847	8.733	0.361	-401	0.010	Dominates ICA - only
NGCCT - only	28518	1030	8.735	0.374	468	0.003	166672
Known overall							
ICA – only	28121	501	9.52	0.29			
NGCCT - only	28302	500	9.54	0.29	181	0.021	8748
NGCCT - ICA	27818	499	9.55	0.29	-484	0.004	Dominant

Scenario NGCCT £207

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 strategy ICA-only 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 the ICA-only was the most expensive strategy but when the price is increased the strategy NGCCT-only 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.

Table 64: Scenario analysis NGCCT £207 CAD suspected population

Suspected	**Costs**		**QALYs**				
	Mean	**se**	**Mean**	**se**	**iCosts**	**iQALYs**	**ICER**
Obese							
NGCCT – only	6132	1195	10.509	0.171			
NGCCT – ICA	6319	1228	10.511	0.167	187	0.002	88132
ICA – only	6960	1209	10.516	0.165	641	0.005	129189
Arrhythmias							
NGCCT – only	6071	1178	9.418	0.175			
NGCCT – ICA	6221	1207	9.419	0.173	149	0.001	171745
ICA – only	6737	1216	9.445	0.168	517	0.026	19545
High heart rate							
NGCCT – ICA	6828	1320	10.966	0.158			
ICA – only	7372	1293	10.967	0.155	544	0.001	481876
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	102208
Intolerance beta-blockers							
NGCCT – ICA	6455	1298	11.541	0.150			
ICA – only	7009	1217	11.542	0.149	554	0.000	6278463
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	235333

Table 65: Scenario analysis NGCCT £207 Known CAD population

Known	**Costs**		**QALYs**				
	Mean	**se**	**Mean**	**se**	**iCosts**	**iQALYs**	**ICER**
Obese							
ICA – only	29710	935	8.847	0.471			
NGCCT – ICA	29238	928	8.851	0.469	-471	0.004	Dominates ICA - only
NGCCT – only	29309	928	8.870	0.463	70	0.019	3727
Arrhythmias							
ICA – only	27437	898	6.567	0.498			
NGCCT – only	27762	941	6.592	0.502	325	0.025	12894
NGCCT – ICA	27127	904	6.602	0.495	-635	0.010	Dominant
High heart rate							
ICA – only	30418	1161	11.226	0.379			
NGCCT – ICA	30094	1157	11.248	0.377	-324	0.022	Dominates ICA - only
NGCCT – only	30465	1174	11.249	0.378	371	0.001	295660
HCS							
ICA – only	31132	1062	9.262	0.549			
NGCCT – only	30865	1084	9.302	0.545	-267	0.040	Dominates ICA - only
NGCCT – ICA	30685	1058	9.302	0.543	-181	0.000	Dominant
Intolerance beta-blockers							
ICA – only	29346	998	10.013	0.401			
NGCCT – ICA	29023	1005	10.033	0.398	-324	0.020	Dominates ICA - only
NGCCT – only	29385	1014	10.046	0.387	362	0.014	26423
Previous Stent							
ICA – only	28461	843	8.727	0.359			
NGCCT – only	28729	884	8.729	0.360	268	0.003	100271
NGCCT – ICA	28103	854	8.739	0.354	-626	0.009	Dominant
Previous CABG							
ICA – only	28473	845	8.722	0.364			
NGCCT – only	28598	1025	8.734	0.357	125	0.012	10450
NGCCT – ICA	28117	851	8.744	0.367	-481	0.010	Dominant
Known overall							
ICA – only	28268	510	9.52	0.29			
NGCCT – ICA	27920	494	9.54	0.28	-348	0.020	Dominates ICA - only
NGCCT – only	28296	511	9.54	0.29	376	0.004	103297

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 66: Scenario analysis prior likelihood suspected population 0.3

Suspected	**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	50007
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	16655
High heart rate							
NGCCT – ICA	10036	326.32	10.828	0.1568			
NGCCT – only	9786.7	330.37	10.83	0.1572	-249	0.002	Dominates NGCCT - ICA
ICA – only	10538	332.76	10.84	0.1544	752	0.009	80684
HCS							
NGCCT – only	8839.8	303.35	10.036	0.1776			
NGCCT – ICA	9111.6	546.38	10.039	0.1771	272	0.003	82843
ICA – only	9706	317.08	10.056	0.1711	594	0.017	34761
Intolerance beta-blockers							
NGCCT – ICA	9453.2	639.39	11.413	0.1482			
NGCCT – only	9238	332.08	11.418	0.1503	-215	0.005	Domiates NGCCT - ICA
ICA – only	9984.8	344.16	11.419	0.1457	747	0.000	5935679
Suspected overall							
NGCCT – only	9061	172	10.44	0.11			
NGCCT – ICA	9355	232	10.44	0.11	294	0.001	294000
ICA – only	9790	182	10.46	0.11	435	0.015	29000

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% confidence interval. ICA–only is still the most effective strategy. However, the incremental QALYs gained by the ICA–only strategy has become smaller in comparison with the base case analysis. Since the ICA induces more complications than the NGCCT this scenario analysis can be seen as best case scenario for the NGCCT strategies.

In the worst case scenario (Table 68) for the NGCCT, the complication rates are set at the lower limit of the 95% confidence interval, the ICA–only 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.

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

Suspected	**Costs**		**QALYs**				
	Mean	**se**	**Mean**	**se**	**iCosts**	**iQALYs**	**ICER**
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	1190,7	10,512	0,164	868	0,006	138953
Arrhythmias							
NGCCT – only	6051	1144	9,420	0,174			
NGCCT – ICA	6199	1170	9,423	0,174	147	0,003	52093
ICA – only	6746	1184	9,448	0,168	547	0,025	22017
High heart rate							
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
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	141072
Intolerance 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	83500
ICA – only	6547	565	10,591	0,108	585	0,004	146250

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

Suspected	**Costs**		**QALYs**				
	Mean	**se**	**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	122501
Arrhythmias							
NGCCT – only	6050	1148	9,4257	0,174			
NGCCT – ICA	6200	1176	9,4262	0,175	150	0,001	290135
ICA – only	6745	1183	9,4553	0,168	545	0,029	18689
High heart rate							
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	10,97	0,155	744	0,002	366638
High Coronary Calcium Score							
NGCCT – only	5991	1152	10,199	0,171			
NGCCT – ICA	6175	1220	10,200	0,171	184	0,000	512161
ICA – only	6824	1164	10,210	0,166	649	0,011	60086
Intolerance 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	583943
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	86556

6.3 Cost-effectiveness of NGCCT in congenital heart disease

6.3.1 Model structure

The main model structure of the YRM for patients with congenital heart disease is identical to the structure discussed in detail in section 6.2.1.5. For the congenital heart disease patients a number of scenario analyses were conducted, e.g. varying the age of cancer incidence. These are only variations in key parameters, not in the model structure. Further details are provided below.

6.3.2 Model parameters

6.3.2.1 Base case

In the base case for congenital heart disease patients 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 CAD patients. The only difference is in the radiation doses for congenital heart disease patients. These were based on an expert opinion, accounting for the particular diagnostic circumstances of congenital heart disease patients (Table 69). We used these results to define five different age groups: 1 year old (infants), 5 and 10 year olds (young children), and 25 and 35 year olds (adults).

Congenital heart disease patients can suffer from a range of cyanotic or non-cyanotic of heart diseases. The timing of diagnosis and treatment and, hence, the use of a CT, depends on the particular disease in question, but in most cases occurs in the first years of life. Depending on the disease further treatment might be necessary later in life. For aortic arch abnormalities (double aortic arch, vascular ring), for example, a CT is done at diagnosis, usually in the first year of life. Similarly, for pulmonary atresia and ventricular septal defect a CT is done in the first year of life and then again at age 2 or 3; and for total anomalous pulmonary venous drainage /scimitar only one CT is done immediately before surgery (age 2-3). For lesions with both a vascular and airway component a CT is usually done usually immediately 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, supported by expert opinion, was to assume a reduction of 50% as compared to the standard 64-slice CT.

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

Age	CT64	NGCCT
Very small children	1.6 [1-4]	.8 [.5-2]
Medium sized Children	3 [1-8]	1.5 [.5-4]
Adults	6 [4-25]	3 [1-12]

6.3.2.2 Scenario Analysis

In the scenario analyses a number of key parameters for congenital heart disease patients were varied. These were a) using the minimum radiation dose, b) the maximum radiation dose, c) an earlier age of 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.

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 of cancer incidence scenario, were taken from the cancer model in the YRM.[11] The earlier age with the corresponding disease costs and remaining QALYs is shown in Table 70. Note that for the congenital heart disease patients age group (age at exposure below 40), the YRM takes the incidence age of 40 for breast cancer by default. The values for the BEIR model were published by the National Research Council for a 1999 US population.[101] The BEIR study developed a more conservative risk model to estimate the relationship between exposure to ionizing radiation and harmful health effects, primarily based on the cancer incidence data from the Life Span Study for the period 1958-1998 and based on DSO2 dosimetry data.[11]

For all 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 29. 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.

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

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

Table 71: Probability for lifetime incidence of cancer for an exposure for 10mSv according to the BEIR model for age groups indicated for NGCCT[11]

	Risk of all cancers (for exposure to 10mSv)	
Age at exposure	**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

6.3.3 Base case results

Table 73 shows the intermediate result of the probability of life-time 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 of exposure. Table 74 shows the absolute QALYs for each age group by 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 £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.

Table 73: Probability of life time cancer for different ages in the base case scenario for congenital heart disease patients

Age	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

Age	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

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

Age	Difference in QALYs between NGCCT and CT64	Number of patients to be scanned
1	-0.000071	14,085
5	-0.00015	6,711
10	-0.00014	7,246
25	-0.00036	2,817
35	-0.0004	2,519

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

Age	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

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

	Threshold Value	
Age	**£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: ICER for base case scenario (Cost per NGCCT scan: £169.26)

	ICER	
Age	**Price per CT64 Scan £133**	**Price per CT64 Scan £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

6.3.4 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 of cancer incidence, expected disease costs, and the expected remaining QALYs are varied (for details see Table 29. The key parameters for the scenario analysis are outlined above.

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

Table 79: Probability of life time cancer for different ages (BEIR radiation-cancer model)

Age	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

6.3.4.1 Sensitivity analysis

In Figure 24 the CE 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, 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.

Figure 24: Cost effectiveness plane for PSA of base case scenario for five different age groups (remark: origin not included)

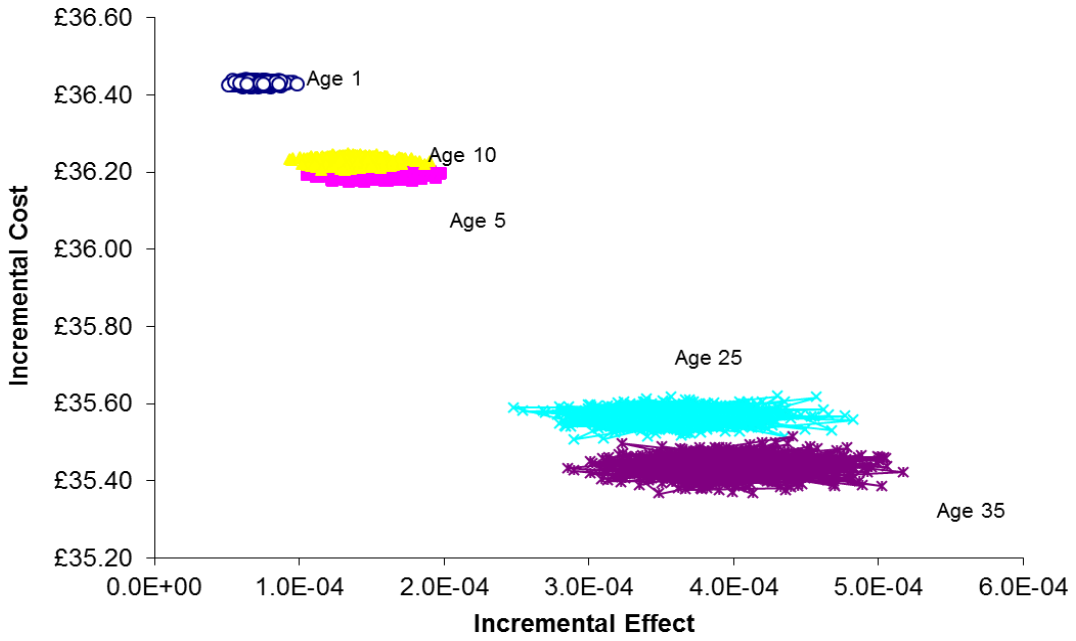


Table 80: Summary statistic of the distribution of the incremental effects, the incremental costs, and the ICER of the PSA in the base case scenarios

	Age 1			Age 5			Age 10			Age 25			Age 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
Standard deviation	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	£8,940
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
Min	0.000007	£0.00	£54,377	0.000016	£0.01	£25,622	0.000014	£0.01	£27,425	0.000034	£0.02	£9,698	0.000037	£0.02	£8,570
Max	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

6.3.4.2 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 of 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.

Only in the NGCCT friendly scenario do the ICERs decrease significantly, ranging from £28,000 per QALY gained for the youngest patients to £4,300 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 above £30,000 indicates that, even with the uncertainty about the various assumptions in mind, it can reasonable 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.

Table 81: Absolute radiation induced cancer costs for scenario analysis in GPB

	a) Minimum		b) Maximum		c) Early Cancer		d) BEIR model		e) NGCCT friendly	
Age	**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 (0.02830)3	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

	a) Minimum		b) Maximum		c) Early Cancer		d) BEIR model		e) NGCCT friendly	
Age	**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	**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	a) Minimum	b) Maximum	c) Early Cancer	d) BEIR model	d) 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	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

	a) Minimum	b) Maximum	c) Early Cancer	d) BEIR model	e) Benign
Age	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: ICER (£ per QALY gained) for scenario analysis with cost per NGCCT scan: £169.26 and cost per CT64 scan £132.62

Age	a) Minimum	b) Maximum	c) Early Cancer	d) BEIR model	e) NGCCT *friendly*
1	785,466	194,919	224,935	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	4,653
35	128,361	18,018	34,658	60,489	4,297

Table 88: ICER for scenario analysis with cost per NGCCT scan: £169.26 and cost per CT64 scan £105.55

Age	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	9,474

6.4 Summary

In this chapter, we assessed the cost-effectiveness of NGCCT in two different populations. The first is the comparison of NGCCT versus ICA in difficult to image CAD patients, the second is the comparison of NGCCT versus 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 decide if a revascularisation is necessary.

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 .[8]
2. a life–death Markov model for "healthy" patients without CAD .[9]
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) .[10]
5. a model to assess the impact of imaging due to radiation on cancer morbidity and mortality[11]

The latter of these five models, the York Radiation Model, 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 CAD patients 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 to NGCCT-only is so high (£71,000) that it is unacceptable given the conventional thresholds of £20,000 and £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 to NGCCT-ICA is so high (£726,230) that it is unacceptable.

When taking uncertainty into account, these findings are confirmed. In the suspected population, in the range of thresholds below £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 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 89: Summary baseline cost-effectiveness

	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	28234	9.516			
NGCCT – ICA	27785	9.537	-449	0.022	Dominates ICA only
NGCCT - only	28228	9.538	443	0.001	726,230

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, while the TP 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, while ICA complications cannot occur. Overall, in the population of suspected CAD, the strategy NGCCT-only has the lowest overall mortality rate, less than half 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 realize 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 FPs decreases. This explains to some extend 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 sceanarios were explored to assess the impact of the main assumptions. Only in the most unlikely scenario, i.e. an avarge 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 above £30,000 indicates that, even with the uncertainty about the various assumptions in mind, it can reasonable 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.

7 DISCUSSION

7.1 Statement of principal findings

7.1.1 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 high heart rates 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. Further, though there were no data specifically for β-blocker intolerant patients, it should be noted that no study reporting per patient data for patients with high heart rates used additional β-blockers before imaging. It may therefore be inferred that NGCCT could reasonably be used to image patients who are intolerant to β-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 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 which 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.

7.1.2 Cost-effectiveness

The health economic analysis of the use of NGCCT in difficult to image CAD patients 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 to NGCCT-only is so high (£71,000) that it is unacceptable given the currently used thresholds of £20,000 and £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 to NGCCT-ICA is so high (£726,230) that it is unacceptable. When taking uncertainty into account, these findings were confirmed. In the suspected population, in the range of thresholds below £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 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 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 strategy NGCCT-only 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 versus 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 above £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.

7.2 Strengths and limitations of assessment

7.2.1 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 un-published studies. Because of the known difficulties in identifying test accuracy studies using study design-related search terms,[3] 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, e.g. 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.[102] Formal assessment of publication bias in systematic reviews of test accuracy studies remains problematic and reliability is limited.[102] We did not undertake a statistical assessment of publication bias in this review. However, our search strategy included a variety of routes to identify un-published 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 (Appendix 5). The review process followed recommended methods to minimise the potential for error and/or bias[1]; studies were independently screened for inclusion by two reviewers and data extraction and quality assessment were done 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,[1, 2] and has been

widely adopted by researchers and key organisations such as the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE) in the UK, and Institut für Qualität and 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) is soon to be 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. 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). The QUADAS-2 tool has been used in this assessment, with the permission of the QUADAS steering group of which the DAR team lead is a member. 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 (Appendix 3) and in summary in the results (Section 5.6). 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 or impossible 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 CAD patients. 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 high heart rates might have excluded patients with previous re-vascularisations. In this scenario, judgement of the risk of bias is further complicated because, though the study may have reported the total number of patients excluded because of previous re-vascularisation, it is unlikely to have reported how many of these patients were in the high heart rate subgroup. It is therefore unclear what proportion of the relevant patient group (those with high heart rates) 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.[103] Un-corrected estimates of sensitivity and specificity derived from such data are likely to be accurate, but imprecision will be underestimated.[103] 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 false negative patients at the expense of increasing false positives. 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, where a positive test is defined as one or more positive segments, exclusion of a non-diagnostic segment which 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.[1] Wherever possible, we have used the bivariate model[5] to generate pooled estimates of sensitivity and specificity for each difficult to image patient group considered. This model analyses sensitivity and specificity and specificity jointly, retaining the paired nature of the original data, and has been shown to produce equivalent results to the hierarchical SROC (HSROC) model in the absence of other study-level covariates.[6] There were no data sets of sufficient size (minimum ten) to allow statistical exploration of sources of heterogeneity by including additional co-variables in the SROC model. In cases where a bivariate model could not be fitted because the number of studies was small (four), 2 x 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,[104] we have not included summary likelihood ratios and have instead adopted sensitivity and specificity as the primary outcomes for our review.[104]

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.[23] 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,[105-109] and the assumption of 100% sensitivity is therefore weaker. Several factors contribute to this problem: ICA provides two-dimensional visualisation, where as 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; frequent absence of a normal reference segment (in the presence of diffuse reference segment disease, percent stenosis will underestimated the true extent of vessel narrowing).[23] If the assumption of 100% sensitivity for ICA does not hold and false negatives 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 false positive index test results are thus over estimated. However, despite its limitations, ACC/AHA guidelines state that coronary angiography remains the accepted reference standard for assessment of anatomic coronary disease.[23]

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 invasive coronary angiography is ≥70% diameter stenosis of at least one major epicardial artery segment or ≥50% diameter stenosis in the left main coronary artery.[#4795} 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[62] or ≥70% diameter reduction[41] 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[43, 49, 53] reported funding from NGCCT manufacturers.

7.2.2 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 CAD patients.

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, e.g. 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 in section 7.2.1, 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[12] and for the known CAD group on the value assumed in the CEmarc study.[65] For the suspected CAD group, the likelihood estimate is actually more an assumption than an estimate. According to the clinical guideline for stable chest pain, 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), age, gender, diabetes, smoking and hyperlipidemia. For the likelihood estimate in the known CAD population, it is not entirely certain that the CEmarc 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.

Information on the final main driver, the complication rates, was derived from various sources. Since the rate of myocardial infarction 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.[93, 94] The overall complication rate (myocardial infarction and stroke) taken from Serruys et al. is based on a RCT.[94] The authors only presented overall complication rates at 1 year 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. from the overall complication rate presented in Serruys et al.[93, 94] 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, where complications of diagnostic ICA were reported over a period of 10 years in 41 cardiac centres.[88] Thus, the reliability of the complication rates for ICA used in this model may be expected to be higher than for revascularisation.

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 sub-set. 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 only considers 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.

7.3 Uncertainties

7.3.1 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.[15-17] It is therefore possible, though 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 ten 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% to 100% and 73% to 98%, respectively.[110-119]

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

As noted in section 7.2.1, strengths and limitations of the clinical effectiveness assessment, the effect on test accuracy of multiple difficult to image criteria within patients remains uncertain. Only two studies included in this review[54, 60] reported data for patients with two distinct difficult to image criteria (high heart rate 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 sub-group. Three studies did report subgroup specific non-diagnostic image rates in different populations; these were 5% for patients with arrhythmias,[49] 6.8% for patients with HHR[42] and 9% for patients with previous stent implantation.[43] Though these studies indicate that the proportions of otherwise difficult or impossible to image patients who would remain 'non-diagnostic', even with the use of NGCCT, are likely to be low, further studies are need to confirm this.

It should be further noted that, whilst 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.

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 (Phillips 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,[39-41] though the authors of one of these[40] had used Somatom Definition in an earlier study which was also included in this review.[42] One study reported using Aquilion ONE for the assessment of in-stent re-stenosis[43] 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.

7.3.2 Cost-effectiveness

As noted in section 7.3.1, 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 which 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 to a FN during this period, as well as the marginally reduced risk of experiencing a cardiovascular 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.

8 CONCLUSIONS

8.1 Implications for service provision

The results of our systematic review suggest that NGCCT is likely to be sufficiently accurate to diagnose clinically 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 otherwise difficult or impossible 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 three years, half of the CT scanners and MRIs in the UK will need to be replaced.[84] 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 cost-effective for difficult to image CAD patients. Though invasive coronary angiography 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 amount of quality-adjusted life years. Whether NGCCT should be used with or without ICA depends on the CAD population. However, it is important to remember that our results are only valid within the group of difficult to image CAD patients; they are not be extrapolated to the whole population of CAD suspected or known patients, since for these patients non-invasive 64-slice CT remains a good option.

8.2 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. However, data were relatively sparse and Further, high quality accuracy studies, particularly 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 criteria, 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.[120, 121]

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 pre-defined 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 multi-centre 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 multi-centre tracker study. Such a study should enable the collection of data comparing numbers of misdiagnoses, clinical outcomes, and health-related quality of life 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.

This assessment was unable to identify any studies which 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' one of the recommendations was to establish a national registry for people who are undergoing initial assessment for stable angina.[12] 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 is 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 registry could increase robustness of the health economic findings.

9 REFERENCES

[1] Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care [internet]*. York: University of York, 2009 [cited 12.1.10] Available from: http://www.york.ac.yk/inst/crd/systematic_reviews_book.htm

[2] Cochrane Diagnostic Test Accuracy Working Group. *Handbook for DTA Reviews [internet]*: Cochrane Collaboration, 2011 [cited 12.1.11] Available from: http://srdta.cochrane.org/handbook-dta-reviews

[3] 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* 2010.

[4] National Institute for Health and Clinical Excellence. *Diagnostics Assessment Programme: interim methods statement (version 2) [Internet]*. London: NICE, 2010 [cited 12.1.11]. 46p. Available from: http://www.nice.org.uk/media/164/3C/DAPInterimMethodsStatementProgramme.pdf

[5] 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(10):982-90.

[6] 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.

[7] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11):1539-58.

[8] Walker S. *Email regarding CEmarc model [Personal communication]*. York: Centre for Health Economics, University of York, March 2011.

[9] Office of Population Censuses and Surveys, Government Statistical Service, Office for National Statistics. Mortality statistics. Cause: a review of the Registrar General on deaths by cause, sex, and age, in England and Wales. *Series DH2*. London: HMSO, 2006.

[10] 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(9):1081-6.

[11] McKenna C, Wade R, Faria R, Yang H, Stirk L, Gummerson N, et al. *EOS 2D/3D X-ray Imaging System: Technology Assessment Report for NICE from CRD/CHE Technology Assessment Group*. York: University of York, 2011.

[12] 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 [Internet]*. London: NICE, 2010 [cited 20.04.11] Available from: http://guidance.nice.org.uk/CG95

[13] British Heart Foundation (BHF). *UK coronary heart disease statistics 2009-10 [Internet]*. London: BHF, 2010 [cited 18.05.11] Available from: http://www.bhf.org.uk/publications/view-publication.aspx?ps=1001141

[14] Cooper A, Calvert N, Skinner J, Sawyer L, Sparrow K, Timmis A, et al. *Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. Full guideline 95*. London: National Clinical Guideline Centre for Acute and Chronic Conditions, 2010 [cited 12.1.11]. 393p. Available from: http://guidance.nice.org.uk/CG95

[15] Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, et al. Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. *Health Technol Assess* 2008;12(17):iii-143.

[16] Schuetz GM, Zacharopoulou NM, Schlattmann P, Dewey M. Meta-analysis: noninvasive coronary angiography using computed tomography versus magnetic resonance imaging. *Ann Intern Med* 2010;152(3):167-77.

[17] Khan R, Rawal S, Eisenberg MJ. Transitioning from 16-slice to 64-slice multidetector computed tomography for the assessment of coronary artery disease: are we really making progress? *Can J Cardiol* 2009;25(9):533-42.

[18] British Heart Foundation. *Incidence of congenital heart disease [Internet]*, 2005 [cited 12.1.11] Available from: http://www.heartstats.org/datapage.asp?id=3395

[19] Cheng Z, Wang X, Duan Y, Wu L, Wu D, Chao B, et al. Low-dose prospective ECG-triggering dual-source CT angiography in infants and children with complex congenital heart disease: first experience. *Eur Radiol* 2010;20(10):2503-11.

[20] Hope SA, Crossett M, Nasis A, Seneviratne S. Early experience with Aquilion One 320 slice computerised tomography scanner in paediatric and congenital heart disease. *Fifth World Congress of Paediatric Cardiology and Cardiac Surgery*. Cairns, Australia, 2010 21-26 Jun.

[21] NHS Purchasing and Supply Agency, Centre for Evidence-based Purchasing. *Market review: advanced CT scanners for coronary angiography. CEP10043*. London: Centre for Evidence-based Purchasing, 2010. 79p.

[22] Noto TJ, Jr., Johnson LW, Krone R, Weaver WF, Clark DA, Kramer JR, Jr., et al. Cardiac catheterization 1990: a report of the Registry of the Society for Cardiac Angiography and Interventions (SCA&I). *Cathet Cardiovasc Diagn* 1991;24(2):75-83.

[23] Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, et al. ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol* 1999;33(6):1756-824.

[24] National Institute for Health and Clinical Excellence. *Management of stable angina. NICE guideline: methods, evidence and guidance. Draft for consultation [Internet]*. London: NICE, 2010 [cited 20.05.11]. 471p. Available from: http://www.nice.org.uk/nicemedia/live/11878/54376/54376.pdf

[25] National Institute for Health and Clinical Excellence. *Ischaemic heart disease: coronary artery stents. Technology Appraisals 71 [Internet]*. London: NICE, 2003 [cited 20.04.11] Available from: http://guidance.nice.org.uk/TA71

[26] National Institute for Health and Clinical Excellence. *Drug-eluting stents for the treatment of coronary artery disease. Technology Appraisals 152 [Internet]*. London: NICE, 2008 [cited 20.04.11] Available from: http://guidance.nice.org.uk/TA152

[27] NHS choices. *Congenital heart disease [Internet]*: NHS, 2009 [cited 18.05.11] Available from: http://www.nhs.uk/Conditions/Congenital-heart-disease/Pages/Introduction.aspx

[28] Tidy C. *Congenital heart disease in children [Internet]*. Leeds: Patient UK, 2011 [cited 18.05.11] Available from: http://www.patient.co.uk/doctor/Congenital-Heart-Disease-%28CHD%29-in-Children.htm

[29] Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010;31(23):2915-57.

[30] Harbord RM, Whiting P. metandi: Meta-analysis of diagnostic accuracy using hierarchical logistic regression. *Stata J* 2009;9(2):211-29.

[31] Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol* 2006;6:31.

[32] Paul N, Nguyen E, Doyle D, Crean A, Bret P. Prospective ECG gated low dose CT angiography with 320-MDCT. Presented at 2nd World Congress of Thoracic Imaging and Diagnosis in Chest Disease, 2009 30 May-2 Jun; Valencia, Spain. *J Thorac Imaging* 2009;24(3):w4.

[33] Sun ML. Diagnostic Accuracy of Dual-Source CT Coronary Angiography with Prospective ECG Triggering on Different Heart Rate Patients. *Cardiology* 2010;117:114-115.

[34] Leschka S, Scheffel H, Husmann L, Wildermuth S, Marincek B, Kaufmann PA, et al. Influence of Body-Mass-Index, Calcium-Score and heart heart rate on the accuracy of DSCT-coronary angiography. *Dtsch Med Wochenschr* 2007;132(46):S35-S35.

[35] Stinn B, Leschka S, Schmid F, Thurnheer M, Schultes B, Wildermuth S. CT-Coronary angiography: Improvement of evaluation quality of coronary artery for morbid obesity with the new Dual-Source CT in comparison to 64-lines CT. *Dtsch Med Wochenschr* 2007;132(46):S36-S36.

[36] Kepka C, Opolski MP, Kruk M, Pregowski J, Michalowska I, Demkow M, et al. Dual-source computed tomography angiography in patients after bypass grafting - Comparison with invasive coronary angiography. *Postepy Kardiol Interwencyjnej* 2010;6(1):12-20.

[37] Pflederer T, Seltmann M, Marwan M, Ropers D, Daniel WG, Achenbach S. Detection of coronary artery stenoses in patients with previous coronary revascularisation by 128-slice dual source computed tomography. Abstract 953. Presented at European Society of Cardiology, ESC Congress, 2010 28 Aug-1 Sep; Stockholm, Sweden. *Eur Heart J* 2010;31:152.

[38] Rixe J, Rolf A, Erkapic D, Koch A, Moellmann H, Nef H, et al. Usefulness of dual-source computed tomography for the detection of coronary artery disease in

patients with arrhythmia: comparison to invasive angiography. Abstract P1364. *Eur Heart J Suppl* 2009;30(206).

[39] Van Mieghem CA, Weustink A, Meijboom B, Pugliese F, Serruys PW, de Feyter PJ. Abstract 2328: clinical value of ct coronary angiography in symptomatic patients after percutaneous coronary intervention. *Circulation* 2007;116(II_509).

[40] Ropers D, Ropers U, Pflederer T, Bachmann S, Daniel WG, Achenbach S. Accuracy of dual source CT coronary angiography in patients after coronary bypass surgery: Comparison to invasive angiography in 78 patients. *J Am Coll Cardiol* 2008;51(10):A143-A143.

[41] LaBounty T, Leipsic J, Mancini GBJ, Heilbron B, Patel S, Kazerooni E, et al. A prospective multicenter study evaluating the diagnostic accuracy of high-definition coronary computed tomographic angiography: an intent-to-diagnose analysis. Presented at American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention, 2010 14-16 Mar; Atlanta, United States. *J Am Coll Cardiol* 2010;55(10 Suppl 1):A68.E637.

[42] Ropers U, Ropers D, Pflederer T, Anders K, Kuettner A, Stilianakis NI, et al. Influence of heart rate on the diagnostic accuracy of dual-source computed tomography coronary angiography. *J Am Coll Cardiol* 2007;50(25):2393-8.

[43] de Graaf FR, Schuijf JD, van Velzen JE, Boogers MJ, Kroft LJ, de Roos A, et al. Diagnostic accuracy of 320-row multidetector computed tomography coronary angiography to noninvasively assess in-stent restenosis. *Invest Radiol* 2010;45(6):331-40.

[44] Alkadhi H, Scheffel H, Desbiolles L, Gaemperli O, Stolzmann P, Plass A, et al. Dual-source computed tomography coronary angiography: influence of obesity, calcium load, and heart rate on diagnostic accuracy. *Eur Heart J* 2008;29(6):766-76.

[45] Brodoefel H, Tsiflikas I, Burgstahler C, Reimann A, Thomas C, Schroeder S, et al. Cardiac dual-source computed tomography: effect of body mass index on image quality and diagnostic accuracy. *Invest Radiol* 2008;43(10):712-8.

[46] Brodoefel H, Burgstahler C, Tsiflikas I, Reimann A, Schroeder S, Claussen CD, et al. Dual-source CT: effect of heart rate, heart rate variability, and calcification on image quality and diagnostic accuracy. *Radiology* 2008;247(2):346-55.

[47] Leber AW, Johnson T, Becker A, von Ziegler F, Tittus J, Nikolaou K, et al. Diagnostic accuracy of dual-source multi-slice CT-coronary angiography in patients with an intermediate pretest likelihood for coronary artery disease. *Eur Heart J* 2007;28(19):2354-60.

[48] Lin CJ, Hsu JC, Lai Y, Wang KL, Lee JY, Li AH, et al. Diagnostic accuracy of dual-source CT coronary angiography in a population unselected for degree of coronary artery calcification and without heart rate modification. *Clin Radiol* 2010;65(2):109-117.

[49] Marwan M, Pflederer T, Schepis T, Lang A, Muschiol G, Ropers D, et al. Accuracy of dual-source computed tomography to identify significant coronary artery disease in patients with atrial fibrillation: comparison with coronary angiography. *Eur Heart J* 2010;31(18):2230-7.

[50] Meng L, Cui L, Cheng Y, Wu X, Tang Y, Wang Y, et al. Effect of heart rate and coronary calcification on the diagnostic accuracy of the dual-source CT coronary angiography in patients with suspected coronary artery disease. *Korean J Radiol* 2009;10(4):347-54.

[51] Oncel D, Oncel G, Tastan A. Effectiveness of dual-source CT coronary angiography for the evaluation of coronary artery disease in patients with atrial fibrillation: initial experience. *Radiology* 2007;245(3):703-11.

[52] Oncel D, Oncel G, Tastan A, Tamci B. Evaluation of coronary stent patency and in-stent restenosis with dual-source CT coronary angiography without heart rate control. *AJR Am J Roentgenol* 2008;191(1):56-63.

[53] Pflederer T, Marwan M, Renz A, Bachmann S, Ropers D, Kuettner A, et al. Noninvasive assessment of coronary in-stent restenosis by dual-source computed tomography. *Am J Cardiol* 2009;103(6):812-7.

[54] Pugliese F, Weustink AC, Van Mieghem C, Alberghina F, Otsuka M, Meijboom WB, et al. Dual source coronary computed tomography angiography for detecting in-stent restenosis. *Heart* 2008;94(7):848-54.

[55] Pugliese F, Alberghina F, Weustink AC, Otsuka M, Mollet NR, de Feyter PJ, et al. Dual-source computed tomography angiography for the assessment of in-stent restenosis in coronary arteries. *AJR Am J Roentgenol* 2007;188(5):A4.

[56] Rist C, Johnson TR, Mueller-Starck J, Arnoldi E, Saam T, Becker A, et al. Noninvasive coronary angiography using dual-source computed tomography in patients with atrial fibrillation. *Invest Radiol* 2009;44(3):159-167.

[57] Scheffel H, Alkadhi H, Plass A, Vachenauer R, Desbiolles L, Gaemperli O, et al. Accuracy of dual-source CT coronary angiography: first experience in a high pre-test probability population without heart rate control. *Eur Radiol* 2006;16(12):2739-47.

[58] Tsiflikas I, Drosch T, Brodoefel H, Thomas C, Reimann A, Till A, et al. Diagnostic accuracy and image quality of cardiac dual-source computed tomography in patients with arrhythmia. *Int J Cardiol* 2010;143(1):79-85.

[59] Drosch T, Reimann A, Brodoefel H, Tsiflikas I, Thomas C, Heuschmid M, et al. Diagnostic accuracy and image quality of cardiac dual-source computed tomography in patients with arrhythmia. *Circulation* 2008;118(18):S845-S845.

[60] Weustink AC, Nieman K, Pugliese F, Mollet NR, Meijboom BW, van Mieghem C, et al. Diagnostic accuracy of computed tomography angiography in patients after bypass grafting. Comparison with invasive coronary angiography. *JACC Cardiovasc Imaging* 2009;2(7):816-824.

[61] Weustink AC, Neefjes LA, Kyrzopoulos S, Van Straten M, Eu RN, Meijboom WB, et al. Impact of heart rate frequency and variability on radiation exposure, image quality, and diagnostic performance in dual-source spiral CT coronary angiography. *Radiology* 2009;253(3):672-680.

[62] Zhang LJ, Wu SY, Wang J, Lu Y, Zhang ZL, Jiang SS, et al. Diagnostic accuracy of dual-source CT coronary angiography: the effect of average heart rate, heart rate variability, and calcium score in a clinical perspective. *Acta radiol* 2010;51(7):727-740.

[63] de Jonge GJ, van Ooijen PMA, Piers LH, Dikkers R, Tio RA, Willems TP, et al. Visualization of anomalous coronary arteries on dual-source computed tomography. *Eur Radiol* 2008;18(11):2425-32.

[64] National Institute for Health and Clinical Excellence. *Management of stable angina. NICE guideline. Draft for consultation [Internet]*. London: NICE, 2010 [cited 20.04.11]. 31p. Available from: http://www.nice.org.uk/nicemedia/live/11878/52141/52141.pdf

[65] Walker S. CEMARC cost-effectiveness analysis model. York: Centre for Health Economics, University of York, 2011.

[66] Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, et al. Cost-effectiveness of thrombolysis with recombinant tissue plasminogen activator for acute ischemic stroke assessed by a model based on UKNHS costs. *Stroke* 2004;35(6):1490-1497.

[67] National Collaborating Centre for Chronic Conditions. *Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). NICE clinical guideline 68 [Internet]*. London: National Institute for Health and Clinical Excellence, 2008 [cited 18.5.11]. 37p. Available from: http://www.nice.org.uk/nicemedia/live/12018/41331/41331.pdf

[68] Fox KM, Bertrand M, Ferrari R, Remme WJ, Simoons ML, Remme WJ, et al. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362(9386):782-788.

[69] Daly CA, Clemens F, Sendon JLL, Tavazzi L, Boersma E, Danchin N, et al. The initial management of stable angina in Europe, from the Euro Heart Survey: a description of pharmacological management and revascularisation strategies initiated within the first month of presentation to a cardiologist in the Euro Heart Survey of Stable Angina. *Eur Heart J* 2005;26(10):1011-1022.

[70] Deckers JW, Goedhart DM, Boersma E, Briggs A, Bertrand M, Ferrari R, et al. Treatment benefit by perindopril in patients with stable coronary artery disease at different levels of risk. *Eur Heart J* 2006;27(7):796-801.

[71] 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 Center, 2011.

[72] Shemesh J, Stroh CI, Tenenbaum A, Hod H, Boyko V, Fisman EZ, et al. Comparison of coronary calcium in stable angina pectoris and in first acute myocardial infarction utilizing double helical computerized tomography. *Am J Cardiol* 1998;81(3):271-5.

[73] Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;336(7659):1475-82.

[74] Banasiak W, Pociupany R, Wilkins A, Ponikowski P. Characteristics of patients with coronary artery disease managed on an outpatient basis in the population of Poland. Results of the multicentre RECENT trial. *Kardiol Pol* 2007;65(2):132-42.

[75] Hall EJ, Brenner DJ. Cancer risks from diagnostic radiology. *Br J Radiol* 2008;81(965):362-378.

[76] Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. *AJR Am J Roentgenol* 2001;176(2):289-296.

[77] Wall B, Hillier M, Haylock R, Hart D, Jansen J, Shrimpton P. Radiation risks from medical x-ray examinations as a function of the age and sex of the patient (draft report - academic in confidence). Didcot: Health Protection Agency; Centre for Radiation, Chemical and Environmental Hazards, 2011.

[78] The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. *Ann ICRP* 2007;37(2-4):1-332.

[79] Shrimpton P, Hillier M, Lewis M, Dunn M. Doses from computed tomography (CT) examinations in the UK: 2003 review. Didcot: National Radiological Protection Board, 2005. Available from: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947420292

[80] United Nations Scientific Committee on the Effects of Atomic Radiation. *Sources and effects of ionizing radiation. UNSCEAR 2008: report to the General Assembly with scientific annexes*. New York: United Nations, 2010. Available from: http://www.unscear.org/unscear/en/publications/2008_1.html

[81] Linet MS, Kim KP, Rajaraman P. Children's exposure to diagnostic medical radiation and cancer risk: epidemiologic and dosimetric considerations. *Pediatr Radiol* 2009;39(Suppl 1):s4-26.

[82] Department of Health. *NHS Reference Costs 2010/11. Collection Guidance [Internet]*. London: Department of Health, 2010 [cited 19.5.11]. 183p. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_122803

[83] ImPACT Group. *Buyer's guide: multi-slice CT scanners. CEP08007 [Internet]*. London: Centre for Evidence-Based Purchasing, 2009 [cited 19.5.11]. 181p. Available from: http://www.impactscan.org/clix/clix.php?http://nhscep.useconnect.co.uk/ShowDocument.ashx?id=79&i=true

[84] National Audit Office. *Managing high value capital equipment in the NHS in England [Internet]*. London: The Stationery Office, 2011 [cited 19.5.11]. 42p. Available from: http://www.nao.org.uk/publications/1011/nhs_high_value_equipment.aspx

[85] Personal Social Services Research Unit. *Unit Costs of Health and Social Care*. Canterbury: University of Kent, 2010 [cited 16.5.11]. 257p. Available from: http://www.pssru.ac.uk/pdf/uc/uc2010/uc2010.pdf

[86] Hofstra L. *Expert opinion treatment of CAD-suspected patients [Personal communication]*, May 2011.

[87] NHS Information Centre for Health and Social Care. *Hospital Episode Statistics: healthcare resource groups - HRG version 3 [Excel spreadsheet] [Internet]*. London: Health and Social Care Information Centre, 2010 [cited 20.5.11] Available from: http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=206

[88] West R, Ellis G, Brooks N, Joint Audit Comm British Cardiac S. Complications of diagnostic cardiac catheterisation: results from a confidential inquiry into cardiac catheter complications. *Heart* 2006;92(6):810-814.

[89] Batyraliev T, Ayalp MR, Sercelik A, Karben Z, Dinler G, Besnili F, et al. Complications of cardiac catheterization: a single-center study. *Angiology* 2005;56(1):75-80.

[90] Chandrasekar B, Doucet S, Bilodeau L, Crepeau J, deGuise P, Gregoire J, et al. Complications of cardiac catheterization in the current era: a single-center experience. *Catheter Cardiovasc Interv* 2001;52(3):289-295.

[91] Smith LDR, Spyer G, Dean JW. Audit of cardiac catheterisation in a district general hospital: implications for training. *Heart* 1999;81(5):461-464.

[92] Bridgewater B, Grayson AD, Brooks N, Grotte G, Fabri BM, Au J, et al. Has the publication of cardiac surgery outcome data been associated with changes in practice in northwest England: an analysis of 25,730 patients undergoing CABG surgery under 30 surgeons over eight years. *Heart* 2007;93(6):744-8.

[93] Tarakji KG, Sabik JF, 3rd, Bhudia SK, Batizy LH, Blackstone EH. Temporal onset, risk factors, and outcomes associated with stroke after coronary artery bypass grafting. *JAMA* 2011;305(4):381-90.

[94] Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJRM, Schonberger JPAM, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001;344(15):1117-1124.

[95] Rajani R, Lindblom M, Dixon G, Khawaja M, Hildick-Smith D, Holmberg S, et al. Evolving trends in percutaneous coronary intervention. *Br J Cardiol* 2011;18(2):73-76.

[96] Kind P, Hardman G, Macran S. *UK population norms for EQ-5D. Discussion paper 172*. York: Centre for Health Economics, 1999

[97] National Institute for Clinical Excellence. *Guide to the methods of technology appraisal*. London: NICE, 2008 [cited 16.5.11]. 80p. Available from: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

[98] Longworth L, Buxton MJ, Sculpher M, Smith DH. Estimating utility data from clinical indicators for patients with stable angina. *Eur J Health Econ* 2005;6(4):347-53.

[99] Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making* 2006;26(4):410-20.

[100] Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, et al. Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke Study. *Stroke* 2000;31(9):2080-6.

[101] National Research Council, Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation. *Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2*. Washington: National Academies Press, 2006.

[102] Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol* 2005;58(9):882-93.

[103] Zhou X, McClish D, Obuchowski NA. *Statistical methods in diagnostic medicine*. New York: Wiley Interscience, 2002.

[104] Zwinderman AH, Bossuyt PM. We should not pool diagnostic likelihood ratios in systematic reviews. *Stat Med* 2008;27(5):687-97.

[105] Blankenhorn DH, Curry PJ. The accuracy of arteriography and ultrasound imaging for atherosclerosis measurement. A review. *Archives of Pathology & Laboratory Medicine* 1982;106(10):483-9.

[106] Arnett EN, Isner JM, Redwood DR, Kent KM, Baker WP, Ackerstein H, et al. Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and necropsy findings. *Ann Intern Med* 1979;91(3):350-6.

[107] Roberts WC, Jones AA. Quantitation of coronary arterial narrowing at necropsy in sudden coronary death: analysis of 31 patients and comparison with 25 control subjects. *Am J Cardiol* 1979;44(1):39-45.

[108] Grondin CM, Dyrda I, Pasternac A, Campeau L, Bourassa MG, Lesperance J. Discrepancies between cineangiographic and postmortem findings in patients with coronary artery disease and recent myocardial revascularisation. *Circulation* 1974;49(4):703-8.

[109] Vlodaver Z, Frech R, Van Tassel RA, Edwards JE. Correlation of the antemortem coronary arteriogram and the postmortem specimen. *Circulation* 1973;47(1):162-9.

[110] 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(6):500-506.

[111] 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(3):143-51.

[112] 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(3):223-228.

[113] 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(3):165-171.

[114] Chen S-y, Su Y-s, Xie P-y, Xu S-l, Fang Y-q, Huang A-r. [Clinical value of dual-source CT in evaluating coronary artery disease]. *Nan Fang Yi Ke Da Xue Xue Bao* 2010;30(9):2125-7.

[115] Fang XM, Chen HW, Hu XY, Bao J, Chen Y, Yang ZY, et al. Dual-source CT coronary angiography without heart rate or rhythm control in comparison with conventional coronary angiography. *Int J Cardiovasc Imaging* 2010;26(3):323-31.

[116] Herzog BA, Husmann L, Burkhard N, Gaemperli O, Valenta I, Tatsugami F, et al. Accuracy of low-dose computed tomography coronary angiography using prospective electrocardiogram-triggering: first clinical experience. *Eur Heart J* 2008;29(24):3037-3042.

[117] Heuschmid M, Burgstahler C, Reimann A, Brodoefel H, Mysal I, Haeberle E, et al. Usefulness of noninvasive cardiac imaging using dual-source computed tomography in an unselected population with high prevalence of coronary artery disease. *Am J Cardiol* 2007;100(4):587-92.

[118] Johnson TR, Nikolaou K, Busch S, Leber AW, Becker A, Wintersperger BJ, et al. Diagnostic accuracy of dual-source computed tomography in the diagnosis of coronary artery disease. *Invest Radiol* 2007;42(10):684-691.

[119] Nance JW, Jr., Bastarrika G, Kang DK, Ruzsics B, Vogt S, Schmidt B, et al. High-temporal resolution dual-energy computed tomography of the heart using a novel hybrid image reconstruction algorithm: initial experience. *J Comput Assist Tomogr* 2011;35(1):119-25.

[120] Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003;326(7379):41-4.

[121] Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med* 2003;138(1):W1-12.

APPENDICES

Appendix 1: Literature search strategies

Clinical Effectiveness search strategies

Medline (OvidSP): 2000-2011/2/wk 2
Searched 17.2.11

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$)).ti,ab,ot,hw. (1)
15 or/1-14 (3962)
16 heart defects, congenital/ or aortic coarctation/ or cor triatriatum/ or eisenmenger complex/ or "isolated noncompaction of the ventricular myocardium"/ or leopard syndrome/ or marfan syndrome/ or "tetralogy of fallot"/ or "trilogy of fallot"/ or turner syndrome/ (59436)
17 exp Coronary Disease/ or myocardial ischemia/ or exp myocardial infarction/ (289267)
18 ((pulmonary or aortic or aorta or coronary or cardiac or valve) adj2 (stenosis or atresia)).ti,ab,ot,hw. (49077)
19 (congenital$ 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$)).ti,ab,ot,hw. (43228)
21 (CAD or IAA or VSD or CHD or LVOT or PVOD or UVH or TAPVD or TAPVR or PAPVD or PAPVR or MAPCA or MAP-CA).ti,ab,ot. (34019)
22 (TOF or TAPVC or COA or IAA or SS or PAPVC).ti,ab,ot. (63756)
23 (Lutembacher$ 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$.ti,ab,ot,hw. (3)
42 ((coronary or heart) adj2 disease).ti,ab,ot,hw. (240566)
43 (MI or IHD).ti,ab,ot,ab. (24125)
44 (isch?emic heart disease$ or myocardi$ isch?em$ or angina$).ti,ab,ot,hw. (106061)
45 ((right or double) adj2 aort$ 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/ (16383)
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$)).ti,ab,ot,hw. (2926)
67 exp Heart Neoplasms/ (11963)
68 exp Teratoma/ (16305)
69 Myxoma/ (5162)
70 (aortic root or myxoma$ or angiomyxoma$).ti,ab,ot,hw. (12088)
71 or/16-70 (605347)
72 animals/ not (animals/ and humans/) (3450666)
73 71 not 72 (542288)
74 15 and 73 (370)
75 limit 74 to yr="2000 -Current" (339)

Medline In-Process (OvidSP): 2000-2011/2/16
Medline Daily Update (OvidSP): 2000-2011/2/16
Searched 17.2.11

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 (13434)
72 animals/ not (animals/ and humans/) (1216)
73 71 not 72 (13398)
74 15 and 73 (34)
75 limit 74 to yr="2000 -Current" (33)

Embase (OvidSP): 2000-2011/wk 6
Searched 17.2.11

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$)).ti,ab,ot,hw. (1)
14 or/1-13 (4512)
15 congenital heart malformation/ or cor triatriatum/ or coronary vessel malformation/ or eisenmenger complex/ or heterotaxy syndrome/ (29152)
16 fallot tetralogy/ (8913)
17 exp aorta anomaly/ (17993)
18 coronary artery anomaly/ (2536)
19 scimitar syndrome/ (387)
20 LEOPARD syndrome/ (248)
21 Marfan syndrome/ (5781)
22 heart atrium septum defect/ (9190)
23 Turner syndrome/ (7509)
24 exp coronary artery disease/ (167530)
25 exp heart infarction/ (198634)
26 heart muscle ischemia/ (58741)
27 arterial trunk/ (735)
28 mucocutaneous lymph node syndrome/ (5745)
29 exp heart aneurysm/ (8434)
30 norwood procedure/ (477)
31 aorta aneurysm/ or aorta dissecting aneurysm/ or aorta sinus aneurysm/ (16981)
32 teratoma/ (16384)
33 exp myxoma/ (6377)
34 heart tumor/ (7896)
35 mustard operation/ (376)
36 ((pulmonary or aortic or aorta or coronary or cardiac or valve) adj2 (stenosis or atresia)).ti,ab,ot,hw. (50571)
37 (congenital$ 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$)).ti,ab,ot,hw. (46328)
39 (CAD or IAA or VSD or CHD or LVOT or PVOD or UVH or TAPVD or TAPVR or PAPVD or PAPVR or MAPCA or MAP-CA).ti,ab,ot. (44393)
40 (TOF or TAPVC or COA or IAA or SS or PAPVC).ti,ab,ot. (72919)
41 (Lutembacher$ 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$.ti,ab,ot,hw. (6)
60 ((coronary or heart) adj2 disease).ti,ab,ot,hw. (335859)
61 (isch?emic heart disease$ or myocardi$ isch?em$ or angina$).ti,ab,ot,hw. (164773)
62 (MI or IHD).ti,ab,ot. (32623)
63 (isch?emic heart disease$ or myocardi$ isch?em$ or angina$).ti,ab,ot,hw. (164773)
64 ((right or double) adj2 aort$ 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. (13782)
80 or/15-79 (805212)
81 animal/ or animal experiment/ (3045231)
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. (4666017)
83 or/81-82 (4666017)
84 exp human/ or human experiment/ (12216815)
85 82 not (82 and 84) (3748300)

86 80 not 85 (725233)
87 14 and 86 (560)
88 limit 87 to yr="2000 -Current" (527)

Cochrane Database of Systematic Reviews (CDSR) (Internet) Issue 1:2011. 2000-2011
Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) Issue 1:2011. 2000-2011
Searched 17.2.11

#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 3 references.
CENTRAL search retrieved 154 references.

Database of Abstracts of Reviews of Effects (DARE) (Internet) 2000-2011/02/15
NHS Economic Evaluation Database (NHS EED) (Internet) 2000-2011/02/15
Health Technology Assessment Database (HTA) (Internet) 2000-2011/02/15
Searched 15.2.11

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 (SCI) (Web of Science): 2000-2011/03/05
Searched 9.3.11

# 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 9.3.11

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**

mRCT – metaRegister of Controlled Trials (Internet)
http://www.controlled-trials.com/mrct/search.html
Searched 9.3.11

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**

WHO International Clinical Trials Registry Platform (ICTRP) (Internet)
http://www.who.int/ictrp/en/
Searched 9.3.11

Advanced search option
– Recruitment status = ALL
- Date limit: 01/01/2000-09/03/2011

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
http://www.cardiosource.org/Meetings/Previous-Meetings-OLD.aspx
Searched 22.3.11

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 (ESC) (Internet): all dates
http://www.escardio.org/congresses/past_congresses/Pages/past-ESC-congresses.aspx
Searched 22.3.11

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 (SCCT) (Internet): 2006-2007, 2009-2010
http://www.scct.org/annualmeeting/2010/index.cfm
Searched 22.3.11

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**				

n.b. no free content or full abstracts, therefore could only browse abstract titles in programme.

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

*2007 = unable to search or copy within PDF, therefore browsed listings.

American Heart Association (AHA) (Internet): 2007-2010
Searched 22.3.11

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: 2000-2011/03/wk 2
Searched 18.3.11

1 economics/ (25965)
2 exp "costs and cost analysis"/ (154360)
3 economics, dental/ (1814)
4 exp "economics, hospital"/ (17009)
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$).ti,ab. (327719)
9 (expenditure$ not energy).ti,ab. (13900)
10 (value adj1 money).ti,ab. (18)
11 budget$.ti,ab. (14162)
12 or/1-11 (439089)
13 ((energy or oxygen) adj cost).ti,ab. (2243)
14 (metabolic adj cost).ti,ab. (578)
15 ((energy or oxygen) adj expenditure).ti,ab. (12794)
16 or/13-15 (15012)
17 12 not 16 (435668)
18 letter.pt. (707514)
19 editorial.pt. (270646)
20 historical article.pt. (271900)
21 or/18-20 (1237508)
22 17 not 21 (411802)
23 Somatom definition flash.ti,ab,ot,hw. (4)
24 DSCT.ti,ab,ot,hw. (250)
25 (Aquilion-1 or Aquilion-one).ti,ab,ot,hw. (9)
26 Brilliance ict.ti,ab,ot,hw. (1)
27 (Discovery ct750 or Discovery ct-750).ti,ab,ot,hw. (1)
28 (640row$ 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/) (3467241)
38 36 not 37 (3093)
39 22 and 38 (124)
40 limit 39 to yr="2000 -Current" (86)

Costs filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited

13.1.11]. Available from:
http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED

Medline In-Process Citations: 2000-2011/03/17
Medline Daily Update: 2000-2011/03/17
Econ filter + Somatom
Searched 18.3.11

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$).ti,ab. (22066)
9 (expenditure$ not energy).ti,ab. (661)
10 (value adj1 money).ti,ab. (2)
11 budget$.ti,ab. (1260)
12 or/1-11 (23355)
13 ((energy or oxygen) adj cost).ti,ab. (147)
14 (metabolic adj cost).ti,ab. (36)
15 ((energy or oxygen) adj expenditure).ti,ab. (513)
16 or/13-15 (674)
17 12 not 16 (23148)
18 letter.pt. (16125)
19 editorial.pt. (9820)
20 historical article.pt. (136)
21 or/18-20 (26064)
22 17 not 21 (22849)
23 Somatom definition flash.ti,ab,ot,hw. (0)
24 DSCT.ti,ab,ot,hw. (21)
25 (Aquilion-1 or Aquilion-one).ti,ab,ot,hw. (0)
26 Brilliance ict.ti,ab,ot,hw. (0)
27 (Discovery ct750 or Discovery ct-750).ti,ab,ot,hw. (0)
28 (640row$ 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:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited

13.1.11]. Available from:
http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED

Embase (OvidSP): 2000-2011/wk 11
Searched 21.3.11

1 health-economics/ (29992)
2 exp economic-evaluation/ (164874)
3 exp health-care-cost/ (158402)
4 exp pharmacoeconomics/ (135363)
5 or/1-4 (379713)
6 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (423085)
7 (expenditure$ not energy).ti,ab. (16910)
8 (value adj2 money).ti,ab. (886)
9 budget$.ti,ab. (17926)
10 or/6-9 (441343)
11 5 or 10 (667209)
12 letter.pt. (722150)
13 editorial.pt. (367790)
14 note.pt. (437051)
15 or/12-14 (1526991)
16 11 not 15 (597817)
17 (metabolic adj cost).ti,ab. (639)
18 ((energy or oxygen) adj cost).ti,ab. (2509)
19 ((energy or oxygen) adj expenditure).ti,ab. (14898)
20 or/17-19 (17385)
21 16 not 20 (593880)
22 animal/ or animal experiment/ (3061249)
23 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (4692356)
24 or/22-23 (4692356)
25 exp human/ or human experiment/ (12289869)
26 24 not (24 and 25) (3767804)
27 21 not 26 (568041)
28 Somatom definition flash.mp. (12)
29 DSCT.mp. (352)
30 (Aquilion-1 or Aquilion-one).mp. (22)
31 Brilliance ict.mp. (4)
32 (Discovery ct750 or Discovery ct-750).mp. (2)
33 (640row$ 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:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Embase (Ovid) weekly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 17.3.11]. Available from: http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#embase

Paediatric Economic Database Evaluation (PEDE) (Internet): 2000-2009
http://pede.ccb.sickkids.ca/pede/search.jsp
Searched 21.3.11

Searched 'Title, Abstract, or Keywords', 2000-2009

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**

PEDE search retrieved **0** records.

Health Economics Evaluation Database (HEED) (Internet): up to 2011/03/21
http://onlinelibrary.wiley.com/book/10.1002/9780470510933
Searched 21.3.11

Compound search, (all data), 2000-2011

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

GIN: International Guidelines Library
http://www.g-i-n.net
2005-2011/03/16
Searched 16.3.11

Limited to 2005-2011, 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)
http://www.guideline.gov/
Searched 16.3.11

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 (NICE) Guidance (Internet)
http://guidance.nice.org.uk/
Searched 16.3.11

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

TRIP database (Internet)
http://www.tripdatabase.com/
Searched 16.3.11

Limited to Guidelines only; 2005-2011

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

Health Technology Assessment (HTA) (Internet): 2005-2011
http://www.york.ac.uk/inst/crd/
Searched 16.3.11

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 weren't 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 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 pre-specify 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 3 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" ➔ 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 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 invasive coronary angiography 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 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[44]

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 pre-specify 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 2x2 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).

- ❖ 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 2008a[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 pre-specify 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 2x2 table:

Initial reasons for exclusion: refusal/withdrawal of consent (8), impaired renal function (2), previous bypass surgery (7), acute coronary syndrome necessitating immediate invasive coronary angiography (1). One patient with a normal CTA withdrew consent and didn't receive the reference standard (excluded after enrolment). All other patients received both tests. However, it was not clear whether 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

STUDY ID: Brodoefel 2008b[45]

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 pre-specify 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 2x2 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[43]

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 3 patients with increased heart rate and contraindications to β-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 pre-specify 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 2x2 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[41]

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 pre-specify 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 2x2 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[47]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection:
Consecutive patients with intermediate likelihood of CAD, referred for coronary angiography.

- ❖ 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 pre-specify 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 2x2 table:
One Patient was excluded from analysis due 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[48]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection:
Retrospective analysis of a selection of patients from a consecutive series, only patients who had received both CT and ICA were included. Previous coronary stent implantation or bypass were exclusion criteria. The stated inclusion criteria suggested that only patients with positive CT examinations were included, but this was not consistent with the reported results.

- ❖ 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 pre-specify 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 2x2 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[49]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection:
Consecutive patients with AF. 10 patients with rapid AF (HR > 100bpm) unresponsive to β-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 pre-specify 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 2x2 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[50]

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 pre-specify 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 2x2 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%. 1 patient was excluded but it is not 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[51]

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 pre-specify 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 2x2 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[52]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection:
Consecutive patients with suspected in-stent re-stenosis. 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 pre-specify 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 2x2 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[53]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection:

Consecutive patients with suspected in-stent re-stenosis. Lesions with > 1 implanted stent (≥ 2 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 (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 pre-specify 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 2x2 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[37]

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 pre-specify 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 2x2 table:
All patients appear to have been included in the analyses.

Describe the time interval between index and reference standard and any actions taken:
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: Pugliese 2011[54, 55]

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 (6 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 pre-specify 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 2x2 table:
133 patients with chest pain after stent implantation were referred for conventional angiography. 33 were excluded: 4 because of renal impairment, 3 due to contrast allergy, 6 due to

AF/irregular heart rate, 20 didn't 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[56]

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 pre-specify 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 indexRISK: LOW test have introduced bias?

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 RISK: LOW reference standard have introduced bias?

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[38]

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. Un-assessable segment were considered to be positive.

- ❖ Were the index test results interpreted without knowledge of the results of the reference standard? Unclear
- ❖ Did the study pre-specify 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 2x2 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:
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: Ropers 2007[42]

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 pre-specify 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 2x2 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 to 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[40]

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 pre-specify 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 2x2 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. I 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[57]

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 pre-specify 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 2x2 table:
All patients/segments appear to have been included in the analyses, though 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[58, 59]

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 pre-specify 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 2x2 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[39]

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 pre-specify 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 2x2 table:
All patients appeared to have been included in the analysis. Both in-stent re-stenoses and native vessel stenoses were included in the analysis.

Describe the time interval between index and reference standard and any actions taken:
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: Weustink 2009a[61]

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 pre-specify 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 2x2 table:

1143 consecutive patients were enrolled that 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 2009b[60]

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 pre-specify 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**
- ❖ 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 2x2 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 atrial fibrillation, 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[62]

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 4 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 pre-specify 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 2x2 table:

Information partially contradictory
121 patients with suspected CAD gave informed consent and had both CTCA and CAG. 6 patients were excluded because they didn't meet the inclusion criteria (4 because of stent follow-up, 1 who didn't receive a CAG because of occluded iliac arteries, 1 due to chest pain during examination). 113 patients were included (for 2 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[44]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – 46 Patients continued their baseline treatment with β-blockers, no additional medication for heart-rate control was given. Contrast agent – 80 ml of iodixanol (Visipaque 320, 320 mg/ml, GE Heathcare, Buckinghamshire, UK), i.v., flow rate of 5 ml /s, followed by 30 ml saline. Scans performed from tracheal bifurcation to diaphragm. Scan parameters – detector collimation 2 x 32 x 0.6 mm^3, slice collimation 2 x 64 x 0.6 mm^3, gantry rotation time 330 ms, pitch 0.2–0.5, tube current time product 350 mAs per rotation, and tube potential 120 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 false positive. Positive stenosis was defined as diameter	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 >50%.

Study ID	Index test (assessed technology) details	Reference standard details
	reduction >50%, measured with an electronic calliper tool. Any disagreements between observers were resolved by consensus.	
Brodoefel 2008b[45]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – 94 patients Had baseline treatment with β-blockers. No additional β-blockers were given. Contrast agent – 80 ml of iomeprol (Imeron 400, Altana, Konstanz, Germany), i.v., flow rate of 5 ml /s, followed by 60 ml chaser bolus. Scan parameters – collimation 32 x 0.6 mm, slice acquisition 64 x 0.6 mm, gantry rotation time 330 ms, 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 ≥50%. Where there were multiple lesions per segment, the segment was classified by the worst stenosis.	Catheter angiography – transfemoral and transradial Judkins technique, ≥2 projections for the right coronary artery and ≥6 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 ≥50%.
Brodoefel 2008a[46]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – 75% Of the total patient	Catheter angiography – transfemoral and transradial Judkins technique, ≥2 projections for the right coronary artery and ≥6 projections for the left coronary artery, preformed by two

Study ID	Index test (assessed technology) details	Reference standard details
	population (not reported for HHRor HCS subgroups) were routinely taking β-blockers, no additional β-blockers were administered to any patient. Contrast agent – 80 ml of iomeprol (Imeron 400, Altana, Konstanz, Germany), i.v., flow rate of 5 ml /s, followed by 60 ml chaser bolus. Scan parameters – collimation 32 x 0.6 mm, slice acquisition 64 x 0.6 mm, gantry rotation time 330 ms, 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 ≥50%. Where there were multiple lesions per segment, the segment was classified by using the worst stenosis.	experienced cardiologists. Interpretation – One observer who was blinded to CT results assessed all angiograms. Positive stenosis was defined as diameter reduction ≥50%. Where there were multiple lesions per segment, the segment was classified by using the worst stenosis.
de Graaf 2010[43]	CT scanner – Aquilion ONE, Toshiba Medical Systems, Otawara, Japan. Use of β-blockers – Metoprolol was administered orally, 1 hour before data acquisition, to all patients with HR >65 bpm, unless contraindicated. Patients with a heart rate between 65 and 75 bpm received 50mg	Catheter angiography – 'standard techniques,' no further details reported Interpretation – One experienced observer, blinded to CT results. Positive stenosis was defined as lumen reduction ≥50%%, or the presence of significant stent edge (<5 mm from edge) stenosis in the view with the most

Study ID	Index test (assessed technology) details	Reference standard details
	metolprolol, patients with HR ≥ received 100mg metoprolol. Contrast agent – Tri-phasic injection of 60-80 ml of iomeprol (Iomeron 400, Bracco, Milan, Italy), flow rate of 5 or 6 ml /s, followed by 20 ml of 50% contrast/saline mix and finally 25 mL saline at 3 ml /s. Scan parameters – gantry rotation time 350 ms, tube current 400 to 580 mA (dependent upon BMI), and tube voltage 100 to 135 kV (dependent upon BMI). All images were acquired during a 5s 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 re stenosis was defined as lumen reduction ≥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 un-interpretable stents; non-diagnostic stents were classified as positive.	severe luminal narrowing.
LaBounty 2010[41]	CT scanner – 128-slice, dual source,	Catheter angiography – no details reported

Study ID	Index test (assessed technology) details	Reference standard details
	manufacturer not specified. Use of β-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 ≥50%.	Interpretation – blinded, experienced core laboratory. Positive stenosis was defined as diameter reduction ≥50%.
Leber 2007[47]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – No patients received β-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 20s, followed by 100 ml saline at 5 ml /s. Scan parameters – collimation 0.6 mm, 64 slices, gantry rotation time 330 ms, pitch 0.2–0.44, tube current 560 mA per rotation, and tube voltage 120 kV. Interpretation – Two independent	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
	investigators assessed the DSCT images. Positive stenosis was defined as diameter reduction >50%.	
Lin 2010[48]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – No patients received β-blockers prior to imaging. Contrast agent – continuous injection of 50 to 70 ml of iopamidol (Iopamiro 370 mg I/ml, Bracco, Milano, Italy) according to patient size, flow rate of 5 to 7 ml/s, followed by 50 ml saline. Scan parameters – collimation 32 x 0.6 mm, slice acquisition 64 x 0.6 mm, gantry rotation time 330 ms, pitch 0.2–0.43, tube current 400 mAs 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 >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 >50%.
Marwan 2010[49]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – 46 (77%) Of participants were on long-term β-blockers. In addition, 3 (5%) participants received 100 mg atenolol orally, before imaging, and 21 (35%) received	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.

Study ID	Index test (assessed technology) details	Reference standard details
	i.v. metoprolol (5-20 mg) before scanning. 8 patients (13.3) received diltiazem. Contrast agent – 60 to 110 ml of iopromide (370 mg iodine/ ml, Ultravist 370, Schering, Berlin, Germany), flow rate of 6 ml /s, followed by 50 ml saline. Scan parameters – collimation 2 x 64 x 0.6 mm, rotation time 330 ms, pitch 0.2–0.43, tube current 360 mAs or 400 mAs (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 >50%. Patients with one or more un-evaluable 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.	Positive stenosis was defined as diameter reduction ≥50%.
Meng 2009[50]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – no β-blockers were administered for scanning.	Catheter angiography – standard Judkins technique, ≥2 projections for the right coronary artery and ≥6 projections for the left coronary artery.

Study ID	Index test (assessed technology) details	Reference standard details
	Contrast agent – continuous injection of 80 ml bolus of iohexol (350 mg iodine/ ml, Amersham Heath, Princeton, NJ), flow rate of 5 ml/s, followed by 50 ml saline. Scan parameters – detector collimation 32 x 0.6 mm, slice acquisition 64 x 0.6 mm, gantry rotation time 330 ms, pitch 0.2–0.5, tube current 400 mAs 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 >50%.	Interpretation – One experienced cardiologist who was blinded to CT results assessed all angiograms. Positive stenosis was defined as diameter reduction >50%.
Oncel 2007[51]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – no additional medication for heart-rate control given. Contrast agent – bolus 70 ml iopromidum (Ultravist 350/ ml, Schering, Berlin, Germany), flow rate of 6 ml /s, followed by 50 ml bolus of saline at 5 ml /s. Scan parameters – with collimation, 64 x 0.6 mm slice thickness, rotation time 0.33 s, pitch	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
	0.26–0.45, tube current 900 mAs, 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.	
Oncel 2008[52]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – no β-blockers were given before scanning. Contrast agent – bolus 70 ml iomeprol (400 mg I/ ml Iomeron, Bracco, Italy), flow rate of 6 ml /s, followed by 50 ml bolus of saline at 5 ml /s. Scan parameters – collimation 32 x 0.6 mm, slice acquisition 64 x 0.6 mm, gantry rotation time 330 ms, pitch 0.2–0.47, tube current 390 mAs 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	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 ≥50% anywhere within the stent or within the 5mm segment proximal or distal to the stent margins..

Study ID	Index test (assessed technology) details	Reference standard details
	to ICA results and clinical information. Any disagreements were resolved by consensus. Positive in-stent re-stenosis was defined as diameter reduction ≥50%. Persistent stenosis was defined as ≥50% narrowing 5 mm proximal and distal to the stent.	
Pflederer 2009[53]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – Patients with a heart rate > 65 bpm received 100mg atenolol p.o. 45- 60 min. before DSCT. If heart rate remained > 65 bpm up to 4 doses metoprolol 5mg were given i.v. Contrast agent – bolus 60 to 95 ml iopromide (370 mg I/ ml Ultravist 3070, Schering, Berlin, Germany), flow rate of 6 ml/s, followed by 50 ml bolus of saline at 6 ml/s. Scan parameters – collimation 0.6 mm, simultaneous collection of 2 x 64 slices, gantry rotation time 330 ms, pitch 0.2–0.43, tube current 400 mAs, 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	Catheter angiography – to acquire ≥2 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.

Study ID	Index test (assessed technology) details	Reference standard details
	stenosis. Positive in-stent re-stenosis was defined as diameter reduction ≥50%. For patient based assessment non-assessable stents were classified as having in-stent re-stenosis using DSCT	
Pflederer 2010[37]	CT scanner – Somatom Definition FLASH, Siemens Healthcare, Forchheim, Germany. Use of β-blockers – NR Contrast agent – 60 to 90 ml i.v. unspecified contrast agent, flow rate of 6 ml/s. Scan parameters – collimation 2x128x0.6 mm, gantry rotation time 280 ms. 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 >50%.
Pugliese 2008[54] and Pugliese 2007[55]	CT Scanner – Somatom Definition, Siemens, Forchheim, Germany. Use of β-blockers – 70 (70%) Of patients were on treatment with β-blockers, none received additional β-blockers prior to scanning. Contrast Agent – 60-100ml contrast agent (Iomeron 400 mg/ml, Bracco, Italy) was injected into the antecubital vein at a flow rate	Catheter angiography – no details reported Interpretation - A single observer unaware of the CT results examined the angiograms before contrast injection to identify the sites of stent implantation. Positive in-stent re-stenosis was defined as luminal narrowing >50%.

Study ID	Index test (assessed technology) details	Reference standard details
	of 5.0 ml/s, followed by a saline chaser (40 ml). Scan parameters – collimation 2x32x0.6 mm gantry rotation time 330 ms, pitch 0.20 - 0.43, tube current 412 mAs/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 re-stenosis 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 un-interpretable and in-stent re-stenosis could not be excluded the stents were considered to have re-stenosis.	
Rist 2009[56]	CT scanner – Somatom Definition, Siemens Medical Systems, Forchheim, Germany. Use of β-blockers – β-blockers were not administered before the examination, 16 patients were receiving continuous β-blocker treatment, which was not interrupted for the examination.	Catheter angiography – ≥2 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 ≥50%.

Study ID	Index test (assessed technology) details	Reference standard details
	Contrast agent – body weight adapted (1.25 ml/kg Ultravist, Iopromide 370 I/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 ms, pitch 0.2–0.43, tube current time product 410 mAs/rotation, effective tube current time product 360 mAs, 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%.	
Rixe 2009[38]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – β-blockers were not administered before the examination. Contrast agent – no details reported. Scan parameters – collimation 64 x 0.6 mm, no further details. Interpretation – No details of who interpreted scans were reported. Positive stenosis was defined as diameter reduction >50%. Un-	Catheter angiography – no details reported 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
	assessable segments were regarded as having significant stenosis.	
Ropers 2007[42]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – β-blockers were not administered before the examination. 34 patients were taking routinely β-blockers, which were not discontinued for the examination. Contrast agent – ≥60 ml (Omnipaque 350, Schering AGF, Berlin, Germany) i.v., flow rate 5 ml/s, followed by 50 ml saline at 5 ml/s. Scan parameters – collimation 0.6 mm, 2 x 64 slices, gantry rotation time 330 ms, pitch 0.2–0.43, tube current 400 mAs/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 >50%. Un-evaluable 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 >50%.
Ropers 2008[40]	CT scanner – DSCT-Scanner, no details reported.	Catheter angiography – no details reported Interpretation – No details of who interpreted

Study ID	Index test (assessed technology) details	Reference standard details
	Use of β-blockers – NR Contrast agent – NR Scan parameters – collimation 0.6 mm, 2 x 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 ≥50%.	angiograms were reported. Positive stenosis was defined as diameter reduction ≥50%.
Scheffel 2006[57]	CT scanner – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany. Use of β-blockers – β-blockers were not administered before the examination. Three patients took β-blockers as part of their baseline medication. Contrast agent – bolus 80 ml iodixanol i.v. (Visipaque 320, 320 mg/ ml, GE Healthcare, Buckinghamshire, UK), followed by 30 ml saline at 5 ml /s. Scan parameters – collimation 32 x 0.6 mm, 64 x 0.6 mm slice acquisition, gantry rotation time 330 ms, 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	Catheter angiography – 'standard techniques with multiple views stored ', no details reported. Interpretation – assessed by one experienced observer, blind to CT results. Positive stenosis was defined as diameter reduction >50%.

Study ID	Index test (assessed technology) details	Reference standard details
	were resolved by consensus. Positive stenosis was defined as diameter reduction >50%.	
Tsiflikas 2010[58] and Drosch[59]	CT – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany Use of β-blockers – 35 of 41 Patients were on daily β-blockers treatment. NR Contrast agent – 70 mL (90mL in patients with coronary artery bypass grafts) Imeron 400mg iodine/ml at a flow-rate of 5 mL/s, followed by a saline chaser bolus (50 mL, flow-rate 5mL/s) Scan parameters – 0.6 mm collimation (cardiac mode), 330 ms gantry rotation time, pitch 0.2 – 0.43 (automatically adapted to the patients' heart rate). Tube current for both tubes was 560mA and tube voltage was 120 kV. Interpretation – All CT data sets were interactively assessed by two experienced observers who were not aware of patient's clinical information or the coronary angiographic findings. Positive stenosis was defined as >50% diameter reduction.	Catheter angiography – No details reported 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 define as >50% diameter reduction.
Van Mieghem 2007[39]	CT – DSCT (unspecified). No further details reported.	Catheter angiography – no details reported. Interpretation – Positive stenosis was defined

Study ID	Index test (assessed technology) details	Reference standard details
	Interpretation – Positive stenosis was defined as > 50% diameter reduction. No further details reported.	as > 50% diameter reduction. No further details reported.
Weustink 2009b[60]	CT – Somatom Definition Siemens Healthcare, Forchheim, Germany Use of β-blockers – No β-blockers were administered before scanning. 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 to 5.0 ml/s). Scan parameters –collimation 2 x 32 x 0.6, rotation time 330 ms, pitch 0.20-0.53, tube current 380 mAs/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 datasets. Any disagreements were resolved by discussion. Positive stenosis was defined as ≥50% lumen diameter reduction.	Catheter angiography – no details reported Interpretation – One experienced cardiologist, unaware of the results of the CTA, identified all graft segments, distal runoffs, and native coronary segments. Lesions with ≥50% lumen diameter reduction in 2 orthogonal planes were considered positive for stenosis. Distal runoff 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 <1.5 mm were excluded. Stents with un-interpretable lumen were classified as having in–stent re-stenosis.
Weustink 2009a[61]	CT – Somatom Definition Siemens Healthcare, Forchheim, Germany	Catheter angiography – no details reported

Study ID	Index test (assessed technology) details	Reference standard details
	Use of β-blockers – no β-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/sec) in an antecubital vein followed by a saline chaser (40 mL; flow rate, 5.5 mL/sec). Scan parameters - two x-ray tubes, 32 detector rows of 0.6 mm each, rotation time 330 msec, pitch 0.2-0.53, tube voltage, 120 kV; and full tube current, 625mA (independent of patient size). Interpretation – 2 Experienced observers each with 5 or more 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 analyzed even if the image quality was impaired.	Interpretation – 3 cardiologists with 5 or more 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 ≥ 50%.

Study ID	Index test (assessed technology) details	Reference standard details
Zhang 2010[62]	CT – Somatom Definition, Siemens Medical Solutions, Forchheim, Germany) Use of β-blockers – No β-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/s). Scan parameters –rotation time of 0.33 s, tube voltage of 120 kVp, effective tube current of 330 mAs, 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 datasets. Positive stenosis was defined as ≥50% diameter reduction. A true positive 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, Wisc., 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.

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[44]	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. {ref Morise 1997}	Renal insufficiency (creatinine > 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 Calcium score 568±807 Type II DM 14 (18.7%) Family history CAD 8 (10.7%) Hyperlipidemia 32 (42.7%) Symptomic angina 64 (85.3%)
Brodoefel 2008b[45]	Total 125 Obese 44	Patients scheduled for catheter angiography for suspected CAD or suspected progression of known CAD.	Renal insufficiency (serum creatinine >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 Calcium score 741±968 DM 15 (34.1%) Hypertension 41 (93.2%)
Brodoefel 2008a[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 >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	Total: Age (years) 62 ± 10 Male/female 80/20 Adiposis 61 (61%) HR 64.9±13.2 Calcium score 786.5±965.9 DM 24 (24%)

Study ID	Total participants (n) Participant group (n)	Inclusion criteria	Exclusion criteria	Participant characteristics
			surgery.	Hypertension 85 (85%)
de Graaf 2010[43]	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/min, known allergy to iodinated contrast media, severe claustrophobia, pregnancy, high heart rate in the presence of contraindications to β-blockade.	Stented: Age (years) 65±13 Male/female 37/16 BMI (kg/m^2) 27±3 HR 59±12 DM 12 (23%) Family history of CAD 16 (30%) Hypertension 43 (81%) Hypercholesterolemia 45 (85%) Previous MI 28 (53%) Previous bypass graft 8 (15%)
LaBounty 2010[41]	Total 81 With stents, unclear (54 stents)	NR	NR	NR
Leber 2007)[47]	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.{ref Morise 1997}	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) DM 8 (8.9%) Family history of CAD 27 (30%) Hypertension 65 (72.2%) Hypercholesterolemia 36 (40%) Angina 73 (81.1%) Permanent β-blocker use 23 (25.6%)
Lin 2010[48]	Total 44 HHR 18	Patients suspected CAD and inconclusive cardiac	Allergy to iodinated contrast material, renal insufficiency	HR≥70 bpm: Age (years) 59.2±10.3

Study ID	Total participants (n) Participant group (n)	Inclusion criteria	Exclusion criteria	Participant characteristics
		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.	(creatinine level >120 µmol/l), pregnancy, hemodynamic instability, previous coronary stent implantation or bypass, >3 months between CT and ICA.	Male/female 13/5 BMI (kg/m^2) 26.6±2.6 HR 80.1±10.4 DM 4 (22.2%) Family history of CAD 4 (22.2%) Hypertension 7 (38.9%) Angina 13 (72.2%)
Marwan 2010[49]	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 β-blockers and calcium-channel blockers (mean HR >100 bpm).	AF: Age (years) 71±7 Male/female 34/26 BMI (kg/m^2) 29±5 HR 70±15 DM 16 (27%) Family history of CAD 10 (17%) Hypertension 56 (93%) Long term β-blockers 46 (77%) High likelihood of CAD 24 (40%) Intermediate likelihood of CAD 21 (35%)
Meng 2009[50]	Total 109 HHR 50 HCS 17	Patients with suspected CAD.	Allergy to iodinated contrast media, thyroid disorder, renal insufficiency (creatinine >120 µmol/l), pregnancy, hemodynamic instability, previous stent implantation or bypass graft.	Total: Age (years) 63±9 Male/female 68/41 BMI (kg/m^2) 26.9±3.3 HCC (Agatston units) 226.5 HR (bpm) 71.8±13.2 DM 15 (13.7%) Hypertension 75 (68.8%)
Oncel	Total 15	Patients with AF who were	Unstable clinical condition,	AF:

Study ID	Total participants (n) Participant group (n)	Inclusion criteria	Exclusion criteria	Participant characteristics
2007[51]	AF 15	suspected of having co-existing CAD and were scheduled to undergo ICA.	known allergy to iodinated contrast media, elevated serum creatinine (>1.5 mg/dl, >132.6 µmol/l), previous stent implantation or bypass graft, inability to follow breath-hold instructions.	Age (years) 58.5±9.1 Male/female 9/6 HR 83.7±8.9 bpm
Oncel 2008[52]	Total 35 With stents 35 (48 stents)	Patients with suspected in-stent re-stenosis, 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 >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 DM 8 (23%) Family history of CAD 18 (52%) Hypertension 21 (59%) Hypercholesterolemia 24 (68%) Angina 22 (63%) Serum creatinine 1±0.29 mg/dl
Pflederer 2009[53]	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 >1 implanted stent (≥2 stents implanted in bifurcation lesions, contiguous or slightly overlapping stents, and stent-in-stent implantation, any stent diameter < 3.0 mm, and stents implanted	With stents: Age (years) 65±11 Male/female 70/42 BMI (kg/m^2) 28.0±3.9 HR 60±9 bpm

Study ID	Total participants (n) Participant group (n)	Inclusion criteria	Exclusion criteria	Participant characteristics
			in bypass grafts.	
Pflederer 2010[37]	Total 55 Revascularised 55 (42 bypass grafts and 78 stents)	Patients with previous revascularisation who were scheduled for ICA.	NR	Total: HR 58±7 bpm
Pugliese 2008[54] and Pugliese 2007[55]	Total: 100 Stent: 100 Stent + High HR: 31	Patients with chest pain and prior stent implantation.	Serum creatinine > 120 μmol/l, irregular heart rhythm, known allergy to iodinated contrast media	All: Age (years) 62±10 M/F 78/22 Obesity (BMI ≥ 30 kg/m^2) 23 (23%) DM 21 (21%) Family history of CAD 29 (29%) Hypertension (≥ 160/95 or ongoing treatment) 45 (45%) Hypercholesterolemia (> 200 mg/dl (5.18 mmol/l) 51 (51%)
Rist 2009[56]	Total 68 AF 68	Patients with chronic AF who were referred for CT coronary angiography.	Hyperthyroidism (TSH <0.3 mU/l), renal insufficiency (serum creatinine>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 (bpm) 77±25
Rixe 2009[38]	Total 30 AF 30	Patients with AF and suspected CAD.	NR	AF: Age (years) 64.9±14 Male/female 21/9 HR 73±16
Ropers	Total 100	Consecutive patients	Renal insufficiency (creatinine	HHR:

Study ID	Total participants (n) Participant group (n)	Inclusion criteria	Exclusion criteria	Participant characteristics
2007[42]	HHR 44	recruited for a first diagnostic angiogram for suspected CAD.	>1.5 mg/dl), in non-sinus rhythm, previously known CAD, previous stent implantation or bypass graft, acute coronary syndrome, hemodynamic instability.	Age (years) 60 Male/female 29/15 BMI (kg/m^2) 28 HR (bpm) 76±9
Ropers 2008[40]	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[57]	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 >120 µmol/l), pregnancy, hemodynamic 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±8.4bpm 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±15.1bpm 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±14.2bpm

Study ID	Total participants (n) Participant group (n)	Inclusion criteria	Exclusion criteria	Participant characteristics
				Calcium score 821±904 DM 19 (63.3%) Family history of CAD 16(53.3%) Hypertension 23 (76.7%) Angina 21 (70%)
Tsiflikas 2010[58] and Drosch[59]	Total: 44 Arrhythmia: 44	Patients scheduled for invasive coronary angiography because of suspected or known coronary artery disease without stable sinus rhythm.	Elevated serum creatinine levels > 1.5 mg/dl, unstable angina, thyroid disease, pregnancy, or patients with previous allergic reactions to iodinated contrast media.	Arrhythmia: Age (years): 68±9 M/F 31/13 BMI (kg/m^3) 27.9±4.3 Obesity 26 (59%) HR 69±14 bpm Calcium score 762 (range 0-4949.7) AF 25 (57%) DM 9 (20%) Hypertension 38 (86%) Family history of CAD 31 (70%) Previous stent implantation 19 (41%) Previous bypass graft 5 (11%) β-blocker use 35 (85%)
Van Mieghem 2007[39]	Total: 33 Stents: 33	Symptomatic patients, scheduled for invasive coronary angiography, who had previous PCI with large diameter (≥3 mm) stents.	Previous bypass graft.	NR
Weustink 2009b[60]	Total: 52 CABG: 52 CABG + high HR: NR	Symptomatic patients after surgical revascularisation with sinus heart rhythm, able to breath-hold for 15 s, and	Allergy to iodinated contrast media, impaired renal function (serum creatinine >120 μmol), AF, logistic inability to undergo a	CABG: Age (years) 66±13.2 M/F 41/11 BMI (kg/m^2) 27.2±5.8

Study ID	Total participants (n) Participant group (n)	Inclusion criteria	Exclusion criteria	Participant characteristics
		no previous coronary intervention	CT scan before ICA	HR 64.4±14.3 bpm DM 19 (37) Family history of CAD 21 (40%) Hypertension 16 (31) Previous MI 22 (42%) Long-term β-blockers 47 (90) Single bypass graft 11(21) Two bypass grafts 31 (60) Three bypass grafts 9 (17)
Weustink 2009a[61]	Total 927 Intermediate HR: 170 HHR: 85	Symptomatic patients with suspected or known coronary artery disease.	Previous surgical revascularisation, atrial fibrillation with fast ventricular response, known allergy to iodinated contrast media, impaired renal function (serum creatinine > 120 μmol).	Intermediate HR group: Age (years): 61.0±11.4 M/F 193/140 HR 71.9±3.7 bpm Long-term β-blocker use 134 (40.2%) High HR group: Age (years) 56.2±10.3 M/F 88/83 HR 88.8±8.4 bpm Long-term β-blocker use 53 (31.0%)
Zhang 2010[62]	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), hemodynamic stability, non-pregnant status for women of child-bearing age, and	Failure to undergo CCA due to occluded iliac arteries, chest pain during examination	Total: Age(years) 64±12 M/F 82/31 Atypical Angina 46 (40.7%) Typical Angina 37 (32.7%) Unstable CAD 30 (26.5%)

Study ID	Total participants (n) Participant group (n)	Inclusion criteria	Exclusion criteria	Participant characteristics
		without previous stent or bypass surgery. Patients with non-sinus rhythm, obesity, or high coronary calcium were not excluded.		

Appendix 5: Table 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 in difficult to image CAD patients of 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 section 5.1.

index test – The study did not assess the effectiveness of one of the four assessed technologies specified in section 5.1.

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 section 5.1, OR, for diagnostic test accuracy studies, insufficient data were reported to allow the construction of 2 x2 contingency tables (numbers of TP, FN, FP, and TN test results).**

study design **– The study design was not one of those specified in section 5.1, OR the study included <10 participants in the relevant patient groups.**

[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(2):117-21. – **outcomes, M**

[2] Achenbach S, Ropers U, Kuettner A, Anders K, Pflederer T, Komatsu S, et al. Randomized comparison of 64-slice single- and dual-source computed tomography coronary angiography for the detection of coronary artery disease. *JACC Cardiovasc Imaging* 2008;1(2):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(1):170-175. – **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(6):500-506. – **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(1):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(7):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(18):S845-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(9A):8B-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(16):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(3):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 catheterization]. *Radiologe* 2007;47(4):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; 2009 22-25 Oct; Brisbane, Australia. *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, 2009 39-31 Sep; Orlando, United States. *J Am Coll Cardiol* 2009;53(10):A267-A268. – **population**

[14] Chang Gung Memorial Hospital. The correlation of heart hemodynamic status between 320 multidetector computed tomography, echocardiography and cardiac catheterization in patients with coronary artery disease.NCT01083134 [ongoing trial]. 2010 [cited 11.5.11]. Available from: http://ClinicalTrials.gov/show/NCT01083134 – **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(15):1916-1923. – **outcomes** (2x2 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(3):223-228. – **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(3):165-171. – **population**

[18] Chen S-y, Su Y-s, Xie P-y, Xu S-l, Fang Y-q, Huang A-r. [Clinical value of dual-source CT in evaluating coronary artery disease]. *Nan Fang Yi Ke Da Xue Xue Bao* 2010;30(9):2125-7. – **population**

[19] Chinnaiyan KM, McCullough PA, Flohr TG, Wegner JH, Raff GL. Improved noninvasive coronary angiography in morbidly obese patients with dual-source computed tomography. *J Cardiovasc Comput Tomogr* 2009;3(1):35-42. – **outcomes**

[20] de Graaf FR, Schuijf JD, van Velzen JE, Kroft LJ, de Roos A, Reiber JH, et al. Diagnostic accuracy of 320-slice multi-slice computed tomography in the non-invasive assessment of obstructive atherosclerosis. *Circulation* 2009;120(18):S334-S334. – **population**

[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(15):1908-15. – **population**

[22] Dewey M, Oncel D, Oncel G, Tastan A. Coronary CT angiography in patients with atrial fibrillation. *Radiology* 2008;248(2):701-2. – **study design**

[23] Dewey M, Vavere AL, Arbab-Zadeh A, Miller JM, Sara L, Cox C, et al. Patient characteristics as predictors of image quality and diagnostic accuracy of mdct compared with conventional coronary angiography for detecting coronary artery stenoses: core-64 multicenter international trial. *AJR Am J Roentgenol* 2010;194(1):93-102. . – **index test**

[24] Dewey M, Zimmermann E, Deissenrieder F, Laule M, Dbel HP, Rutsch W, et al. 320-slice computed tomography for detection of coronary artery stenoses. Presented at American College of Cardiology 58th Annual Scientific Session and i2 Summit: Innovation in Intervention, 2009 39-31 Mar; Orlando, United States. *J Am Coll Cardiol* 2009;53(10):A265. – **population**

[25] Dewey M, Zimmermann E, Deissenrieder F, Laule M, Dubel HP, Schlattmann P, et al. Noninvasive coronary angiography by 320-row computed tomography with lower radiation exposure and maintained diagnostic accuracy: Comparison of results with cardiac catheterization in a head-to-head pilot investigation. *Circulation* 2009;120(10):867-875. – **study design, M**

[26] Dewey M, Zimmermann E, Laule M, Rutsch W, Hamm B. Three-vessel coronary artery disease examined with 320-slice computed tomography coronary angiography. *Eur Heart J* 2008;29(13):1669. – **population**

[27] Dikkers R, Willems TP, Piers LH, de Jonge GJ, Tio RA, van der Zaag-Loonen HJ, et al. Coronary revascularisation treatment based on dual-source computed tomography. *Eur Radiol* 2008;18(9):1800-8. – **population**

[28] Domachevsky L, Gaspar T, Peled N, Shnapp M, Halon DA, Lewis CBS, et al. Non-invasive cardiac imaging of morbidly obese patients using the brilliance iCT. *MedicaMundi* 2010;54(1):29-34. – **study design, M**

[29] Duan H, San K-j, Wang J, Han D. [Analyzing the correlation between coronary artery stenosis and left ventricular function and myocardial ischemia using dual-source computed tomography]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2010;32(6):683-9. – **population**

[30] Earls JP, Schrack EC. Prospectively gated low-dose CCTA: 24 months experience in more than 2,000 clinical cases. *Int J Cardiovasc Imaging* 2009;25(Supp 2):177-187. – **study design, M**

[31] Fang XM, Chen HW, Hu XY, Bao J, Chen Y, Yang ZY, et al. Dual-source CT coronary angiography without heart rate or rhythm control in comparison with conventional coronary angiography. *Int J Cardiovasc Imaging* 2010;26(3):323-31. – **population**

[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 [cited 11.5.11]. Available from: http://ClinicalTrials.gov/show/NCT00632918 – **outcomes**

[33] Fareed A, Oraby M, Nasr GM, Maklady F, Dupouy P. Evaluation of Coronary CT scans radiation dose and image quality using different scanning protocol on a 256-slice CT scanner. *Eur Heart J Suppl* 2010;12(F):F59-F59. – **population**

[34] George RT, Kitagawa K, Laws K, Lardo AC, Lima JA. Combined adenosine stress perfusion and coronary angiography using 320-row detector dynamic volume computed tomography in patients with suspected coronary artery disease. *Circulation* 2008;118(18):S936-S936. – **population**

[35] George RT, Lardo AC, Kitagawa K, Yousuf O, Chang HJ, Arbab-Zadeh A, et al. Combined perfusion and non-invasive coronary angiography in patients with suspected coronary disease using 256 row, 0.5 mm slice thickness non-helical multi-detector computed tomography. *Circulation* 2007;116(16):2589. – **population**

[36] Gutstein A, Wolak A, Lee C, Dey D, Ohba M, Suzuki Y, et al. Predicting success of prospective and retrospective gating with dual-source coronary computed tomography angiography: development of selection criteria and initial experience. *J Cardiovasc Comput Tomogr* 2008;2(2):81-90. – **population, M**

[37] Haraldsdottir S, Gudnason T, Sigurdsson AF, Gudjonsdottir J, Lehman SJ, Eyjolfsson K, et al. Diagnostic accuracy of 64-slice multidetector CT for detection of in-stent restenosis in an unselected, consecutive patient population. *Eur J Radiol* 2010;76(2):188-194. – **index test**

[38] Hausleiter J, Gramer B, Meyer T, Bischoff B, Hadamitzky M, Spiegel S, et al. Myocardial CT perfusion with a high-pitch low-dose protocol. Presented at European Society of Cardiology, ESC Congress, 2010 28 Aug-1 Sep, Stockholm, Sweden. *Eur Heart J* 2010;31:581. – **population**

[39] Herzog BA, Husmann L, Burkhard N, Gaemperli O, Valenta I, Tatsugami F, et al. Accuracy of low-dose computed tomography coronary angiography using prospective electrocardiogram-triggering: first clinical experience. *Eur Heart J* 2008;29(24):3037-3042. – **population**

[40] Heuschmid M, Burgstahler C, Reimann A, Brodoefel H, Mysal I, Haeberle E, et al. Usefulness of noninvasive cardiac imaging using dual-source computed tomography in an unselected population with high prevalence of coronary artery disease. *Am J Cardiol* 2007;100(4):587-92. – **population**

[41] Ho KT, Chua KC, Klotz E, Panknin C. Stress and rest dynamic myocardial perfusion imaging by evaluation of complete time-attenuation curves with dual-source CT. *JACC Cardiovasc Imaging* 2010;3(8):811-820. – **population**

[42] Hope SA, Crossett M, Nasis A, Seneviratne S. Early experience with the Aquilion One 320 slice computerised tomography scanner in paediatric and congenital heart disease. Presented at 5th World Congress of Paediatric Cardiology and Cardiac Surgery, 2010 21-16 Jun; Cairns, Australia. *Cardiol Young* 2010;20:37. – **outcomes, M**

[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* 2010. – **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* 2010. – **reference standard, M**

[45] Izumi M, Fujiwara R, Ono Y, Ito H. First impact of 320-slice area detector computed tomography for evaluation of coronary images as compared with 64-slice spiral detector computed tomography. Presented at 9th International Conference of Non-Invasive Cardiovascular Imaging, 2009 10-13 May; Barcelona, Spain. *Eur Heart J* 2009;11(Suppl):S3. – **population**

[46] Johnson TR, Nikolaou K, Busch S, Leber AW, Becker A, Wintersperger BJ, et al. Diagnostic accuracy of dual-source computed tomography in the diagnosis of coronary artery disease. *Invest Radiol* 2007;42(10):684-691. – **population**

[47] Kepka C, Pregowski J, Kruk M. Dual source computed tomography in coronary imaging. *Postepy Kardiol Interwencyjnej* 2008;4(1):31-34. – **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(5):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; 2010 5-8 Aug; Adelaide, Australia. *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, 2010 28 Aug-1 Sep; Stockholm, Sweden. *Eur Heart J* 2010;31:152. – **population**

[51] Korosoglou G, Mueller D, Lehrke S, Steen H, Hosch W, Heye T, et al. Quantitative assessment of stenosis severity and atherosclerotic plaque composition using 256-slice computed tomography. *Eur Radiol* 2010;20(8):1841-1850. – **population, M**

[52] Kroft LJM, Roelofs JJH, Geleijns J. Scan time and patient dose for thoracic imaging in neonates and small children using axial volumetric 320-detector row CT compared to helical 64-, 32-, and 16- detector row CT acquisitions. *Pediatr Radiol* 2010;40(3):294-300. – **population, M**

[53] Leber A, Ovrehus K, Tittus J, Johnson T, Becker C, Becker A. Noninvasive coronary angiography by dual source computed tomography in patients with an intermediate pretest likelihood for coronary artery disease. *Circulation* 2007;116(16):2593. – **population**

[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(18):448-448. – **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(9):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(2):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 [cited 11.5.11]. Available from: http://ClinicalTrials.gov/show/NCT00622167 – **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(18):384-384. – **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(7):773-775. – **population**

[60] Nance JW, Jr., Bastarrika G, Kang DK, Ruzsics B, Vogt S, Schmidt B, et al. High-temporal resolution dual-energy computed tomography of the heart using a novel hybrid image reconstruction algorithm: initial experience. *J Comput Assist Tomogr* 2011;35(1):119-25. – **population**

[61] Nasis A, Leung MC, Antonis PR, Cameron JD, Lehman SJ, Hope SA, et al. Diagnostic accuracy of noninvasive coronary angiography with 320-detector row computed tomography. *Am J Cardiol* 2010;106(10):1429-35. – **study design** (<10 participants)**, M**

[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, 2009 21-25 Sep; San Francisco, United States. *Am J Cardiol* 2009;104(6A):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, 2010 14-16 Mar; Atlanta, United States. *J Am Coll Cardiol* 2010;55(10 Suppl 1):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, SCCT2010, 2010 15-18 Jul; Las Vegas, United States. *J Cardiovasc Comput Tomogr* 2010;4(4 Suppl 1):s49. – **outcomes**

[65] Opolski MP, Pregowski J, Kepka C, Kruk M, Pracon R, Ruzyllo W. Dual source computed tomography in visualization of coronary artery anomalies. *Postepy Kardiol Interwencyjnej* 2008;4(4):133-145. – **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(6):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(8A):97I-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(3):186-194. – **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(7):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(23):2902-2907. – **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(43):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(7):478-481. – **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(2):195-203. – **population**

[74] Rocha JA, Blankstein R, Shturman LD, Bezerra HG, Okada DR, Rogers IS, et al. Incremental value of adenosine-induced stress myocardial perfusion imaging with dual-source CT at cardiac CT angiography. *Radiology* 2010;254(2):410-419. – **population**

[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, 2009 29-31 Mar; Orlando, United States. *J Am Coll Cardiol* 2009;53(10):A259. – **population**

[76] Ropers D. Heart rate-independent dual-source computed tomography coronary angiography: growing experience. *J Cardiovasc Comput Tomogr* 2008;2(2):115-6. – **study design**

[77] Ropers U, Karakaya S, Wechsel M, Anders K, Ropers D, Kuettner A, et al. Randomized comparison of dual source computed tomography and 64-slice multi-detector computed tomography for the detection of coronary artery stenoses. *Circulation* 2006;114(18):448-448. – **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(2):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(5):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 ischemia: comparison with SPECT. *Circulation* 2008;118(18):S838-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 ischemia-initial experience. *Eur Radiol* 2008;18(11):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(3):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(1):226-227. – **study design**

[84] Schoenhagen P, Nagel E. Noninvasive assessment of coronary artery disease anatomy, physiology, and clinical outcome. *JACC Cardiovasc Imaging* 2011;4(1):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(18):S381-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(6):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, 2010 11-13 Aug; Beijing, China. *Cardiology* 2010;117:114-115. – **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(4):321-321. – **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(2):212-8. – **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(1):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* 2010. – **population, M**

[92] University Medical Centre Groningen. Computed tomographic angiography or conventional coronary angiography in clinical decision making. NCT00566059 [completed trial]. 2007 [cited 11.5.11]. Available from: http://ClinicalTrials.gov/show/NCT00566059 – **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 [cited 11.5.11]. Available from: http://ClinicalTrials.gov/show/NCT00482651 – **index test**

[94] Wagdi P, Alkadhi H. The impact of cardiac CT on the appropriate utilization of catheter coronary angiography. *Int J Cardiovasc Imaging* 2010;26(3):333-344. – **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(3):434-441. – **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(2):160-165. – **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, 2010

15-18 Jul; Las Vegas, United States. *J Cardiovasc Comput Tomogr* 2010;4(4 Suppl 1):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(18):448-448. – **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(9):114A-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(5):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, 2010 21-25 Sep; Washington, United States. *J Am Coll Cardiol* 2010;56(13 Suppl 1):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, 2010 28 Aug-1 Sep, Stockholm, Sweden. *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(2):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(1):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(3):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(6):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(Suppl 1):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, 2010 14-16 May; Atlanta, United States. *J Am Coll Cardiol* 2010;55(10 Suppl 1):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(3):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(17):5209-22. – **outcomes**

[8] Einstein AJ. Radiation risk from coronary artery disease imaging: how do different diagnostic tests compare? *Heart* 2008;94(12):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(12):927-32. – **index test**

[10] Gaudio C, Evangelista A, Pasceri V, Pannarale G, Varrica S, Romitelli S, et al. Visualization of coronary arteries and coronary stents by low dose 320-slice multi-detector computed tomography in a patient with atrial fibrillation. *Int J Cardiol* 2010. – **study design**

[11] Gerber TC, Carr JJ, Arai AE, Dixon RL, Ferrari VA, Gomes AS, et al. Ionizing 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(7):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(12):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(Supp 2):267-278. – **population**

[14] Heilbron BG, Leipsic J. Submillisievert coronary computed tomography angiography using adaptive statistical iterative reconstruction: a new reality. *Can J Cardiol* 2010;26(1):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(Supp 2):231-239. – **study design**

[16] Hsieh J, Londt J, Vass M, Li J, Tang X, Okerlund D. Step-and-shoot data acquisition and reconstruction for cardiac x-ray computed tomography. *Med Phys* 2006;33(11):4236-48. – **study design**

[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(2):191-7. – **study design**

[18] Kitagawa K, Lardo AC, Lima JAC, George RT. Prospective ECG-gated 320 row detector computed tomography: implications for CT angiography and perfusion imaging *Int J Cardiovasc* 2009;25(Supp 2):201-208. – **study design**

[19] Klass O, Walker M, Siebach A, Stuber T, Feuerlein S, Juchems M, et al. Prospectively gated axial CT coronary angiography: comparison of image quality and effective radiation dose between 64- and 256-slice CT. *Eur Radiol* 2010;20(5):1124-31. – **outcomes**

[20] LaBounty TM, Earls JP, Leipsic J, Heilbron B, Mancini GBJ, Lin FY, et al. Effect of a standardized quality-improvement protocol on radiation dose in coronary computed tomographic angiography. *Am J Cardiol* 2010;106(11):1663-7. – **index test**

[21] LaBounty TM, Leipsic J, Min JK, Heilbron B, Mancini GBJ, Lin FY, et al. Effect of padding duration on radiation dose and image interpretation in prospectively ECG-triggered coronary CT angiography. *AJR Am J Roentgenol* 2010;194(4):933-7. – **outcomes**

[22] Law WY, Yang CC, Chen LK, Huang TC, Lu KM, Wu TH, et al. Retrospective gating vs. prospective triggering for noninvasive coronary angiography: assessment of image quality and radiation dose using a 256-slice CT scanner with 270 ms gantry rotation. *Acad Radiol* 2011;18(1):31-9. – **outcomes**

[23] Lehman S, Malaiapan Y, Antonis P, Zhang M, Cameron J, Meredith I, et al. Assessment of coronary plaque presence and composition by 320-slice cardiac computed tomography: a comparative study using intravascular ultrasound. Presented at New Zealand Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand, 2010 5-8 Aug; Adelaide, Australia. *Heart Lung Circ* 2010;19:s164. . – **reference standard**

[24] Leipsic J, Labounty TM, Heilbron B, Min JK, Mancini GBJ, Lin FY, et al. Estimated radiation dose reduction using adaptive statistical iterative reconstruction in coronary CT angiography: the ERASIR study. *AJR Am J Roentgenol* 2010;195(3):655-60. – **outcomes**

[25] Leipsic J, Labounty TM, Heilbron B, Min JK, Mancini GBJ, Lin FY, et al. Adaptive statistical iterative reconstruction: assessment of image noise and image quality in coronary CT angiography. *AJR Am J Roentgenol* 2010;195(3):649-54. – **outcomes**

[26] Lell M, Marwan M, Schepis T, Pflederer T, Anders K, Flohr T, et al. Prospectively ECG-triggered high-pitch spiral acquisition for coronary CT angiography using dual source CT: technique and initial experience. *Eur Radiol* 2009;19(11):2576-83. – **outcomes**

[27] Lembcke A, Hein PA, Borges AC, Rogalla P. One-stop-shop cardiac diagnosis in a single heart beat using 320-slice computed tomography: ascending aortic aneurysm, hypertrophic cardiomyopathy and mixed valvular heart disease. *Eur J Cardiothorac Surg* 2009;35(4):726. – **study design**

[28] Leschka S, Stolzmann P, Desbiolles L, Baumueller S, Goetti R, Schertler T, et al. Diagnostic accuracy of high-pitch dual-source CT for the assessment of coronary stenoses: first experience. *Eur Radiol* 2009;19(12):2896-903. – **population**

[29] Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, et al. Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. *Health Technol Assess* 2008;12(17):iii-143. – **index test**

[30] Perisinakis K, Seimenis I, Tzedakis A, Papadakis AE, Damilakis J. Individualized assessment of radiation dose in patients undergoing coronary computed tomographic angiography with 256-slice scanning. *Circulation* 2010;122(23):2394-402. – **population**

[31] Rybicki FJ, Melchionna S, Mitsouras D, Coskun AU, Whitmore AG, Steigner M, et al. Prediction of coronary artery plaque progression and potential rupture from 320-detector row prospectively ECG-gated single heart beat CT angiography: Lattice Boltzmann evaluation of endothelial shear stress *Int J Cardiovasc Imaging* 2009;25(Supp 2):289-299. – **study design**

[32] Schuijf JD, Delgado V, Van Werkhoven JM, de Graaf FR, Van Velzen JE, Boogers MM, et al. Novel clinical applications of state-of-the-art multi-slice computed tomography *Int J Cardiovasc Imaging* 2009;25(Supp 2):241-254. – **study design**

[33] Uehara M, Funabashi N, Komuro I. Predictors of various artifacts in coronary arterial images in subjects with chronic atrial fibrillation by 320 slice computed tomography considering reconstruction method. Presented at American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in

Intervention, 2010 14-16 Mar; Atlanta, United States. *J Am Coll Cardiol* 2010;55(10 Suppl 1):A67.E626. – **study design**

[34] Walker MJ, Olszewski M, Desai MY, Halliburton SS, Flamm SD. New radiation dose saving technologies for 256-slice cardiac computed tomography angiography. *Int J Cardiovasc Imaging* 2009;25(Supp 2):189-199. – **study design**

[35] Weigold WG, Olszewski ME, Walker MJ. Low-dose prospectively gated 256-slice coronary computed tomographic angiography. *Int J Cardiovasc Imaging* 2009;25(Supp 2):217-230. – **study design**

[36] Wink O, Hecht HS, Ruijters D. Coronary computed tomographic angiography in the cardiac catheterization laboratory: current applications and future developments. *Cardiol Clin* 2009;27(3):513-29. – **study design**

Appendix 6: NICE guidance relevant to treatment of congenital heart disease in childhood.

Chest pain of recent onset. NICE clinical guideline 95 (2010). Available from www.guidance.nice.org.uk/CG95

Unstable angina and NSTEMI. NICE clinical guideline 94 (2010). Available from www.guidance.nice.org.uk/CG94

Stable angina: NICE draft clinical guideline for consultation.
Guidance on the use of coronary artery stents. NICE technology appraisal guidance 71 (2003). Available from www.guidance.nice.org.uk/TA71

Drug eluting stents for the treatment of coronary artery disease. NICE technology appraisal guidance 152 (2008). Available from www.guidance.nice.org.uk/TA152

SeQuent Please balloon catheter for in-stent coronary restenosis. NICE medical technologies guidance 1 (2010). Available from www.guidance.nice.org.uk/MTG1

Off-pump coronary artery bypass grafting. NICE interventional procedure guidance 35 (2004). Available from www.nice.org.uk/guidance/IPG35 (currently being updated with an expected publication in January 2011)

Balloon dilatation of pulmonary valve stenosis. NICE interventional procedures guidance 67 (2004). Available from www.guidance.nice.org.uk/IPG67

Balloon angioplasty with or without stenting for coarctation or recoarctation of aorta in adults and children. NICE interventional procedures guidance 74 (2004). Available from www.guidance.nice.org.uk/IPG74

Balloon dilatation with or without stenting for pulmonary artery or non-valvar right ventricular outflow tract obstruction in children. NICE interventional procedures guidance 76 (2004). Available from www.guidance.nice.org.uk/IPG76

Balloon dilatation of systemic to pulmonary arterial shunts in children. NICE interventional procedures guidance 77 (2004). Available from www.guidance.nice.org.uk/IPG77

Balloon valvuloplasty for aortic valve stenosis in adults and children. NICE interventional procedures guidance 78 (2004). Available from www.guidance.nice.org.uk/IPG78

Endovascular atrial septostomy. NICE interventional procedure guidance 86 (2004). Available from www.guidance.nice.org.uk/IPG86

Radiofrequency valvotomy for pulmonary atresia. NICE interventional procedure guidance 95 (2004). Available from www.guidance.nice.org.uk/IPG95

Endovascular closure of atril septal defect. NICE interventional procedure guidance 96 (2004). Available from www.guidance.nice.org.uk/IPG96

Endovascular closure of patent ductus arteriosus. NICE interventional procedure guidance 97. Available from www.guidance.nice.org.uk/IPG97

Intraoperative fluorescence angiography in coronary artery bypass grafting. NICE interventional procedure guidance 98 (2004). Available from www.nice.org.uk/guidance/IPG98

Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction. NICE interventional procedure guidance 237 (2007). Available from www.guidance.nice.org.uk/IPG237

Hybrid procedure for interim management of hypoplastic left heart syndrome in neonates. NICE interventional procedures guidance 246 (2007). Available from www.guidance.nice.org.uk/IPG246

Percutaneous laser revascularisation for refractory angina pectoris. NICE interventional procedures guidance 302 (2009). Available from www.nice.org.uk/guidance/IPG302

Transmyocardial laser revascularisation for refractory angina pectoris. NICE interventional procedures guidance 301 (2009). Available from www.nice.org.uk/guidance/IPG301

Transcatheter endovascular closure of perimembranous ventricular septal defect. NICE interventional procedure guidance 336 (2010). Available from www.guidance.nice.org.uk/IPG336

Endoscopic saphenous vein harvest for coronary artery bypass grafting. NICE interventional procedures guidance 343 (2010). Available from www.guidance.nice.org.uk/IPG343