MULTI-SLICE COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY FOR THE DETECTION OF CORONARY ARTERY DISEASE IN A DISTRICT HOSPITAL SETTING

A thesis by

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I dedicate this thesis to Dr Kerry Jane Hogg (b 1959; d 25th December 2010) whose clinical excellence and devotion to her patients inspired my career in cardiology.

She is greatly missed.

Declaration

The work described in this thesis was carried out while I was employed as a Clinical Research Fellow in the Department of Cardiology at Stobhill Hospital in Glasgow between August 2006 and August 2008.

Multi-slice CT coronary angiography was performed by Mrs M Drummond and Mrs JA Kelly, supervised by myself and reported by Dr J Shand, Dr G McKillop and Dr N Johnston. Invasive coronary angiography was performed and reported by Dr FG Dunn, Dr KJ Hogg, Dr NER Goodfield and Dr H Eteiba. Statistical and health economic analyses were performed at the Robertson Centre for Biostatistics under the supervision of Dr A McConnachie, Dr CM Messow and Dr A Walker.

The remainder of the work was carried out by myself. The writing of the thesis was entirely my own work.

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Table of Contents

Index of Tables

Index of Tables

Chapter 6

Chapter 7

Chapter 8

Index of Figures

Index of Figures

Chapter 5

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List of Abbreviations

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACCURACY	Assessment by coronary computed tomography angiography of individuals undergoing invasive coronary angiography study
AF	Atrial fibrillation
AHA	American Heart Association
ANOVA	Analysis of variance
AUC	Area under the curve
AUS	Australia
BEIR	Biological effects of ionizing radiation
BHF	British Heart Foundation
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CATSCAN	Coronary assessment by computed tomography scanning and catheter angiography study
CorE-64	Coronary artery evaluation using 64-row multi-detector computed tomography angiography study
CI	Confidence interval
cm	Centimetre
CT	Computed tomography
CT-CA	Computed tomography – coronary angiography
Cx	Circumflex
$Ca2^{+}$	Calcium

DSCT	Dual source computed tomography
DSCT-CA	Dual source computed tomography – coronary angiography
D1	First diagonal artery
D2	Second diagonal artery
EBCT	Electron beam computed tomography
ECG	Electrocardiographic
ESC	European Society of Cardiology
ETT	Exercise tolerance test
GCP	Good clinical practice
HR	Heart rate
I-CA	Invasive coronary angiography
ICER	Incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation
IQR	Interquartile range
ISD	Information services division
JAP	Japan
κ	Kappa
kV	Kilovolts
LAD	Left anterior descending
LMS	Left main stem
LV	Left ventricular
MRA	Magnetic resonance angiography
MSCT	Multi-slice computed tomography
MSCT-CA	Multi-slice computed tomography coronary angiography
mA	milliamps
mmHg	millimetres of mercury
mGy	milligrays

ml	millilitres
mm	millimetres
ms	milliseconds
mSv	millisieverts
NHS	National health service
NICE	National Institute for Health and Clinical Excellence
NPV	Negative predictive value
OM1	First obtuse marginal
OM2	Second obtuse marginal
OR	Odds ratio
PCI	Percutaneous coronary intervention
PDA	Posterior descending artery
PPV	Positive predictive value
QALY	Quality-adjusted life years
RCA	Right coronary artery
REC	Research ethics committee
ROC	Receiver operator curve
SCOT	Scotland
SD	Standard deviation
Sn	Sensitivity
Sp	Specificity
UE	Unevaluable
UK	United Kingdom
USA	United States of America
X-Ray	Radiograph
2D	2-dimensional
3D	3-dimensional

Summary

Coronary artery disease (CAD) is the leading cause of mortality in Scotland (population 5.2 million), accounting for around 9000 deaths each year. Accurate diagnosis of the presence and extent of CAD is essential to guide management. Invasive coronary angiography (I-CA) is the gold standard diagnostic investigation but is associated with a small risk of significant vascular complications. Over the last decade multi-slice computed tomography coronary angiography (MSCT-CA) has emerged as a non-invasive imaging modality capable of visualising the coronary arteries. Incremental advances in scanner technology have greatly improved the accuracy of MSCT-CA in comparison to I-CA.

Implementation of MSCT-CA in routine clinical practice in Scotland is desirable in terms of patient safety and convenience in addition to reducing pressure on cardiac catheterisation laboratory time. The latter is particularly relevant considering the recent introduction of primary percutaneous intervention for myocardial infarction. However, at the time of conducting this study the evidence for MSCT-CA accuracy was limited and only minimal guidance on appropriate use of MSCT-CA was available. Furthermore, the majority of existing evidence for MSCT-CA accuracy was derived from specialist academic centres with substantial experience in the technique and the accuracy of MSCT-CA in smaller centres with variable expertise and a more heterogeneous population was unknown.

The aim of this prospective, comparative study was to determine the accuracy of MSCT-CA in comparison to I-CA for the detection of significant CAD in patients presenting to a district general hospital in Scotland and to consider the health economic implications of introducing MSCT-CA into routine clinical practice.

One hundred patients with suspected CAD on the basis of symptoms and non-invasive stress testing underwent both 40-Slice MSCT-CA and I-CA. Studies were reported by independent, blinded radiologists and cardiologists and compared using the 15-Segment model of the American Heart Association. A stenosis of ≥ 50% was considered significant. The accuracy of MSCT-CA was determined in patient-based, artery-based and segment-based analyses and the impact of various patient characteristics on image quality and diagnostic accuracy was evaluated. Inter-observer agreement was determined for both MSCT-CA and I-CA and the possibility of a "learning curve effect" investigated. The cost-effectiveness of an "MSCT-CA first" strategy was considered in a health economic analysis.

The primary analysis considered MSCT-CA accuracy on a per patient basis. Patient prevalence of significant CAD was 38%. Patients with MSCT-CAs deemed not fully evaluable were included and considered to have significant underlying CAD. This strategy was considered clinically relevant as in practice a patient with an unevaluable MSCT-CA would proceed to I-CA for definitive diagnosis. This work demonstrated that 40-Slice MSCT-CA has a high sensitivity (92%) and a high negative predictive value (NPV) (91%) for the detection of significant CAD on a per patient basis. Specificity and positive predictive value (PPV) were less impressive and significantly compromised by the inclusion of patients with scans considered not fully evaluable by MSCT-CA. On segment-based and artery-based analyses respectively, distal segments were more often unevaluable than proximal segments owing to their smaller size, and the right coronary and circumflex arteries were the arteries most often unevaluable, likely due to their higher mobilities.

Heart rate during MSCT-CA was not optimally controlled with oral beta blockers and rate limiting calcium channel blockers. The mean number of MSCT-CA evaluable segments

per patient was significantly higher in the lower heart rate group. More than half the study population had coronary artery calcification and there was a non-significant trend towards more unevaluable segments in this patient group. Coronary artery calcification had the effect of reducing NPV while increasing PPV. One third of the study patients were obese and a non-significant trend towards an increasing number of unevaluable segments with increasing body mass index was observed.

Pre-test probability of significant underlying CAD was determined by the Duke Clinical Score. Fifty-nine per cent of patients had a low-intermediate pre-test probability and 41% a high pre-test probability of CAD. The prevalence of significant CAD in the high pre-test probability group and the low-intermediate pre-test probability group was 73% and 14% respectively. Correspondingly, the sensitivity and PPV of MSCT-CA were higher in the high pre-test probability group while specificity and NPV were lower.

Inter-observer agreement of the MSCT-CA reporters was substantial and comparable to that of the I-CA reporters in the patient-based analysis. A small observed improvement in MSCT-CA reporter diagnostic specificity during the study was not statistically significant.

This study demonstrated MSCT-CA to be cost effective in the detection of significant CAD in a patient population with low-intermediate pre-test probability and hence fairly low prevalence of disease. Savings would be increased with improved MSCT-CA specificity. A strategy of screening patients being considered for I-CA on the basis of their risk level and referring 'low-intermediate risk' cases for MSCT-CA could affect around 60% of patients currently referred for diagnostic I-CA in North Glasgow and subsequently avoid I-CA in at least half of these patients.

To permit the development of an effective MSCT-CA service future work must focus on ensuring appropriate training for those performing and reporting MSCT-CA and on the development of local guidelines to govern patient selection for MSCT-CA. Audit of MSCT-CA referrals could determine the extent of adherence to guidelines. Further research could be observational in nature with follow-up of patients who have MSCT-CA and are then referred for I-CA and also follow-up of patients with "negative" MSCT-CA who do not have subsequent I-CA in terms of subsequent cardiac events.

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction to chapter

Over the last decade multi-slice computed tomography coronary angiography (MSCT-CA) has emerged as a non-invasive imaging modality capable of visualising the coronary arteries.[1] Early comparative studies intimated that MSCT-CA had the potential to replace invasive coronary angiography (I-CA) in certain patient groups.[2] Incremental advances in scanner technology have been reflected in clinical studies which have demonstrated considerable accuracy of MSCT-CA in comparison to I-CA for detecting significant coronary artery stenoses.[3,4] However, in 2006, the applicability of these studies to clinical practice in the West of Scotland had not yet been examined and a specific role for MSCT-CA was yet to be defined.

This chapter reviews MSCT-CA with respect to the studies of accuracy available by January 2007 when patient recruitment for the present investigative work was commenced. Chapter 3 provides an up-to-date review of the rapid evolution of MSCT-CA technology and consideration of pertinent studies up to July 2010.

1.2 The gold standard diagnostic test for CAD - invasive coronary angiography

1.2.1 Definition

Invasive coronary angiography (I-CA) is defined as the radiographic visualisation of the coronary vessels after direct injection of radiopaque contrast media.[5] It permits delineation of the coronary anatomy and assessment of the presence and extent of coronary artery stenoses. I-CA also enables consideration of the feasibility of revascularisation therapy by percutaneous or surgical interventions. It is currently the gold standard diagnostic test for coronary artery disease (CAD) providing unrivalled vessel visualisation and lesion definition and the option to perform "same session" therapeutic interventions.

1.2.2 Deficiencies

I-CA is an invasive procedure which may be uncomfortable for the patient and the potential associated complications are well documented. Mortality risk from diagnostic I-CA is estimated from UK registry data at 0.12%.[6] Similarly the risk of peri-procedural myocardial infarction is estimated at up to 0.1%.[7] I-CA-related stroke risk has recently been reported to be as high as 0.2-0.4%.[8] Other complications associated with I-CA are ventricular and supraventricular arrhythmias, athero-embolism and local vascular complications. Patients may also develop nephropathy or allergic reactions secondary to the contrast media and as with other radiological procedures there is a theoretical risk of morbidity and mortality associated with the radiation exposure.[9]

Whilst complications secondary to contrast media and radiation exposure are common to both I-CA and MSCT-CA, given the substantial adverse vascular risk profile of I-CA, a non-invasive investigation capable of assessing coronary anatomy, such as MSCT-CA, is desirable.

1.3 The evolving technology of multi-slice CT coronary angiography

1.3.1 Introduction

Imaging of the coronary arteries by computed tomography has traditionally been very difficult due to their small size and constant motion. Respiratory motion presented a further difficulty to be overcome. Initial spiral CT scanners consisted of an x-ray source and a single detector mounted on opposite sides of a continuously rotating gantry. Cardiac scanning was attempted but motion-free images were not attainable due to the long acquisition time required for complete coverage of the heart.[10] The first multi-detector (multi-slice) CT scanners capable of visualising the coronary arteries were introduced in 1999.[1] These scanners utilised four parallel detector rows to reduce scan time and

retrospective electrocardiographic gating was employed to minimise artefact due to cardiac motion. However, whilst often diagnostic of CAD, imaging was limited to larger more proximal vessels and the scanners were not deemed reliable enough for use in routine clinical practice.[11-13] As technology developed over the next decade MSCT scanners with 16 then 40 and 64 slices were produced.[14] The increase in number of slices was accompanied by shorter gantry rotation times, narrower collimation and near isotropic voxels which substantially enhanced temporal and spatial resolution. These features translated into significant improvements in diagnostic accuracy.[4]

This chapter gives a detailed overview of the technology behind MSCT-CA and of the practicalities of performing it. Thereafter there is discussion on the evidence available prior to January 2007 for the use of MSCT-CA in clinical practice and of the limitations of previous studies. The chapter concludes with a statement of the aims of the current investigative work.

1.3.2 Temporal resolution

Temporal resolution refers literally to the time interval between measurements in the collection of data or to the precision of a measurement with respect to time. In MSCT-CA it indicates the duration of the reconstruction window at the end-diastolic phase of the cardiac cycle and hence, the length of time needed to acquire data for one image. As MSCT-CA images can be reconstructed from a 180^0 rotation of the x-ray gantry (half sector reconstruction), the temporal resolution of a scanner approximates to half the time required for one 360^0 rotation.[2] For example, a 16-slice scanner with a gantry rotation time of 500ms will provide a temporal resolution of 250ms. Short reconstruction windows permit higher temporal resolution and are important to ensure images are not significantly compromised by motion artefact.

Advancements in MSCT scanner technology have substantially improved temporal resolution. Current 64-slice scanners have gantry rotation speeds of 330ms which give a temporal resolution of 165ms using a half sector reconstruction protocol.[15] However, given that the temporal resolution of I-CA is estimated at 33ms[16], clearly further improvements are desirable.

One attempted solution was to alter reconstruction techniques so that rather than obtaining all the data for one image in one cardiac cycle, the data are acquired over several consecutive cardiac cycles. This technique is referred to as multi-segment reconstruction or partial scan reconstruction and can increase the nominal temporal resolution.[17] For example, a 64-slice scanner with a gantry rotation speed of 330ms can provide a temporal resolution of 83ms (a quarter of the rotation speed) if the data are collected over two consecutive cardiac cycles. This technique is favoured particularly in patients with higher heart rates and many centres utilise a protocol that automatically initiates multi-segment reconstruction in patients with heart rates above a certain rate, often arbitrarily 65 or 70 beats per minute.[18] Multi-segment reconstruction has been shown in some studies to improve image quality[19] but this may not always be the case. The major difficulty lies in the fact that the technique relies on the coronary arteries returning to exactly the same point with each cardiac contraction.[20] However, variation in coronary artery position does occur and is particularly evident with variations in heart rate.[21] As heart rate slows or speeds up, the length of diastole and hence diastolic filling increases or decreases respectively. Alterations in ventricular expansion in end-diastole will alter the position of the coronary arteries and so a multi-segment reconstruction becomes an average of non-identical cardiac cycles. This averaging reduces image quality. A further difficulty is that multi-segment reconstruction requires a reduction in pitch (the rate at which the patient table feeds through the scanner / total width of the collimated beam).[22] This augments scan

length and hence radiation exposure and contrast media volume. Furthermore, a longer scan requires a longer breath hold which increases the risk of respiratory motion artefact.

1.3.3 Spatial resolution

Spatial resolution refers literally to a measure of the smallest area identifiable on an image as a discrete separate unit. The spatial resolution of an MSCT scanner dictates the size and shape of the 3D pixels, or voxels, that are displayed on the screen. Ideally voxels should be isotropic (the same size in all dimensions) to enable consistent 3D image quality in any reconstruction plane. Voxels are displayed, according to tissue density and its resultant attenuation, on a black to white scale through varying shades of grey. For example, calcified plaque appears white while air appears black. Higher spatial resolutions require higher numbers of smaller voxels and permit image reconstruction in greater detail.[22] An example of this is the ability of a scanner with high spatial resolution to improve the MSCT-associated artefact of partial volume effect. This can occur in a coronary artery lesion with an element of calcification by the computer averaging the tissue densities within the lesion and producing an image that is only white.[10] A larger number of smaller voxels reduces this effect by enhancing detail around the lesion. Current MSCT scanners have a spatial resolution of 0.4mm in the x and y axes. Spatial resolution in the z axis is dependent on individual slice thickness and can vary from 0.4mm (producing isotropic voxels) to 0.75mm (producing near-isotopic voxels) depending on the scanner. For comparison, the 2D spatial resolution of I-CA is 0.2mm.[20]

1.3.4 Detector rows

The length of an MSCT-CA on a specific scanner is determined by the number of detector rows (or slices). Larger arrays of detectors permit acquisition of larger quantities of data with each rotation of the gantry. Arrays cannot be increased by increasing the size of the individual detectors as this would adversely affect spatial resolution. Instead, the size of

detector array is augmented by increasing the number of detectors. The original MSCT scanners had only four slices and took 30 seconds to scan the whole heart in the cranio-caudal axis and acquire the complete cardiac data set.[1] This necessitated a challenging 30-second breath hold and images were often compromised by respiratory motion artefact. In addition, the 30-second scan time meant data were collected during multiple cardiac cycles. There was, therefore, a greater risk of significant heart rate variation either due to ectopy or to hypoxia-induced tachycardia resulting in artefact due to cardiac motion. The more modern 16-, 40- and 64-slice scanners provide greater coverage per cardiac cycle and scan times are much shorter. Correspondingly, the breath hold required for a 64-slice MSCT-CA is less than 10 seconds.[18] More recently there has been great interest in the emerging 128-, 256- and 320-slice scanners. The 320-slice scanner should technically be able to scan the whole heart in one cardiac cycle therefore eliminating the need for any significant breath hold and markedly reducing the potential for artefact due to cardiac or respiratory motion. Initial 256-slice scanners, however, did not improve image quality as much as expected due to their associated slower gantry rotation speeds providing temporal resolutions equivalent to those of a 16-slice scanner.[23]

1.3.5 Electrocardiographic gating

An MSCT-CA is performed over a period of between 6 and 15 seconds depending on the individual scanner speed. Consequently data are acquired over multiple cardiac cycles. In order to minimise the effects of cardiac motion when reporting MSCT-CA, data are reconstructed with the benefit of a technique termed electrocardiographic (ECG) gating. This permits the reconstruction of specific data from specific sections of consecutive cardiac cycles, enabling selection of data from the part of the cycle with least cardiac motion.

ECG gating can be prospective or retrospective.[24] Prospective gating is most commonly employed in the "step and shoot" mode where scanning is not continuous. In this approach, the scanner recognises the R wave on the ECG and scanning is commenced after a pre-specified time delay. Scanning then stops and resumes at the same point after the next R wave.[25] The major difficulty with this approach is that the gating cannot be automatically modified to deal with a significant variation in heart rate or an ectopic beat. A further issue is that if the pre-specified post-R wave time delay utilised is sub-optimal then image quality will be adversely affected. Prospective gating does have the advantage of reducing overall scanning time and hence radiation dose.[25,26] This, however, needs to be weighed against the risk/benefit ratio of an investigation with any degree of radiation exposure where there is any risk of un-interpretable results.

Retrospective gating is the technique currently used most frequently.[20] This is performed in the spiral mode where data acquisition is continuous and the patient table advances through the scanner at a constant speed. In this approach continuously acquired volumetric data are later reconstructed at several time intervals during diastole. Commonly these reconstructions are at multiple different percentages of the R-R interval e.g. 45%, 65%, 75%, 80%, and this allows the reporter to select the phase with least artefact which is most suitable for analysis (Figure 1.1 (a-c)). Generally 50%-70% of the R-R interval (mid diastole) offers optimal images for the evaluation of most coronary segments while 30-60% (end systole to early diastole) is often useful for analysis of the right coronary artery and analysis of patients with higher heart rates.[27] The phase used for reporting can vary between coronary arteries or segments as required to ensure optimal images. Furthermore, depending on available software, it is possible to manually reposition the R wave indicators in patients with ectopic beats which improves the quality of synchronisation and imaging.[28,29]

Figure 1.1 (a) Oblique coronal maximum intensity projection (MIP) reconstruction at 45% of RR interval demonstrating poorly visible RCA

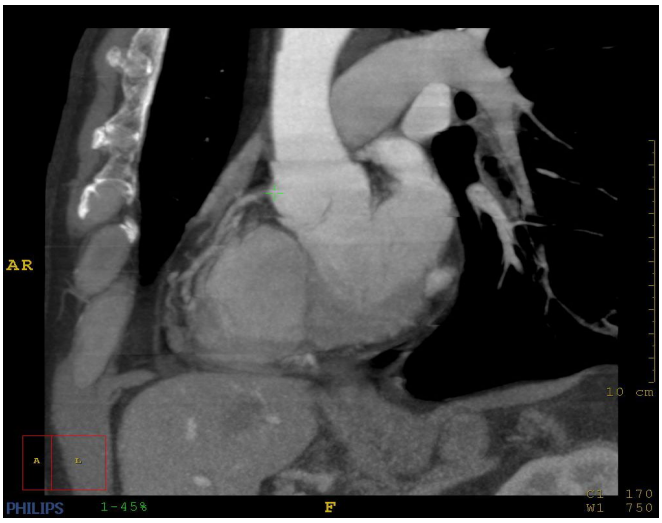


Figure 1.1 (b) Oblique coronal MIP at 50% of RR interval demonstrating poorly visible RCA

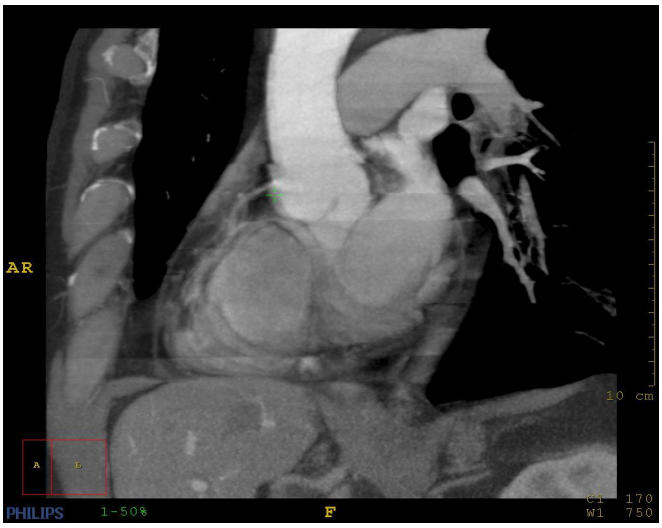
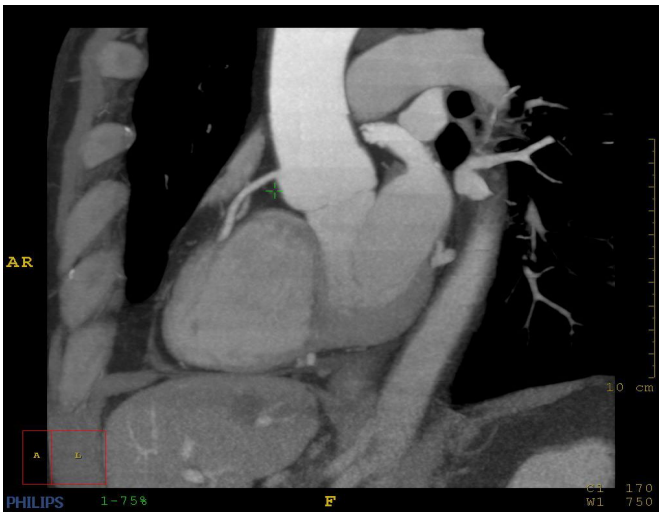


Figure 1.1 (c) Oblique coronal MIP at 75% of RR interval demonstrating clearly visible RCA



1.3.6 Patient preparation

Appropriate patient preparation prior to MSCT-CA is imperative to ensure patient safety and optimal image quality. The clinical question to be answered by the investigation should be reviewed and its validity confirmed. Factors that could interfere with accurate analysis of the scan should be identified and, where necessary, alternative imaging techniques considered. For example, patients need to be in sinus rhythm with minimal ectopy and it should be recognised that scans in patients with prosthetic valve replacements or pacing wires may be significantly compromised by artefact.

Any contraindications to iodinated contrast media administration should be ascertained. Specifically, a serum creatinine level should be measured along with thyroid function tests and any history of previous contrast agent-related allergic reactions should be carefully considered. In the case of a serious allergic reaction to iodinated contrast, the requirement for the investigation should be reviewed and if still necessary then consideration should be given to the use of lower osmolar contrast agents or pre-medication with steroid therapy.[30,31] Concomitant medication should be documented with attention paid to any cardiac rate-limiting medications and to prescription of the oral hypoglycaemic metformin. Most centres have an explicit protocol for patients undergoing CT contrast studies whilst taking metformin. The drug is oftentimes stopped 48 hours before the scan and resumed 48 hours afterwards if serum creatinine level is normal. However, most recent guidance from the Royal College of Radiology states that metformin need not be stopped prior to contrast administration and withholding it after scanning is only necessary if there was evidence of renal impairment prior to scanning.[32] In women of child-bearing age, the possibility of pregnancy should be ruled out.

It is well documented that MSCT-CA image quality is enhanced when patient heart rate is reduced by oral or intravenous beta-blockade.[27,33,34] This effect occurs due to the

prolongation of diastole and hence the scanning interval during which the heart is least mobile. Both the American Heart Association (AHA) and European Society of Cardiology (ESC) recognise that there is convincing evidence for the use of beta-blockers in MSCT-CA but neither advocate a specific protocol.[35,36] In practice, protocols differ between centres but common regimens involve the oral administration of the short-acting beta-blocker metroprolol at a dose of 50-100mg approximately one hour before the scan. Often intravenous metoprolol is used with the dose being up-titrated in 5mg increments to achieve a heart rate of < 65 beats per minute. In patients with contraindications to beta-blockade rate-limiting calcium channel blockers or the selective sinus node I_f channel inhibitor, ivabradine can be given. While there is no doubt that image quality is improved at slower heart rates, doubt has been cast on whether or not this effect is translated into an improvement in diagnostic accuracy.[37] One further consideration is the benefit of giving the patient a clear description of the immediate physical manifestations of a high speed injection of contrast media e.g. flushing, dizziness, nausea. This should reduce the risk of the patient developing anxiety-associated tachycardia secondary to these symptoms.

Some centres advocate the administration of sublingual nitrates immediately prior to MSCT-CA. In theoretical terms this should reduce vasospasm and increase coronary artery diameters hence facilitating image assessment. This, however, has only been demonstrated in one small retrospective, observational cohort study.[38] Sublingual nitrate should only be administered in the absence of hypotension.

Whilst controlling heart rate reduces artefact secondary to excess cardiac motion, it is equally important to minimise artefact secondary to excess respiratory motion. Depending on the MSCT scanner the required breath hold is between 6 and 15 seconds. It is imperative to ensure that the patient is capable of lying flat and of performing the

necessary breath hold. This should be rehearsed with the patient, preferably using the specific automated voice instructions of the scanner e.g. “Breathe in and hold your breath”.

1.3.7 Performing a scan

The patient is positioned in the centre of the scanner and connected to an ECG monitor and a power contrast injector. A large bore intravenous cannula is inserted preferably in an antecubital vein. A scout x-ray is then performed to ensure correct patient alignment.

MSCT imaging of the coronary arteries necessitates contrast enhancement of the coronary blood flow to allow accurate differentiation of the lumen and atherosclerotic plaque. As such, MSCT-CA is performed using an intravenous iodinated contrast medium. Approximately 100-150mls of iodinated contrast media is injected at 3-5mls/second through the power injector. It is imperative that contrast delivery to the coronary arteries is synchronised with image acquisition by the scanner. This is facilitated either by an initial “test bolus” scan or by utilisation of an automated contrast bolus tracker technique.[39] A “test bolus” scan involves the injection of a small amount of intravenous contrast to enable construction of a graph of contrast intensity versus time. This is subsequently used to automatically trigger scanning at the time of optimal enhancement of the coronary arteries. Alternatively, automated contrast bolus tracking times the initiation of scanning with contrast concentration in the ascending or descending aorta reaching a pre-set threshold. Following contrast media injection, a 40-50ml saline “chaser bolus” is administered. This has been shown to reduce the requisite volume of iodinated contrast without adversely affecting coronary artery enhancement.[40] MSCT-CA is most often performed in the cranio-caudal direction but in the presence of coronary artery bypass grafts it is possible to scan caudo-cranially to ensure optimal imaging of the distal native vessels.[41]

1.3.8 Reconstructing data

Following identification of the most appropriate cardiac phase for optimal image evaluation, various display techniques and semi-automated, interactive post-processing protocols are utilised (Figure 1.2 (a-f)). The initial assessment should begin with the axial images since they often contain sufficient information for a broad diagnosis and can direct more precise evaluations as required. In addition, they may demonstrate unsuspected non-cardiac disease in the thorax. Curved multi-planar reformations can be created by manually plotting or automatically tracking the course of a vessel using the axial data set. This permits generation of an image plane using the vessel as its own axis. A curved multi-planar reformation can subsequently be translated to a linear projection which permits rotation of the vessel 360^0 along its axis. This aids the determination and quantification of coronary artery stenoses. The maximum intensity projection algorithm displays only the highest attenuation voxels in the lesion which is useful in terms of improving lesion definition. 3D post-processing software enables the creation of volume rendered images. Aside from being visually pleasing, these 3D images can be rotated permitting accurate assessment of anomalous coronary arteries and bypass grafts.

Figure 1.2 (a) 3D map image demonstrating a normal left system

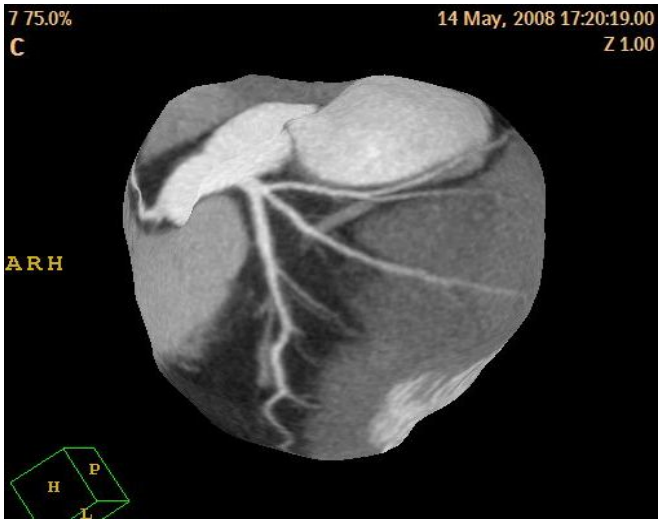


Figure 1.2 (b) 3D map image demonstrating a mid LAD lesion

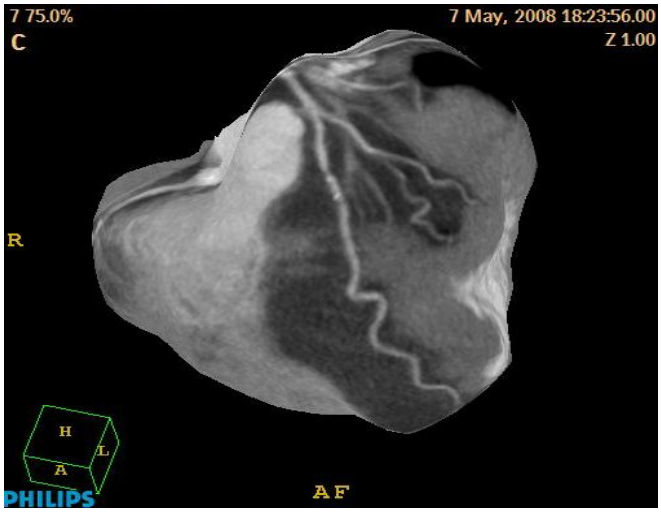


Figure 1.2 (c) Curved multiplanar reformation of a normal circumflex artery

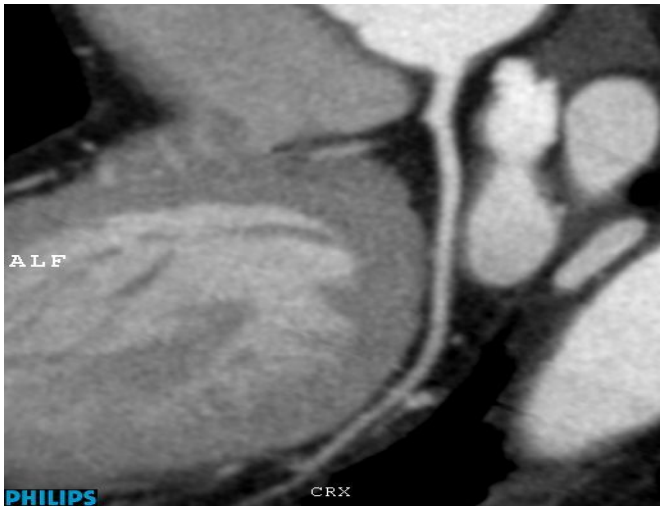


Figure 1.2 (d) Curved multiplanar reformation of an RCA with proximal stenosis

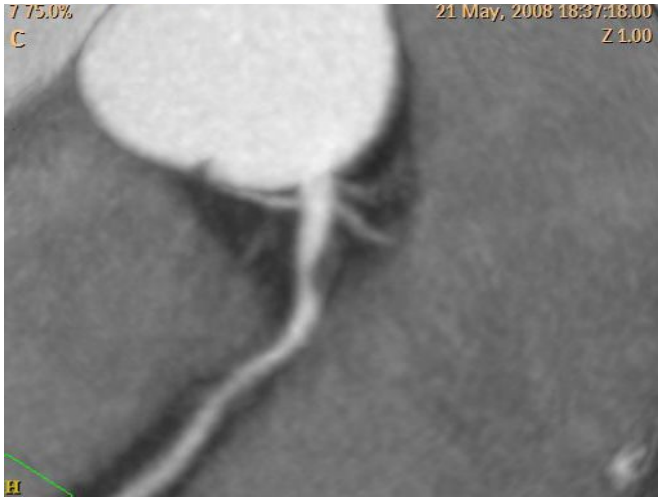


Figure 1.2 (e) Straight multiplanar reformation of a normal RCA

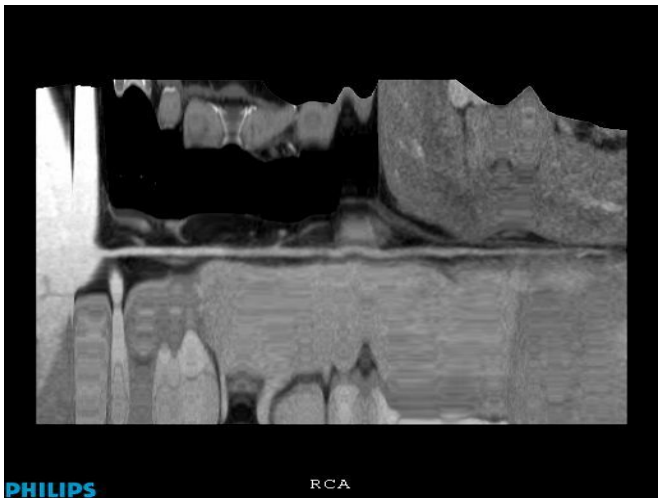
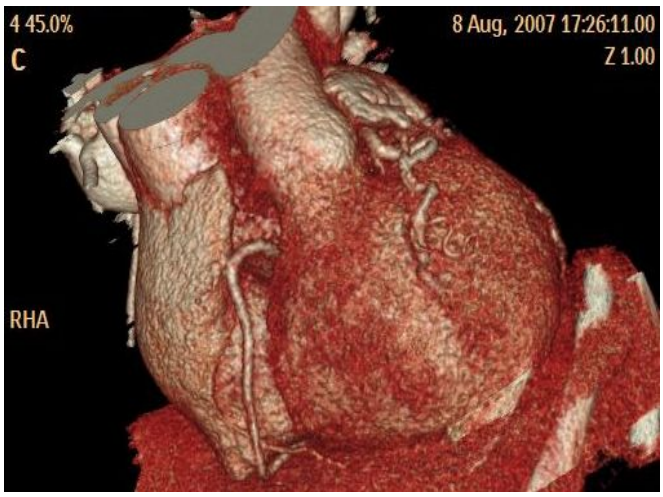


Figure 1.2 (f) Volume rendered image of a normal RCA



1.3.9 Calcium scoring

The association between vascular calcification and obstructive coronary artery disease is well recognised.[42] In the 1980s the development of electron beam computed tomography (EBCT) permitted non-invasive assessment of coronary artery calcium. The Agatston score, based on area and density of calcified plaques, was subsequently established to facilitate quantification of calcium burden.[43] EBCT has now been largely superseded by MSCT-CA which performs the majority of calcium scoring scans. A calcium score is achieved with a low radiation dose, (typically 0.7 to 3 milli-sieverts) non-contrast CT scan during a 10 - 15 second breath hold. Generally an Agatston score for each coronary artery and a total score for the patient is produced. Absolute scores of 0, 1-99, 100-400 and > 400 have been considered to represent no calcification, mild, moderate or severe calcification respectively. Furthermore, increasing scores have been demonstrated to be independent predictors of cardiovascular events.[44]

Calcium scoring is of particular relevance in the context of MSCT-CA for the detection of significant coronary artery disease because it has been demonstrated that the diagnostic accuracy of MSCT-CA is reduced in the presence of higher Agatston scores. Several studies have proposed that an Agatston score of > 400 should be used as a cut-off for proceeding directly to I-CA in order to avoid an unnecessary non-diagnostic investigation.[15,37] Conversely, a recent study demonstrated significant image quality degradation at a much lower cut-off Agatston score of 142 while a more historical study found no appreciable difference in diagnostic accuracy between different Agatston score groups.[45,46]

1.3.10 Limitations of MSCT-CA

MSCT-CA has two major limitations. The first is the radiation dose associated with the study and the second is the potential for images to be compromised by artefact.

1.3.10.1 Radiation

Radiation dosimetry is complex and reliant on multiple estimations but the "effective dose" measured in milli-sieverts (mSv) has emerged as the conventional means of comparing radiation exposures in medical imaging. This measure incorporates total dose, scan length and absorption rates of various tissues and organs. For example, one study estimated the effective dose of I-CA to be 5.6mSv (SD 3.6) while 16-slice MSCT-CA conferred an effective dose of 14.7mSv (SD 2.2).[9] To put this into context, a chest x-ray and a thallium T^{201} scan give effective doses of 0.02 and 23mSv respectively.[47] Subsequent studies using 64-slice MSCT-CA with various scanning protocols have estimated effective dose to range from as little as 7 mSv for men in one study to as much as 21.4 mSv for women in another.[33,48]

It is unclear to what extent exposure to ionising radiation in this context equates with clinical risk i.e. the development of malignancy or genetic damage. It is considered that, in general, females are at higher risk than males due to breast tissue and children are at substantially higher risk than adults due to the presence of more rapid mitosis and greater life expectancy.[47] There are currently no epidemiological data of actual malignancies in populations of patients undergoing MSCT-CA. Thus, extrapolations from epidemiological models comprising data from atomic bomb survivor studies in addition to medical and occupational radiation studies are the mainstay of risk estimation.

The National Academies' Biological Effects of Ionizing Radiation 7th Report (BEIR VII Phase 2) published in 2006 provides a framework for assessing lifetime attributable cancer risk in line with the so-called linear no threshold risk model. This model dictates that the cancer risk observed from exposure to very high doses of radiation e.g. following the nuclear attacks on Hiroshima and Nagasaki proceeds in a linear fashion to the comparably very low doses used in clinical medicine with no specific threshold for the emergence of

risk.[49] This risk assessment method unsurprisingly presents some controversy. Firstly the validity of the linear no threshold risk model is contentious. Indeed, in 2004 the Health Physics Society deemed it to be an over-simplification and stated that risk estimates should not be used at <50 mSv. Furthermore, this assessment tool does not allow for differences in relative biological effectiveness between x-rays and the varying types of ionising radiation on which the tool was based.

While the precise risks associated with the ionising radiation of MSCT-CA remain un-quantified they demand careful consideration and, in line with good clinical practice, use of this investigation must be justifiable and steps should be taken to minimise exposure. As such, various dose reduction protocols have been employed in MSCT-CA. One method is the use of prospective gating, described in 1.3.5 above. However, currently the most effective means of reducing radiation dose is to utilise prospective ECG-dependent tube current modulation. Based on the observation that useful image reconstructions are only possible during diastole, this technique effects an automatic 80% reduction in tube current during systole. As a result, there is high tube current and optimal image quality only during diastole where cardiac motion and hence artefact is minimal. Studies have suggested that this technique can reduce effective dose by up to 35%.[50]

1.3.10.2 Artefact

It is well documented that vessel wall calcification is associated with the presence of coronary artery disease.[42] As a result MSCT-CA images commonly demonstrate calcifications which unfortunately present a significant source of artefact (Figure 1.3 (a-b)). There are three recognised artefactual effects: blooming; beam hardening; and the partial volume effect.

Blooming occurs when the excess optical stimuli from calcification of one voxel affect neighbouring voxels. The size of a calcified lesion is therefore over-estimated and the luminal diameter appears smaller. This type of artefact is particularly problematic when attempting to determine the patency of an intra-coronary stent but can be somewhat attenuated by utilising sharper and noisier kernels.

Beam hardening occurs when the reconstruction algorithm fails to correctly interpret high or low attenuation rays emanating from a high density material such as calcification. This can result in dark bands or streaks or in "cupping" artefacts. "Streaking", in particular, is commonly associated with permanent pacemaker leads which, as a result of their position in the superior vena cava, can render segments of the right coronary artery un-interpretable. Dense, non-diluted contrast material within the superior vena cava can have a similar effect. This can, at least in part, be ameliorated by the use of a saline "chaser bolus" as described in 1.3.7 above.

The partial volume effect occurs when the degree of calcification is overestimated by automatic averaging of all tissue densities within a voxel, i.e. the presence of one small speck of calcium results in the whole voxel being depicted as white.

Cardiac and respiratory motion present a further source of artefact. Cardiac motion artefact occurs due to pulsation and rotational movement and can result in blurring or "stair-step" artefact. This most commonly affects the mid-right coronary artery which is most mobile.[51] Such artefacts can be reduced by careful control of heart rate and also by improving scanner specifications in terms of spatial and temporal resolution. It should be noted that multi-segmental reconstruction algorithms are very sensitive to heart rate variation and therefore not uncommonly result in blurring or "stair-step" artefact (Figure

1.3 (b)). Excess respiratory motion can also cause blurring and is more likely as scan length increases.

Figure 1.3 (a) Heavy calcification of the proximal coronary arteries

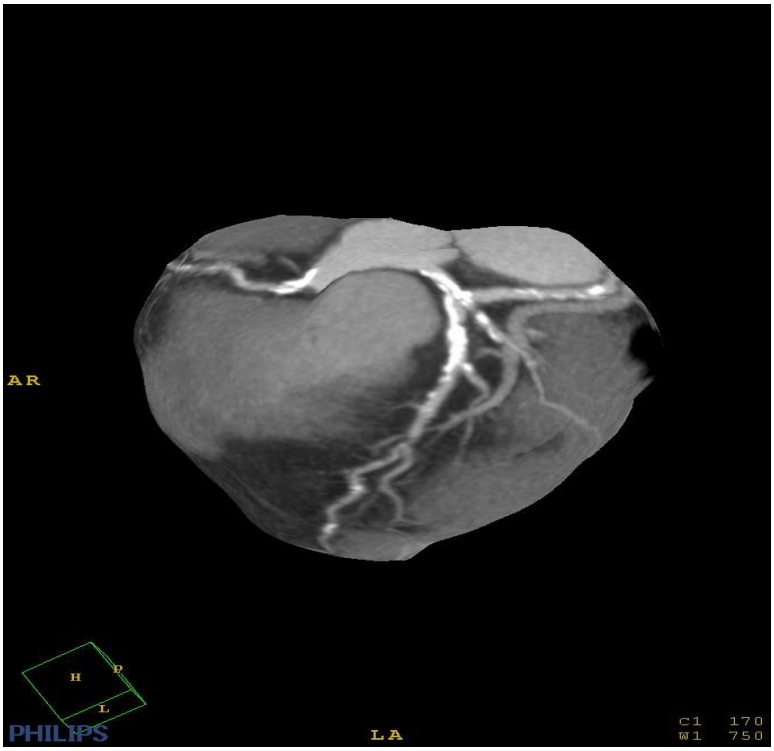
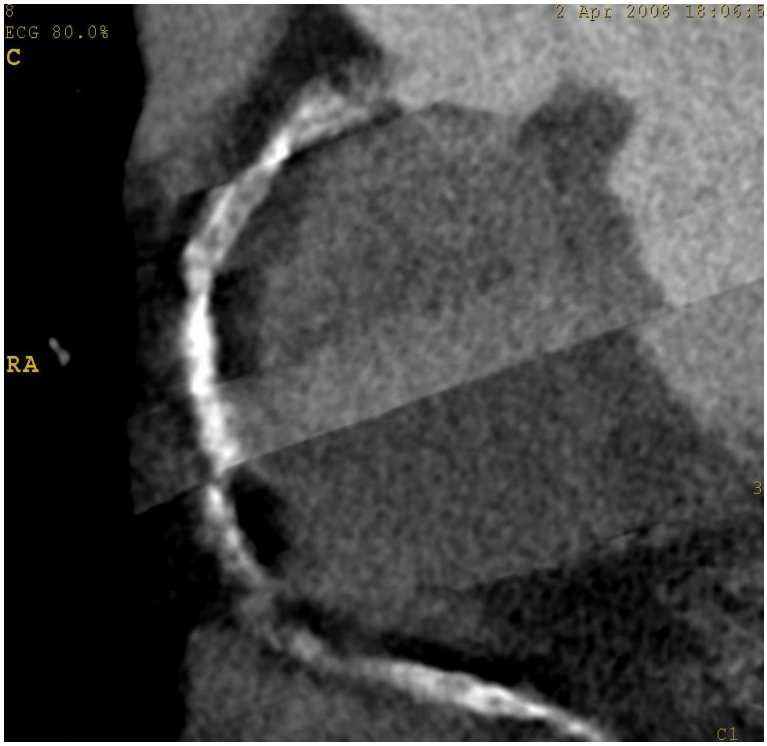


Figure 1.3 (b) Stair-step artefact secondary to coronary motion in addition to heavy calcification compromising luminal assessment



1.4 Evidence-based clinical application of MSCT-CA

1.4.1 Introduction

Over the last decade, the potential applications of MSCT-CA have been the focus of a vast body of scientific and clinical research. More specifically, the role of MSCT-CA in providing anatomical information on the presence and extent of coronary artery stenoses has been the subject of intensive study. Its ability to assess coronary artery bypass graft and intra-coronary stent patency has also been studied along with its facility to characterise coronary artery plaque. It has been shown to effectively define the origin and course of anomalous coronary arteries and to be useful in the assessment of complex congenital heart disease. Its capacity to derive functional information such as left ventricular systolic function has also been considered.

The focus of the current investigative work is the diagnostic accuracy of MSCT-CA in comparison to I-CA for detecting significant coronary artery stenoses and as such this chapter will review all the relevant studies of this nature which had been published when recruitment for the present study commenced in January 2007. A later chapter (chapter 3) will consider the pertinent studies published subsequent to this.

1.4.2 MSCT-CA for detecting CAD - 16-slice studies

By January 2007 there had been 21 published studies assessing the accuracy of 16-slice MSCT-CA for the detection of coronary artery disease (Table 1.1).[52-72] All studies were European with the exception of two carried out in the USA.[57,58] There were two studies performed in the UK.[64,68] In total 1591 patients were involved with the number of patients in each individual study varying between 22 and 187. Eleven studies were performed in patients without previous angiographically demonstrated CAD[52-54,56,58,61,63,64,67,69,71] while the remainder were in mixed patient groups including patients with suspected or known

CAD and with previous percutaneous interventions (PCI) and coronary artery bypass grafting (CABG). The average age of patients studied was 62 years and almost three quarters were male. There was extreme variation in prevalence of CAD amongst the populations studied from 8% to 98% with an average of 58%.

Scanning protocols varied between centres and almost 50% of centres performed multi-segment reconstructions with nominal temporal resolutions as low as 65ms in some studies. The other centres used standard half sector reconstruction protocols with temporal resolutions varying between 188 and 210ms depending on individual scanner specifications. Most studies restricted MSCT-CA analysis to segments with a diameter greater than 1.5mm or 2mm, although some attempted to analyse all segments. Reported exclusion rates varied from 0% of all segments in some studies[56,60,62,63,68,72] to 29% of segments with diameters greater than 2mm in another study.[57] Coronary artery segment classification varied widely from the 7-segment to the 17-segment model of the AHA. Nineteen of the 21 studies reported accuracy on a per segment basis but only 13 studies reported accuracy on the more clinically relevant per patient basis.[52,53,55-60,66,67,69-71]

On a per segment basis sensitivity and specificity varied widely from 30% to 96% and 79% to 99% respectively. Negative predictive value (NPV) was acceptable varying only from 83% to 100% between studies but positive predictive value (PPV) was poor with an average of 60% and a wide range from 36% to 91%.

On a per patient basis sensitivity was better, with reported values varying between 80 and 100%. However specificity, PPV and NPV were poor ranging from 29% to 95%, 50% to 97% and 53% to 100% respectively.

Eleven studies assessed only patients without previously proven CAD.[52-54,56,58,61,63,64,67,69,71] These studies were all small with patient numbers varying between 22 and 65. The mean age of those studied was 62 years and 71% were male. Prevalence of CAD within the patient populations studied ranged from 8% to 84% with an average prevalence of 53%. Ten of these studies reported accuracy on a per segment basis and sensitivity, specificity and PPV were similar to those reported in studies of mixed patient populations but NPV was higher, ranging between 94 and 100%. Only seven of the eleven studies reported accuracy parameters on the more clinically relevant per patient basis.[52,53,56,58,67,69,71] They documented higher sensitivity between 80% and 100%, similar specificity and PPV at 71% to 95% and 57% to 94% respectively and lower NPV at 63% to 100%. In all of these studies the confidence intervals reported for accuracy parameters were wide due to the small patient numbers.

Table 1.1 Studies of 16-slice MSCT-CA accuracy in comparison to I-CA

Author[Ref] (Year - Country)	Temp. Res. ms (MSR)	Patient Group	Patients (excluded)	Mean Age (% Male)	Patient Prev. CAD %	Mean HR bpm (% β Blocker)	AHA Segment model	Segment inclusion (% excluded)	Per Segment Sn (95%CI)	Per Segment Sp (95%CI)	Per Segment PPV (95%CI)	Per Segment NPV (95%CI)	Per Patient Sn (95%CI)	Per Patient Sp (95%CI)	Per Patient PPV (95%CI)	Per Patient NPV (95%CI)
Achenbach[52] (2005 - Germany)	188 (No)	Suspected CAD	48 (2)	62 (50)	52	58 (86)	16	≥ 1.5mm (4)	94 (85-98)	96 (94-97)	68 (57-78)	99 (98-100)	100 (84-100)	83 (62-92)	86 (68-94)	100 (80-100)
Bonmassari [53] (2006 - Italy)	210 (No)	Valvular disease	22 (11)	70 (70)	42	65 (-)	16	All (23)	69	96	58	97	100	80	85	100
Cademartiri[54] (2005 - Netherlands)	210 (No)	Suspected CAD	40 (11)	59 (90)	–	55 (63)	15	≥2mm (0)	96 (89-98)	96 (93-97)	86 (78-93)	99 (96-99)	–	–	–	–
Dewey[55] (2006 - Germany)	146-200 (Yes)	Suspected or known CAD	108 (0)	64 (74)	52	70 (52)	15	≥ 1.5mm (0)	–	–	–	–	92 (82-96)	79 (65-88)	95 (86-98)	95 (92-97)
Erdogan [56] (2006 - Turkey)	210 (No)	Suspected CAD	43 (0)	57 (88)	84	62 (60)	15	All (0)	67	95	69	94	92	71	94	63
Garcia[57] (2006 - USA)	–	Suspected or known CAD ± PCI	187 (0)	60 (68)	32	59 (-)	17	≥2mm (29)	85 (76-96)	91 (90-92)	36 (29-34)	99 (98-100)	98 (95-100)	54 (45-63)	50 (41-59)	99 (96-100)
Hoffmann[59] (2005 - Germany)	140 (Yes)	Suspected or known CAD ± PCI	103 (0)	62 (69)	56	69 (-)	–	≥ 1.5mm (6.4)	95 (90-98)	98 (97-99)	87 (86-90)	99 (99-100)	97 (88-100)	87 (74-95)	90 (80-96)	95 (84-99)
Hoffmann[58] (2004 - USA)	210 (No)	Suspected CAD	33 (0)	57 (82)	67	60 (52)	17	All (17)	70 (57-82)	94 (92-97)	58	97	86 (72-100)	82 (60-100)	90	75
Kaiser[60] (2005 Switzerland)	- (Yes)	Suspected or known CAD ± PCI/grafts	149 (0)	64 (74)	76	63 (69)	16	All (0)	30	91	47	83	86	49	84	53
Kefer[61] (2005 Belgium)	90-120 (Yes)	Suspected CAD	52 (0)	65 (79)	65	66 (62)	15	> 1.5mm (0)	82	79	46	95	–	–	–	–
Kuettner[63] (2005 - Germany)	188 (No)	Suspected CAD	72 (0)	64 (58)	49	64 (51)	13	All (0)	82	98	87	97	–	–	–	–

Table 1.1 Studies of 16-slice MSCT-CA accuracy in comparison to I-CA contd.

Author[Ref] (Year - Country)	Temp. Res. ms (MSR)	Patient Group	Patients (excluded)	Mean Age (% Male)	Patient Prev. CAD %	Mean HR bpm (% β Blocker)	AHA Segment model	Segment inclusion (% excluded)	Per Segment Sn (95%CI)	Per Segment Sp (95%CI)	Per Segment PPV (95%CI)	Per Segment NPV (95%CI)	Per Patient Sn (95%CI)	Per Patient Sp (95%CI)	Per Patient PPV (95%CI)	Per Patient NPV (95%CI)
Kuettner[62] (2005 - Germany)	188 (No)	Suspected or known CAD ± PCI/grafts	120 (4)	64 (67)	-	64 (51)	13	All (0)	85	98	91	96	_	_	_	_
Manghat[64] (2006 - UK)	65-125 (Yes)	Valvular disease	35 (5)	71 (68)	42	62 (47)	13	All (8%)	81 (64-93)	95 (92-97)	58 (42-72)	98 (97-99)	100	_	_	100
Martuscelli [65] (2004 - Italy)	125-250 (Yes)	Suspected or known CAD	61 (3)	58 (92)	67	59 (100)	16	> 1.5mm (16)	89	98	90	98	_	_	_	_
Mollet[66] (2004 - Netherlands)	105-210 (Yes)	Suspected or known CAD ± PCI	127 (1)	59 (89)	83	58 (60)	_	≥2mm (0)	92 (88-95)	95 (93-96)	79 (73-88)	98 (97-99)	100 (96-100)	86 (63-96)	97 (92-98)	100 (81-100)
Mollet[67] (2005 - Germany)	188 (No)	Suspected CAD	51 (0)	59 (73)	63	57 (80)	_	≥2mm (0)	95 (86-99)	98 (96-99)	87 (76-98)	99 (98-99)	100 (88-100)	85 (62-96)	91 (76-97)	100 (80-100)
Morgan-Hughes [68] (2005 - UK)	125-250 (Yes)	Suspected or known CAD ± PCI	57 (1)	61 (81)	56	64 (-)	13	All (0)	83	97	80	97	_	_	_	_
Nikolaou[69] (2006 - Germany)	93-185 (Yes)	Suspected CAD	60 (4)	60 (53)	8	58 (35)	7	Proximal and middle segments (8)	80	99	57	100	80	95	57	98
Rodevand[70] (2006 - Norway)	210 (No)	Suspected or known CAD ± PCI	101 (56)	62 (63)	48	56 (91)	16	≥2mm (21)	76 (63-85)	96 (94-97)	58 (47-69)	98 (97-99)	100 (91-100)	29 (18-43)	57 (46-67)	100 (74-100)
Ropers[71] (2003 - Germany)	200 (No)	Suspected CAD	77 (0)	58 (65)	53	62 (84)	_	≥1.5mm (0)	_	_	_	_	85	78	81	82
Schuijf [72] (2005 - Netherlands)	- (Yes)	Suspected or known CAD ± PCI/grafts	45 (0)	63 (93)	98	65 (78)	7	All (0)	93	91	73	98	_	_	_	_

Temp. Res. (MSR) = temporal resolution (multi-segment reconstruction), PCI = percutaneous intervention (stents), Prev. = Prevalence, HR = heart rate, Sn = sensitivity, Sp = specificity

1.4.3 MSCT-CA for detecting CAD - 40-64-slice studies

Prior to January 2007 only 13 small studies had assessed the accuracy of the newer generation 40-64 slice MSCT-CA for the detection of coronary artery disease (Table 1.2).[15,18,28,33,51,73-80] The majority were European studies while two were American[15,73] and the only 40-slice study was carried out in Singapore.[74] There were no UK-based studies. Altogether 762 patients were studied with the number of patients in individual studies varying from 30 to 81. Most centres recruited mixed patient groups comprised of patients with suspected CAD, known CAD and patients who had previously undergone PCI or CABG. Only three studies specifically assessed MSCT-CA accuracy in patients without previous angiographically demonstrated CAD.[15,33,79] The average age of patients studied was 62 and more than two thirds were male. The prevalence of CAD in the populations studied varied from 31% to 81%.

Scanning protocols varied between centres and in particular the stated scanner temporal resolutions differed. Most studies utilised standard half sector reconstruction protocols and documented temporal resolutions between 165 and 200ms depending on individual scanner specifications. Five studies, however, performed multi-segment reconstructions and quoted temporal resolutions between 53 and 165ms.[18,28,51,74,77] All 13 studies reported MSCT-CA accuracy on a per segment basis although segment identification protocols and exclusion rates varied. The majority of centres classified coronary artery segments according to the 15-segment model of the AHA although 11-segment, 16-segment and 17-segment models were also used. Only eight studies reported accuracy on the more clinically relevant per patient basis.[15,28,33,75,76,78-80] On a per segment basis, sensitivity and PPV were variably reported between 72 and 99% and 56 and 97% respectively. Specificity and NPV were generally higher at between 94 and 99% and 92 and 100% respectively.

Sensitivity was higher when reported on a per patient basis at 94 to 100%. Specificity, however, varied between 79 and 97% while PPV and NPV were variably reported at between 83 and 98% and 86 and 100% respectively. Due to the small number of patients in each individual study the confidence intervals for the per patient accuracy data were wide.

The three studies assessing only patients without previously proven CAD comprised a total of 217 patients.[15,33,79] Patient prevalence of CAD ranged from 31%[79] to 57%.[15] On a per patient basis sensitivity was between 95 and 97%, specificity between 90 and 95%, and NPV between 93 and 98%. PPV was less impressive being between 83 and 93%. Only two of the studies reported confidence intervals and again, due to small patient numbers, these were wide.

Table 1.2 Studies of 64 Slice MSCT-CA Accuracy in Comparison to I-CA

Author[Ref] (Year - Country)	Temp. Res. ms (MSR)	Patient Group	Patients (excluded)	Mean Age (% Male)	Patient Prev. CAD %	Mean HR bpm (% ß Blocker)	AHA segment model	Segment inclusion (% excluded)	Per Segment Sn (95%CI)	Per Segment Sp (95%CI)	Per Segment PPV (95%CI)	Per Segment NPV (95%CI)	Per Patient Sn (95%CI)	Per Patient Sp (95%CI)	Per Patient PPV (95%CI)	Per Patient NPV (95%CI)
Ehara[28] (2006 - Japan)	83-165 (Yes)	Suspected or known CAD ± PCI/grafts	67 (2)	67 (75)	88	72 (22)	14 (not AHA)	All (8)	90 (87-93)	94 (92-96)	89 (86-92)	95 (94-95)	98	86	98	86
Fine[73] (2006 - USA)	165 (No)	Suspected or known CAD	62 (4)	62 (48)	–	– (-)	–	> 1.5 mm (-)	95	96	97	92	–	–	–	–
Ghostine[33] (2006 - France)	165 (No)	LBBB ± suspected CAD	66 (0)	69 (61)	44	67 (100)	15	All (0)	72 (62-81)	99 (98-100)	91 (82-96)	97 (96-98)	97 (82-100)	95 (82-99)	93 (73-99)	97 (85-100)
Leber[18] (2005 - Germany)	83-165 (Yes)	Suspected or known CAD ± PCI	55 (4)	64 (-)	64	62 (36)	15	All (0)	73	97	–	–	–	–	–	–
Leschka[51] (2005 - Switzerland)	93-185 (Yes)	Suspected or known CAD	67 (0)	60 (75)	70	66 (60)	15	≥ 1.5mm (0)	94 (90-96)	97 (96-98)	87 (84-90)	99 (98-99)	–	–	–	–
Lim[74]* (2005 - Singapore)	53 (Yes)	Suspected or known CAD ± PCI	30 (0)	59 (67)	–	61 (-)	16	All (4)	99	98	94	99	–	–	–	–
Mollet[75] (2005 - Netherlands)	165 (No)	Suspected or known CAD	51 (1)	60 (65)	48	58 (73)	17	All (0)	99 (94-99)	95 (93-96)	76 (67-89)	99 (99-100)	100 (91-100)	92 (67-99)	97 (86-99)	100 (73-100)
Nikolaou[76] (2006 - Germany)	165 (No)	Suspected or known CAD ± PCI	68 (4)	64 (82)	57	61 (-)	15	All (10)	82	95	72	97	97	79	86	96
Plass[77] (2006 - Switzerland)	83-165 (Yes)	Known CAD or valvular disease	50 (0)	66 (78)	80	65 (0)	11	≥ 1.5mm (3)	93	97	91	98	–	–	–	–
Pugliese[78] (2006 - Netherlands)	165 (No)	Known CAD	35 (0)	61 (60)	71	58 (77)	17	All (0)	99 (92-100)	96 (93-97)	78 (68-85)	99 (99-100)	100 (87-100)	90 (59-98)	96 (81-99)	100 (69-100)
Raff[15] (2005 - USA)	165 (No)	Suspected CAD	70 (0)	59 (73)	57	65 (100)	15	All (12)	86	95	66	98	95	90	93	93
Ropers[79] (2006 - Germany)	165 (No)	Suspected CAD	81 (3)	58 (62)	31	59 (74)	17	≥ 1.5mm (4)	93 (81-99)	97 (96-98)	56 (43-68)	100 (99-100)	96 (80-100)	91 (80-97)	83 (65-94)	98 (90-100)
Schuijf[80] (2006 - Netherlands)	200 (No)	Suspected or known CAD ± PCI	60 (1)	60 (77)	77	60 (72)	–	- (1.4)	85 (77-93)	98 (97-99)	82 (73-91)	99 (98-100)	94 (86-100)	97 (91-100)	97 (91-100)	93 (84-100)

**The study by Lim et al used a 40-slice MSCT scanner rather than a 64-slice scanner. Abbreviations as per Table 1.1.*

1.4.4 MSCT-CA for detecting CAD - UK studies

By January 2007 only three studies comparing the accuracy of MSCT-CA to I-CA had been performed in the UK.[13,64,68] The first of these studies was carried out in 2003 using the very earliest MSCT scanner with only four slices.[13] In this study 30 patients with suspected or known CAD or previous PCI were assessed using the 7 segment AHA model. Despite only using the 7-segment model, almost a third of segments were deemed unevaluable and therefore excluded. Even excluding these segments accuracy was poor on a per segment basis with sensitivity and PPV being 72% and 53% respectively. Specificity and NPV were better at 86% and 93% respectively. The other two studies used 16-slice scanners and also reported MSCT-CA accuracy on a per segment basis. Both used the 13 segment AHA model. Sensitivity and PPV remained poor but specificity and NPV were good ranging between 95% and 97% and 97% and 98% respectively.

1.5 International and national guidelines

By January 2007 there were three published international or national guidelines regarding the clinical use of MSCT-CA. In 2006 the American College of Cardiology Foundation (ACCF) together with key specialty and sub-specialty groups developed appropriateness criteria where they graded the use of MSCT-CA in various clinical scenarios as either "acceptable", "inappropriate" or "undecided".[81] They considered MSCT-CA to be appropriate in the context of an intermediate pre-test probability of CAD and an un-interpretable or equivocal stress test. MSCT-CA was also considered appropriate in the evaluation of coronary arteries in patients with new onset heart failure of uncertain aetiology. Other appropriate applications of MSCT-CA were the assessment of complex congenital heart disease and suspected coronary anomalies and the evaluation of intra-cardiac masses and pericardial conditions where limited information was available from echocardiography and magnetic resonance imaging.

The European Society of Cardiology (ESC) published guidelines in 2006 for the management of stable angina and these included a subsection with recommendations on the use of MSCT-CA.[35] They considered MSCT-CA to be appropriate in patients with a low pre-test probability of disease in the context of a non-conclusive stress test. This, however, was a Class IIb recommendation based on level C evidence. The AHA also published guidelines for the assessment of CAD by MSCT-CA in 2006.[36] Similarly, they stated that MSCT-CA was an acceptable approach for the assessment of obstructive disease in symptomatic patients with a low to intermediate pre-test likelihood of disease. This was considered a Class IIa recommendation and based on level B evidence. The higher level of evidence referred to in the American guidelines was a meta-analysis suggesting very high sensitivities and specificities for MSCT-CA in the detection of significant CAD[3] which was not available prior to publication of the ESC guidelines.

1.6 Aim

1.6.1 Rationale for this study

CAD is the most common cause of mortality in Scotland, and in January 2007, was accounting for approximately 11,000 deaths each year.[82] The prevalence of CAD in Scottish patients increases with age and is higher in areas of socioeconomic deprivation.[83] Accurate diagnosis of the presence and extent of CAD is imperative to permit initiation of appropriate management strategies. I-CA is the gold standard investigation despite its small, associated risk of significant vascular complications.[6] An Information Services Division (ISD) Scotland publication in 2005 reported that 15,000 I-CAs were being performed annually in Scotland and that this number was increasing.[84] Further escalation in the number of I-CAs carried out in Scotland was anticipated with the imminent introduction of primary angioplasty for myocardial infarction. It was considered that this would almost inevitably increase pressure on cardiac catheterisation laboratory time and

with the government emphasis on waiting time targets, the likely consequence would be increased spending on new laboratories.

Prior to commencing the present work, studies comparing MSCT-CA to I-CA for the detection of CAD had intimated that the major strength of MSCT-CA may be its high NPV for excluding significant disease. If this were the case, then it would follow that patients with suspected CAD and a negative MSCT-CA would not need to undergo I-CA. In 2006 60% of I-CAs in North Glasgow were performed in patients with suspected CAD and up to 20% of these studies were entirely normal or demonstrated only plaque disease (North Glasgow Minerva Data). Introducing MSCT-CA for this patient population would clearly markedly curtail referrals for I-CA. Indeed it was suggested that implementation of such a strategy in routine clinical practice could reduce the number of I-CAs performed for suspected CAD by up to a third.[85] It was considered that effective utilisation of MSCT-CA in this clinical context could have a significant impact on NHS Scotland's ability to meet government imposed waiting time targets. Furthermore, while I-CA facilities in the West of Scotland are now rapidly becoming centralised, it may be feasible for MSCT-CA to be performed in district general hospitals, thereby maximising patient convenience in addition to potentially eliminating the need for a higher risk, more invasive procedure.

In January 2007, available evidence of the accuracy of MSCT-CA in comparison to I-CA was not sufficient to justify widespread implementation of MSCT-CA within the NHS in Scotland. Indeed the only national guideline addressing the use of MSCT-CA in Europe provided minimal guidance on appropriate use of MSCT-CA based on only Class IIb level C evidence. Correspondingly a 2005 report from NHS Quality Improvement Scotland stated that the role of MSCT-CA in clinical practice was yet to be defined.[86]

While there had been 13 small studies assessing the accuracy of the newer generation 40-64-slice MSCT scanners in comparison to I-CA, only three of these studies were performed in the patient population most likely to benefit from the investigation i.e. those with suspected rather than previously proven CAD. These studies included a total of only 217 patients.[15,33,79] While reports of NPV on a per patient basis for MSCT-CA in these studies were between 93% and 98%, only two studies provided 95% confidence intervals and due to the small patient numbers these were wide.

There had been no studies of MSCT-CA accuracy in the Scottish population. Indeed, only three small studies had assessed accuracy in a UK-based population.[13,64,68] One used only a 4-slice MSCT scanner while the others used 16-slice scanners. None of them reported accuracy on the clinically relevant per patient basis. It was considered that the accuracy of MSCT-CA for detection of significant stenoses in a Scottish population may be reduced in comparison to a European population. Firstly, the higher prevalence of CAD in the general population may adversely affect the NPV. Furthermore, accuracy may be compromised by patients in Scotland having an increased tendency to have more coronary artery calcification or higher body mass indices than populations elsewhere. These factors have the potential to make MSCT scans more difficult to interpret as a result of increased artefact and image noise respectively hence making it more difficult to confidently rule out significant stenoses. The consequent reduction in specificity could mean that the number of I-CAs avoided by a negative MSCT-CA is offset by a larger number of unnecessary I-CAs due to false positive MSCT-CAs.

It was not clear to what extent the results of single centre studies from large academic hospitals with considerable expertise in performing and reporting MSCT-CA could be extrapolated to routine clinical practice in a district general hospital setting. The only published multi-centre study by January 2007, (CATSCAN), had evaluated the accuracy of

16-slice MSCT-CA in comparison to I-CA in 187 patients in 11 centres worldwide.[57] Despite all MSCT-CAs being reported by the same expert reporter in an independent core laboratory, in comparison to previous single centre studies, the results were disappointing. Over one third of MSCT-CAs were deemed unevaluable and while sensitivity and NPV were excellent at 98% and 99% respectively specificity and PPV were significantly compromised by the high number of false positive scans at 54% and 50% respectively. A recent Scandinavian study further elucidated the point that the high accuracy of MSCT-CA demonstrated in dedicated academic centres may not be reproducible in a smaller, local hospital setting with limited experience in MSCT-CA.[70] In this study 56 patients were entirely excluded from all analyses due to high heart rates, arrhythmia, motion artefact and "technical difficulties related to the MSCT procedure". The authors then performed a patient-based analysis on the remaining 101 patients in which they considered any unevaluable segments to represent significant stenoses. Despite having already excluded the 56 patients with the most unevaluable scans, the per patient analysis of the remaining patients produced very disappointing specificity and PPV at 29% and 57% respectively. Sensitivity and NPV were both 100% but with the correct diagnosis being achieved in only 63% of patients, the authors concluded that limited diagnostic accuracy and a high number of unevaluable scans restricted the usefulness of MSCT-CA in a community hospital setting. Both this study and CATSCAN failed to reproduce the accuracy parameters for 16-slice MSCT-CA demonstrated in previous single centre studies. It has yet to be determined whether the results of single centre studies from large academic hospitals using the newer generation 40-64-Slice scanners, can be extrapolated to routine clinical practice in a district general hospital setting.

Finally, since the accuracy of 40-slice MSCT-CA for the detection of significant CAD in a Scottish population in a district general hospital setting was unknown it was impossible to determine the potential effects of introducing it into routine clinical practice for selected

patient groups. Widespread implementation of MSCT-CA for assessing patients with suspected CAD in NHS Scotland could not be recommended without considering the likely impact on cardiology services both in terms of economic burden and ability to meet government imposed waiting list targets.

1.6.2 Aim of this research

The principal aim of this research was to evaluate the accuracy of 40-slice MSCT-CA in comparison to I-CA for the detection of significant CAD in the West of Scotland population and to consider the potential implications in terms of financial burden and waiting list targets if there were to be widespread implementation of MSCT-CA in routine clinical practice.

CHAPTER 2

STUDY DESIGN AND METHODOLOGY

2.1 Study design

2.1.1 Hypothesis

The hypothesis of this study was that 40-slice MSCT-CA would have sufficient NPV for excluding significant CAD (stenosis ≥ 50%, defined by the reference gold standard of I-CA) on a per patient basis in the West of Scotland population for it to be introduced into routine clinical practice for the evaluation of patients with suspected CAD. Therefore, the primary aims of this study were:

1. To determine the sensitivity, specificity and the positive and negative predictive values on a per patient basis of 40-slice MSCT-CA for detecting significant coronary stenoses in patients referred for I-CA to investigate suspected CAD.

2. To examine to what extent implementation of MSCT-CA in routine clinical practice would reduce the number of I-CAs performed in patients with suspected CAD and the effect this would have on cardiology services in the West of Scotland in terms of financial burden and waiting list times for I-CA.

2.1.2 Other specific research objectives

This research also aimed to specifically consider the following:

1. Variations in accuracy of 40-slice MSCT-CA for the detection of significant CAD on a per artery and a per segment basis.

2. The influence of gender, body mass index, pre-test probability, heart rate and coronary artery calcification on 40-slice MSCT-CA image quality and accuracy.

3. Inter-observer agreement for 40-slice MSCT-CA analysis and for I-CA analysis.

4. The presence of a "learning curve effect" on the accuracy of analysis of 40-slice MSCT-CA

2.1.3 Design

This study was a prospective, comparative, observational, single-centre, clinical study examining the accuracy of 40-slice MSCT-CA for detecting significant CAD in comparison to the gold standard investigation of I-CA.

2.1.4 Sample size calculation

For the primary aim the study was designed to estimate the NPV of 40-slice MSCT-CA in the West of Scotland population together with the minimum NPV consistent with the data at a 95% confidence level. Assuming, as previously published, a sensitivity and specificity of 95% and 94% respectively[15,33,79], and a 70% prevalence of CAD in the patient population to be examined (North Glasgow Minerva Data), the expected NPV was 89.0%. However, the estimate of NPV, and the associated one-sided 95% confidence interval from this study would be subject to variability secondary to the actual prevalence of CAD, and the achieved sensitivity and specificity in the study sample.

Simulation studies were carried out (statistical software package SPlus for Windows v7) of various sample sizes, based on the assumed sensitivity, specificity and prevalence figures quoted above, to estimate the distribution of Exact one-sided 95% lower confidence limits that would be obtained. Based on 10,000 simulations, it was demonstrated that a sample size of 204 patients would have 70% (beta 0.3) power to obtain a lower 95% confidence limit of at least 80%, and 80% (beta 0.2) power to obtain a lower 95% confidence limit of at least 78.5% at a significance level of 5% (alpha 0.05).

2.2 Study population

2.2.1 Inclusion criteria

Patients were recruited from two Glasgow hospitals between January 2007 and May 2008. They were identified at general cardiology clinics and rapid access chest pain clinics at Stobhill Hospital (a district general hospital in North Glasgow) and at a specialist chest pain clinic at Glasgow Royal Infirmary. All patients referred for inclusion in the study had been assessed by a consultant cardiologist and were considered to require elective I-CA to determine the presence or absence of CAD. This assessment was based on the patients' symptoms along with their risk factors for CAD and the results of non-invasive stress testing i.e. exercise tolerance testing or myocardial perfusion imaging. Referred patients were invited to participate in the study and were provided with a patient information sheet. Informed consent was obtained at a minimum of 48 hours later.

2.2.2 Exclusion criteria

Any patient with known CAD, defined as previous myocardial infarction or previous coronary artery stenoses on I-CA was excluded from the study. Patients with unstable symptoms where the requirement for I-CA was considered urgent were also excluded. Other exclusion criteria relating to patient safety were documented iodine contrast allergy, hyperthyroidism, significant renal dysfunction (defined as serum creatinine > 150μmol/l or > 120μmol/l in a diabetic patient) and possible pregnancy. Exclusion criteria based on anticipated technical difficulties with the MSCT-CA protocol were atrial fibrillation (AF) or frequent ventricular or supraventricular ectopic activity and inability to carry out a 12 second breath hold. General exclusion criteria were mental or legal incapacitation and inability or reluctance to provide informed consent.

2.3 Recruitment

2.3.1 Initial assessment

Each study patient's initial assessment comprised consideration of symptoms, risk factors for CAD, non-invasive stress testing, routine laboratory investigations and medication.

The presenting symptoms of chest pain and/or dyspnoea were determined to be either typical or atypical of underlying CAD. More specifically, the description, site and radiation of chest discomfort were assessed along with its exacerbating and relieving factors and response to glyceryl trinitrate. The duration of symptoms was also recorded.

Risk factors for CAD were male gender, hypertension (defined as blood pressure ≥ 140/90[87] or current antihypertensive medication), hypercholesterolaemia (defined as cholesterol > 5mmol/l[87] or current statin medication), diabetes mellitus, family history of CAD (defined as angina or myocardial infarction in a male relative age < 55 years or a female relative age < 65 years[87]), current or previous smoking and previous personal history of peripheral vascular or cerebrovascular disease. Body mass index was calculated by dividing weight in kilograms by (height in metres)^2.

Most patients entering the study had previously undergone either exercise tolerance testing or myocardial perfusion imaging and the results of these investigations were recorded. Some had also had echocardiography and the results of this investigation were recorded including assessment of left ventricular systolic function and any recording of estimated ejection fraction. Routine laboratory investigations were carried out. Full blood count was assessed as anaemia is a relative contraindication to I-CA. Urea and electrolytes were assessed to ensure patients did not meet an exclusion criterion in terms of serum creatinine

level. Similarly thyroid function tests were performed to rule out hyperthyroidism. Cholesterol level was also measured and recorded.

Each patient's pre-test probability was assessed using the Duke Clinical Score.[88] This well validated tool considers the patient's age, gender and risk factors for CAD along with the characteristics of their presenting symptoms to calculate a score which is directly related to the likelihood of the patient having underlying obstructive CAD (defined as stenosis ≥ 75% of at least one major coronary artery). The percentage risk scores were categorised into three specific risk groups: Low pre-test probability (Score 0-24%), Intermediate pre-test probability (Score 25-74%) and High pre-test probability (Score > 75%).

2.3.2 Patient preparation

At initial assessment each patient's resting heart rate was measured. The MSCT-CA protocol dictated that for technical reasons (see 1.3.2), average heart rate during the scan should be as low as possible and certainly no higher than 80 beats per minute. It was considered that since all study patients had been referred for I-CA due to the suspicion of underlying CAD, all should be on rate-limiting anti-anginal medication. Patients were therefore commenced on oral beta-blockers at the time of recruitment and the dose was titrated aiming for a resting heart rate < 65 beats per minute. Patients with true contraindications to beta-blockade such as asthma were commenced on rate-limiting calcium channel blockers or in a few cases the selective sinus node I_f channel inhibitor, ivabradine.

2.4 Multi-slice CT scans

2.4.1 The MSCT-CA scanner

MSCT-CAs were performed on the Philips Brilliance multi-slice CT scanner with 40 simultaneous detector rows providing 40 by 0.625mm collimation with near isotropic voxels of 0.4 x 0.4 x 0.5, a slice thickness of 0.9mm and an increment of 0.45mm. Gantry rotation time was 400ms with a half-sector acquisition protocol and multi-sector reconstruction permitting an effective temporal resolution of between 50 and 200ms depending on patient heart rate. Tube voltage was either 120kV or 140kV depending on patient weight and effective tube current was 600mAs/slice. Table feed was set at 3.8 mm/rotation i.e. a pitch of 0.2. Prospective ECG dependent tube current modulation was utilised to minimise radiation exposure.

2.4.2 MSCT-CA protocol

A review of inclusion and exclusion criteria was performed prior to MSCT-CA. Specifically renal function was considered and significant concomitant medication documented e.g. beta-blockers, metformin. Any history of allergies was re-assessed. A wide bore cannula was inserted into a large vein (antecubital where possible) and the patient was connected to a monitor that continuously displayed heart rate and rhythm. No additional beta-blockade was given at the time of the scan but if the patient's heart rate was > 80 beats per minute then the scan was postponed to allow titration of beta-blocker (or alternative rate limiter) dose and ensure a starting heart rate of < 80 beats per minute. From January 2008 the protocol was modified to require a starting heart rate of < 70 beats per minute. This modification was made to allow for the observed increase in heart rate during contrast dye administration. Prior to commencing scanning a breath hold trial was performed to ensure the patient was capable of following the instructions and maintaining a breath hold for 12 seconds.

A single axial CT image was utilised to define the area to be scanned from the bifurcation of the trachea to the diaphragm. A region at the origin of the descending aorta was marked to permit subsequent use of automated contrast bolus tracking. This technique enables synchronisation of scan commencement with the arrival of contrast media in the coronary arteries. Iodinated contrast media (Omnipaque 350 [Schering AG, Berlin, Germany] in patients 1-17 and Iomeron 400 [Bracco, Italy] thereafter) was injected via a wide bore cannula in a large vein. Contrast volume and rate of injection varied with patient weight from 90 to 120mls and 5.3 to 6.9mls/second respectively. A 50ml saline "chaser bolus" at an injection rate of 5mls/second was given immediately after the contrast injection. Scanning was automatically triggered when contrast media in the pre-defined area of the descending aorta reached a density of 160 Hounsfield units. A single automated breath-hold command was given and helical scan acquisition commenced three seconds thereafter in order to minimise respiratory related fluctuation in heart rate. Overall scan time was between 10 and 15 seconds depending on cardiac size.

2.4.3 Reconstructing the data

Data were reconstructed from data obtained during a 180^0 gantry rotation utilising either a mono- or multi-segmental algorithm depending on patient heart rate. A volume acquisition approach was employed reconstructing axial images with slice thickness of 0.9mm, and increment of 0.45mm, using a medium soft tissue reconstruction kernel. Retrospective ECG gating permitted optimal heart phase selection. Images were reconstructed at set percentage intervals of the cardiac cycle (45%, 50%, 60%, 75% and 80% of the RR interval) to allow evaluation of the coronary arteries at the cardiac phase with least vessel motion. The reconstructed data were then transferred to a dedicated offline image analysis workstation (Philips Extended Brilliance Workspace).

2.4.4 Reporting MSCT-CA

MSCT-CAs were reported according to the 15-segment model of the AHA.[89] A segment with a luminal diameter reduction ≥ 50% was classified as a significant stenosis. MSCT-CAs were reported by two independent, experienced, consultant radiologists and discrepancies involving stenoses considered by one radiologist, but not the other, to be ≥ 50% were resolved by an independent consultant cardiologist experienced in MSCT-CA. The images from each MSCT-CA were all reconstructed and post-processed by the same consultant radiologist with the subsequent independent reporters having the option to report from the reconstructions available or perform further reconstructions. All reporters were blinded to each other's MSCT-CA reports and to the patients' I-CA reports. All vessels regardless of diameter were assessed, including those distal to total occlusions.

For each vessel the optimal RR interval percentage reconstruction was identified. Stenoses identified in at least two independent orthogonal planes had their percentage of luminal reduction assessed on a semi-quantitative basis (0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 99%, 100% or "unevaluable"). The percentage of stenosis was ascertained by use of planimetry on an axis perpendicular to the course of the segment. Visualisation techniques varied between segments and included straight and curved multiplanar reformations, maximum intensity projections and volume rendering. Image quality for each segment was assessed subjectively as good (indicating the absence of image degrading artefact related to motion, calcification or noise), adequate (indicating evaluation possible with moderate confidence despite the presence of image degrading artefact) or non-diagnostic in the case of unevaluable segments. The degree of calcification of each segment's vessel wall was assessed subjectively as heavy (indicating high density lesions extending longitudinally along the vessel wall, resulting in beam hardening and partial volume artefact), moderate (indicating small, isolated eccentric high density lesions in the vessel wall), or none. A formal Agatston calcium score was not

obtained to avoid the radiation exposure of an additional non-contrast CT scan. This was deemed ethically appropriate given that all study patients were already receiving a significant radiation dose from a retrospectively gated MSCT-CA in addition to that from subsequent I-CA.

2.5 Invasive coronary angiography

2.5.1 I-CA protocol

I-CAs were carried out a minimum of six days after MSCT-CA in order to limit the risk of a second contrast injection and a maximum of four weeks following MSCT-CA in order to maximise continuity of CAD. Urea and electrolytes were assessed immediately prior to I-CA to ensure that there had been no deterioration in renal function following the contrast injection for MSCT-CA. I-CAs were carried out at one of three cardiac catheterisation laboratories in Glasgow Royal Infirmary and the Golden Jubilee National Hospital. It was not deemed necessary to standardise the laboratory used for I-CA as I-CA is the gold standard investigation for determining CAD irrespective of where it is performed and the aim of the study was to compare the accuracy of MSCT-CA to I-CA in a "real life" setting. I-CA was performed applying the Judkins approach via the trans-radial or trans-femoral route and acquiring standard projections. The I-CA images were recorded onto VHS tape, CD-ROM or DVD depending on local recording facilities.

2.5.2 Reporting I-CA

As for MSCT-CA, I-CAs were reported according to the 15-segment model of the AHA[89] and luminal diameter reductions ≥ 50% were classified as significant stenoses. Each ICA was reported by two of four independent consultant cardiologists with considerable experience of performing and reporting I-CA. All reporters were blinded to each other's I-CA reports and to the patients' MSCT-CA reports. All vessels were assessed including

those distal to occlusions. The degree of stenosis in each diseased coronary artery segment was assessed semi-quantitatively in two orthogonal planes. Discrepancies concerning stenoses considered by one consultant, but not the other, to be ≥ 50% were resolved by consensus. This method was considered to best represent current clinical practice.

2.6 Ethical considerations

2.6.1 Good clinical practice

This study complied with the accepted standards of the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and satisfied all national and local laws, rules and regulations relating to clinical study content. The study protocol was approved by the Glasgow Royal Infirmary Local Research Ethics Committee via the Central Office for Research Ethics Committees (REC Reference Number 06/S0704/87).

2.6.2 Informed consent

Patients meeting the inclusion criteria of the study were, by definition, being referred for I-CA. After explanation of the I-CA procedure, with its inherent benefits and risks, patients were informed of the study. The aims, methods, anticipated benefits and potential risks of the study were explained and patients were given the opportunity to ask questions. Patients were then given an unambiguous patient information sheet, carefully written using lay terminology. Patients were informed of their right to abstain from participation in the study and to withdraw consent at any time. All patients had a minimum of 48 hours to consider the information presented in the patient information sheet before deciding on whether or not to participate. Patients who agreed to be enrolled in the study were given an appointment for MSCT-CA and freely given written informed consent was obtained by the principal investigator at attendance of this appointment.

2.6.3 Confidentiality

Each patient was allocated an individual patient identification number which was utilised on paper and electronic documents throughout the study. All anonymised electronic data were securely stored on the personal laptop computer of the principal investigator and subsequently the computer system of the Robertson Centre for Biostatistics.

2.6.4 Monitoring

The study was subject to review at any time by the Glasgow Royal Infirmary Local Research Ethics Committee. The responsibility for monitoring throughout the duration of the study was assumed by supervisor Dr FG Dunn and advisor Dr NER Goodfield.

2.6.5 Amendments

A notice of substantial amendment is defined as an amendment that is likely to affect to a significant degree: the safety or physical or mental integrity of the trial participants, the scientific value of the trial, the conduct or management of the trial or the quality or safety of any investigational medicinal product used in the trial. A notice of substantial amendment to information previously given on the National Research Ethics Service application was submitted to the Glasgow Royal Infirmary Local Research Ethics Committee on 23rd April 2007. This was to request permission to extend recruitment from the general cardiology clinics and rapid access chest pain clinics at Stobhill Hospital, a district general hospital in North Glasgow to include patients attending a specialist chest pain clinic at Glasgow Royal Infirmary in order to improve recruitment rate. This amendment was granted on 4th May 2007.

2.7 Funding

This study was funded by a project grant from the Chief Scientist Office who approved the methodology (Grant No. CZG/2/266).

CHAPTER 3

LITERATURE REVIEW 2007-2010

3.1 Introduction

There have been considerable advances in MSCT scanner technology since commencement of this study. Consequently there has been significant further research with respect to potential expansion of the clinical capabilities of MSCT-CA. Research to date, however, has not provided answers to the questions posed by the present investigative work (see 1.6). Nevertheless, the results of this study must be considered in the context of an up-to-date review of the literature. This section will therefore discuss the more recent attempts to validate 40-64-slice MSCT-CA along with the development of dual source CT-CA and 128-320-slice-MSCT-CA. It will go on to outline the evidence for the use of MSCT-CA in evaluation of patients with coronary artery bypass grafts and intra-coronary stents and then conclude with the most recent national and international guidelines for the implementation of MSCT-CA in clinical practice.

3.2 64-slice MSCT-CA

Since commencement of the present investigative work, numerous further studies evaluating the diagnostic accuracy of 64-slice MSCT-CA have been published. Two meta-analyses have confirmed very high sensitivity and NPV and high specificity and PPV on a per patient basis for 64-slice MSCT-CA in the detection of coronary stenoses $\geq$ 50%.[90,91] The first meta-analysis assessed 27 studies of which 13 studies, comprising 875 patients, presented accuracy parameters on a per patient basis.[90] Sensitivity, specificity, PPV and NPV were 97.5%, 91%, 93.5% and 96.5% respectively. The second meta-analysis considered 28 studies of which 18 studies, comprising 1286 patients, presented accuracy parameters on a per patient basis.[91] Sensitivity, specificity, PPV and NPV were 99%, 89%, 93% and 100% respectively. Overall patient prevalence of CAD in both meta-analyses was 58%. The accuracy of 64-slice MSCT-CA is clearly superior to 16-slice MSCT-CA. This is demonstrated by comparison with a meta-analysis published in 2006 which included data from 18 16-slice studies, one 32-slice study, one 40-slice study and nine 64-slice

studies and found that with an average patient prevalence of 64%, sensitivity, specificity, PPV and NPV were 96%, 74%, 83% and 94% respectively.[92]

The authors of all three meta-analyses concluded that despite most studies to date being performed in patients with a relatively high prevalence of CAD, the likely clinical role for MSCT-CA would be in patients with an intermediate pre-test probability of disease. Those at low risk should not need MSCT-CA or I-CA and those at high risk should proceed directly to I-CA.

While the accuracy of 64-slice MSCT-CA demonstrated by these meta-analyses seems impressive the results should be interpreted with caution. Firstly, as with all meta-analyses, the results were to an extent influenced by heterogeneity between the included studies and were also prone to error due to the well documented small study effect and to publication bias.

Secondly, the individual studies varied in how they dealt with unevaluable segments. Some authors simply excluded them from all analyses while others considered each unevaluable segment to represent a significant stenosis. On a patient-based assessment, the former approach has the potential to falsely elevate specificity, with a corresponding reduction in sensitivity. The latter approach results in more false positive scans with a reduction in specificity and a falsely elevated sensitivity. Considering the unevaluable segments to represent significant stenoses for the per patient analysis is clearly the clinically relevant strategy, as in practice, a patient with a partially unevaluable MSCT-CA would need to proceed to I-CA for a definitive diagnosis. Unfortunately this analytical approach was not adopted by all studies nor was it necessarily made explicit when this was not done.

Finally, the majority of published 64-slice MSCT-CA studies were carried out in highly selected patient groups in large, academic centres with substantial experience in performing and reporting MSCT-CA. It is not clear, therefore, whether or not the significant accuracy alluded to in these studies is transferable to routine clinical practice in a more heterogeneous patient population in smaller centres with variable expertise.

3.3 40-slice studies

Prior to commencement of the present investigative work only one published study had used a 40-slice scanner.[74] Since the beginning of 2007 a further six studies have demonstrated diagnostic accuracy of 40-slice MSCT-CA (Table 3.1).[93-98] Prevalence of CAD varied greatly between studies from 18%[94] to 77%[93] and an effect on the reported accuracy parameters was evident with PPV and NPV for the low prevalence and high prevalence studies respectively being 67%, 98% and 88%, 55%. One study of 85 patients with an intermediate patient prevalence of CAD (53%) reported very high sensitivity, specificity, PPV and NPV; 98%, 93%, 94% and 93% respectively.[96] This would suggest that in the appropriate patient group, the accuracy of 40-slice MSCT-CA is not much different from that of 64-slice MSCT-CA.

Table 3.1 Studies evaluating the accuracy of 40-slice MSCT-CA accuracy in comparison to I-CA

Author[Ref] (Year - Country)	Temp. Res. ms (MSR)	Patient Group	Patients (excluded)	Mean Age (% Male)	Patient Prev CAD %	Mean HR bpm (% ß Blocker)	AHA Segment model	Segment inclusion (% excluded)	Per Segment Sn (95%CI)	Per Segment Sp (95%CI)	Per Segment PPV (95%CI)	Per Segment NPV (95%CI)	Per Patient Sn (95%CI)	Per Patient Sp (95%CI)	Per Patient PPV (95%CI)	Per Patient NPV (95%CI)
Halon[93] (2007 - Israel)	210 (No)	Suspected or known CAD	111	60 (81)	77	_	_	> 1.5mm (13.7)	72 (66-79)	95 (93-96)	71 (64-78)	95 (89-93)	85 (77-92)	62 (43-80)	88 (81-95)	55 (37-73)
Lim[74] (2005 - Singapore)	53 (Yes)	Suspected or known CAD ± PCI	30 (0)	59 (67)	_	61 (-)	16	All (4)	99	98	94	99	_	_	_	_
Pouleur[94] (2007 - Belgium)	52-210 (Yes)	Valvular disease	82 (0)	62 (64)	18	69±13 (51)	16	≥ 1.5mm (1.7)	93	96	_	_	93 (82-100)	90 (82-97)	67 (46-87)	98 (95-100)
Runza[95] (2007 - Italy)	_	Suspected or known CAD	50 (?)	61 (76)	_	_	_	_	94	94	91	96	100	100	100	100
Watkins[96] (2007 - USA)	125-210 (Yes)	Suspected or known CAD ± PCI/grafts	85 (0)	59 (85)	53	59 (-)	17	All (0)	86 (79-92)	97 (95-98)	75 (67-82)	97 (97-99)	98 (93-100)	93 (83-100)	94 (86-100)	93 (91-100)
Grosse[97] (2007 - Austria)	_	Suspected or known CAD	40 (0)	- (70)	75	_	_	All (7.9)	87	99	98	95	_	_	_	_
Tsai[98] (2007 - Taiwan)	210 (No)	Low risk acute coronary syndromes	40 (0)	(71)	_	59.6±8.7 (-)	_	> 1.5mm (1.2%)	98 (94-99)	98 (96-98)	89 (84-93)	99 (98-99)	_	_	_	_

Temp. Res. (MSR) = temporal resolution (multi-segment reconstruction), PCI = percutaneous intervention (stents), Prev. = Prevalence, HR = heart rate, Sn = sensitivity, Sp = specificity

3.4 Multi-centre studies

To date there have been four large prospective multi-centre studies comparing the accuracy of MSCT-CA to I-CA for the detection of significant coronary artery stenoses.[57,99-101]

The earliest of these studies was the international Coronary Assessment by computed Tomography Scanning and Catheter Angiography study (CATSCAN) which evaluated the efficacy of 16-slice MSCT-CA across 11 centres worldwide.[57] The 187 patients studied had been referred for non-emergent I-CA for the evaluation of chest pain and had an intermediate to high pre-test probability of CAD. Patients with previous CABG and recent myocardial infarction were excluded in addition to those with BMI > 40 and those with an Agatston calcium score > 600. MSCT-CA and I-CA were reported at independent core laboratories according to the 17-segment model of the AHA. A stenosis > 50% was considered significant. On a per segment analysis sensitivity, specificity, PPV and NPV were 85% (95% CI 76-96), 91% (95% CI 90-92), 36% (95% CI 29-44) and 99% (95% CI 99-100) respectively. However, 29% of all segments with diameters > 2mm were excluded as they were deemed unevaluable by MSCT-CA due to respiratory or cardiac motion, excessive calcification or poor opacification. For the more clinically relevant per patient analysis, a patient was considered to have significant CAD if at least one segment > 2mm diameter had a stenosis of > 50%. Patients with one or more unevaluable, non-distal segment were also considered to have significant disease. Interestingly, patient prevalence of significant disease in this study was only 32% despite the patients being considered to have an intermediate to high pre-test probability. Per patient sensitivity, specificity, PPV and NPV were 98% (95% CI 95-100), 54% (95% CI 45-63), 50% (95% CI 41-59) and 99% (95% CI 96-100) respectively. This study confirmed the high negative predictive value for MSCT-CA suggested by numerous single-centre studies but demonstrated a significantly higher number of false positives, mostly due to the large number of unevaluable segments. Indeed 38% of scans were considered to be not fully evaluable.

The authors postulated various reasons for the high number of unevaluable scans including their use of quantitative MSCT-CA analysis which has previously been shown to reduce the number of evaluable segments in comparison to a qualitative analysis.[15] In clinical terms, this study suggested that routine implementation of MSCT-CA for assessment of suspected CAD in this patient group would allow I-CA to be safely avoided in up to 37% of patients referred. However, due to the high number of false positives studies, this would be offset by many unnecessary I-CAs being performed.

The Coronary artery Evaluation using 64-row multi-detector computed tomography angiography study (CorE-64) published in 2008 was a prospective, international, multi-centre, study assessing the accuracy of MSCT-CA in nine hospitals across seven countries using centralised, blinded, quantitative analysis.[99] This study included 291 patients with an intermediate to high pre-test probability of significant CAD. Indeed, 20% had previously had a myocardial infarction and 21% had unstable angina at presentation. Correspondingly the prevalence of significant disease in the study population (defined as at least one stenosis ≥ 50% on I-CA) was higher than that in CATSCAN at 56%. As would be expected in a group with a higher prevalence of disease, the NPV in the per patient analysis was reduced to 83% (95% CI 75-89). Sensitivity, specificity and PPV on a per patient basis were 85% (95% CI 79-90), 90% (95% CI 83-94) and 91% (95% CI 86-95) respectively. The lower sensitivity in this study in comparison to the sensitivity of 98% demonstrated in CATSCAN can be explained by their different approaches to scans that were not fully evaluable. While in CATSCAN these scans were considered to be "positive", in CorE-64 they were considered "negative" and therefore not to have any significant disease. CorE-64 also demonstrated that MSCT-CA and I-CA had similar abilities to ascertain disease severity and to identify patients who would subsequently require revascularisation. The authors of this study concluded that while MSCT-CA could accurately determine the presence and severity of significant CAD in symptomatic

patients, the NPV and PPV demonstrated indicate that MSCT-CA could not replace conventional coronary angiography at present.

The Assessment by Coronary Computed tomography Angiography of Individuals Undergoing Invasive Coronary Angiography study (ACCURACY) is the only prospective multi-centre trial to evaluate the diagnostic accuracy of MSCT-CA in patients without known CAD and considered to have an intermediate pre-test probability.[100] This is in line with recent recommendations from the AHA and the ESC based on meta-analyses of single centre studies of MSCT-CA accuracy.[102,103] Correspondingly, the ACCURACY investigators excluded any patient with previous MI or any angiographically documented CAD including those with previous CABG and PCI. In order to ensure the study population was as similar to a "real world" population as possible, no patients were excluded on account of elevated body mass index or elevated Agatston calcium scores. A total of 230 patients were studied across 16 US centres. MSCT-CAs were reported qualitatively using the 15-segment model of the AHA by three independent blinded reporters at a central laboratory and I-CAs were reported quantitatively by a single I-CA reporter blinded to the results of the MSCT-CAs. No MSCT-CAs were deemed unevaluable and all patients were included in the final per patient analysis. Average patient age was 57 years and 59% of patients were male. Average BMI was 31.4 and mean Agatston calcium score was 284±538. The overall patient prevalence of significant CAD defined as the presence of at least one stenosis ≥ 50% identified on I-CA, was 25%. The authors reported an AUC (area under the curve) of 0.96 (95% CI 0.94-0.98) for identification of patients with significant CAD. On the per patient analysis sensitivity, specificity, PPV and NPV were 95% (95% CI 85-99), 83% (95% CI 76-88), 64% (95% CI 53-75) and NPV 99% (95% CI 96-100) respectively.

The most recent multi-centre study was published shortly after ACCURACY and was a prospective study of 360 patients with stable and unstable anginal syndromes referred for I-CA at three University Hospitals.[101] Patients with previous evidence of CAD were included but those with previous PCI or CABG were excluded. An age limit of 80 years was set in order to minimise the presence of severe calcifications which are more common in the elderly. 64-slice MSCT-CA was performed and compared to I-CA for the detection of stenoses ≥ 50% using a modified 17-segment model of the AHA. Mean patient age was 60 years and 68% of patients were male. Average BMI was 27.3 and median Agatston calcium score was 213. Overall patient prevalence of CAD was 68%. On the per patient analysis sensitivity, specificity, PPV and NPV were 99% (95% CI 98-100), 64% (95% CI 55-73), 86% (95% CI 82-90) and 97% (95% CI 94-100) respectively. The poor specificity was considered secondary to the tendency of MSCT-CA to over-estimate the severity of stenoses and to the inclusion of unevaluable segments which for the purpose of analysis were considered positive for significant disease.

Considering the four multi-centre studies together, 16-64-slice MSCT-CA has a very high negative predictive value for ruling out significant CAD. It appears that this is the case across patient groups with low-intermediate prevalence (25%) to those with a high prevalence (68%) of CAD. Specificity, however, has a tendency to be compromised by clinically appropriate inclusion of unevaluable segments. Indeed, the only multi-centre study with a high specificity was CorE-64 where unevaluable segments were ignored.

3.5 Dual source CT-CA

The diagnostic accuracy of MSCT-CA has improved considerably with advancements in scanner technology. The improvements in image quality can predominantly be attributed to the faster gantry rotation speeds of the newer scanners which translate into better temporal resolution and reduced motion artefact. However, even on the newest 128- to

320-slice scanners, the fastest gantry rotation is about 280ms which with a conventional half sector acquisition protocol equates to a temporal resolution of 140ms. This, when compared to the temporal resolution of I-CA of 20ms, is clearly suboptimal. It would seem that increasing gantry rotation speed further is beyond today's technological limits due to the substantial mechanical forces that would be required. Thus, until recently, research has focused on improving effective temporal resolution by pharmacologically lowering patient heart rates and by the utilisation of multi-segment reconstruction protocols. The former strategy is limited by beta-blockade often being either contraindicated or ineffective while the latter approach has been criticised for its potential to reduce image quality due to data reconstructions averaging non-identical cardiac cycles. Multi-segment reconstruction also necessitates a reduction in pitch which subsequently augments scan length and the associated radiation exposure.

The recent introduction of the dual source CT (DSCT) scanner has to an extent overcome some of these difficulties. A DSCT scanner is characterised by two x-ray tubes with two corresponding detectors mounted at 90^0 to each other onto a rotating gantry. With a rotation speed of 330ms, a quarter sector acquisition protocol permits a temporal resolution of 83ms which can be achieved with a single segment reconstruction and independent of patient heart rate. It was considered that this substantial improvement in temporal resolution would virtually eliminate cardiac motion artefact in patients with higher heart rates and in patients with arrhythmia such as atrial fibrillation. Pitch can be adapted to patient heart rate which reduces scan times and hence radiation exposure for patients with faster heart rates. An average scan time for DSCT-CA is between five and nine seconds. A further advantage of the DSCT scanner is that the two individual x-ray tubes can be set to different voltages. This allows the acquisition of dual energy data which improves tissue differentiation and has the potential to improve lumen visualisation in the context of calcification. Additionally, with the combined output of up to 160kW from the two x-ray

sources, obese patients can be imaged more successfully with a lower signal to noise ratio. The initial DSCT scanners were equipped with two 64 detector arrays[104] but more recently 128-slice DSCT scanners have been introduced.[105] These new generation wide array DSCT scanners are capable, in a high pitch mode, of complete cardiac coverage over a single cardiac cycle hence reducing both motion artefact and radiation dose.

To date there have been 16 prospective studies assessing the diagnostic accuracy of DSCT-CA in comparison to I-CA for the detection of significant CAD (Table 3.2).[106-121] These studies have included a total of 1292 patients with the number of patients in individual studies ranging from 15 to 170. Mean age was 62 and patients were predominantly male. The study populations included patients with suspected CAD and patients with known CAD and patient prevalence of CAD ranged widely from 23% to 82%. Heart rate control in these studies appeared similar to that of the 64-slice MSCT-CA studies with only four of the 16 DSCT-CA studies reporting a mean heart rate of > 70bpm (70.3, 71.8, 73 and 83.7).[112,113,115,121] Despite the expectation that DSCT-CA could allow accurate examinations of patients in AF, the majority of studies included only patients in normal sinus rhythm. In two studies a quarter of patients had AF and in another 8% of patients had AF.[110,112,116] Only two small studies specifically included only patients without sinus rhythm.[113,117] One examined 15 patients with AF[113] while the other studied 44 patients "without stable sinus rhythm", comprising 57% of patients with AF and the remainder with frequent ectopic activity or sinus arrhythmia with significant heart rate variability (>10bpm).[117] Only six studies reported their estimated effective radiation dose from DCST-CA.[106,112-114,118,119] This generally ranged from 8.3mSv to 16.9mSv with the lower doses in men and in patients with faster heart rates due to utilisation of pitch adaptive protocols. In one recent study, where a high pitch protocol was employed, estimated effective radiation dose was much lower at 0.9 (0.1) mSv.[119]

On a per segment basis sensitivity varied from 73% to 96.4%, specificity from 87% to 99%, PPV from 61% to 92% and NPV from 94% to 99.4%. On the more clinically relevant per patient analyses sensitivity varied from 81%-100%, specificity from 54% to 100%, PPV from 74% to 100% and NPV from 54% to 100%. The reported per patient accuracy parameters were considerably less impressive in the studies where patients did not have stable sinus rhythm and in studies with higher mean heart rates. The largest study of patients without sinus rhythm (57% AF) reported sensitivity, specificity, PPV and NPV on a per patient basis to be 81%, 54%, 81% and 54% respectively.[117] They attributed this to a high percentage of unevaluable segments as a result of motion artefact. Indeed despite using only the modified 13-segment model of the AHA and even after excluding segments with stents, only 12% of segments were completely free of artefact. The authors also postulated that their results were hampered by a relatively high prevalence of CAD in the patient population with associated higher levels of vessel calcification.

Perhaps surprisingly, the diagnostic accuracy of DSCT-CA does not appear to exceed that of 64-slice MSCT-CA. This may represent less careful patient selection for the DSCT-CA studies than the preceding MSCT-CA studies due to the presumed superiority of DSCT-CA. Indeed mean (SD) Agatston calcium scores in the eight DSCT-CA studies that reported it ranged from 309 (408) to 821 (904), reflecting the study populations' relatively high CAD prevalence.[107-110,115-117,121] Previous 64- MSCT-CA studies have demonstrated significant degradation in image quality with Agatston scores of > 400.[15,37] While DSCT-CA provides a considerable improvement in temporal resolution there is no improvement in spatial resolution which is imperative to reduce calcification associated artefact. A further point is that while standard DSCT-CA allows pitch to be increased and scan duration to be shortened in patients with higher heart rates, those with lower heart rates may still need to complete a 9 second breath hold. This increases the risk of artefact due to

respiratory motion. The newer generation DSCT scanners with high pitch protocol capabilities may overcome this constraint.[105,119]

There has been one randomised comparison of 64-slice MSCT-CA to 64-slice DSCT for the detection of significant CAD as determined by the gold standard I-CA.[106] In this study 200 patients were randomised to either 64-slice MSCT-CA or 64-slice DSCT-CA and then further randomised to receive oral or intravenous beta-blockade as required to achieve a heart rate of < 60 bpm or to receive no additional beta-blockade ("long-term beta-blocker therapy was not stopped"). In the two heart rate control groups, mean heart rate was successfully lowered by 10 bpm in comparison to the other two groups. This study demonstrated a significant improvement in patient evaluability from 69% to 93% for 64-MSCT-CA when heart rate was controlled, $p = 0.005$. This translated to improvements in all accuracy parameters. Patient evaluability with DSCT-CA was significantly higher than with MSCT-CA in the group with no heart rate control: 98% vs 69%, $p < 0.001$ but there was no improvement in evaluability with heart rate control in the DSCT-CA group: 98% vs 96%. The authors concluded that the better temporal resolution of DSCT-CA obviates the need for heart rate control.

In conclusion, while DSCT-CA achieves diagnostic image quality across a wider range of heart rates and to some extent in the context of arrhythmia, it remains limited by its spatial resolution and difficulties in assessing calcified segments.

Table 3.2 Studies of dual source CT-CA accuracy in comparison to I-CA

Author[Ref] (Year - County)	Patient Group	Patients (excluded)	Mean Age (% Male)	Patient Prev. CAD %	Mean HR (SD) bpm	SR or AF?	Segment Inclusion (% excluded)	Per Segment Sn % (95% CI)	Per Segment Sp % (95% CI)	Per Segment PPV % (95% CI)	Per Segment NPV % (95% CI)	Per Patient Sn % (95% CI)	Per Patient Sp % (95% CI)	Per Patient PPV % (95% CI)	Per Patient NPV % (95% CI)
Achenbach[106] (2008 - Germany)	Suspected CAD	100 (0)	61 (66)	40	69 (14)	SR	≥1.5mm (4%)	92 (81-97)	99 (98-100)	90 (79-96)	99 (99-100)	95 (77-99)	94 (79-98)	91 (72-98)	97 (93-99)
Alkadhi[107] (2008 - Switzerland)	Suspected CAD	150 (0)	62.9 (69)	39	68.5 (12.5)	SR	All (0)	95.6 (92.0-97.9)	96.3 (95.3-97.1)	76.0 (70.6-80.8)	99.4 (99.0-99.7)	96.6 (87.2-99.9)	86.8 (77.2-939)	82.6 (70.7-91.6)	97.5 (90.5-99.9)
Brodoefel[108] (2008 - Germany)	Suspected or known CAD	125 (0)	63.4 (68)	68	64.4 (-)	SR	All (stents)	91.6	93.0	75.2	97.9	100	77.5	90.4	100
Brodoefel[109] (2008 - Germany)	Suspected or known CAD	100 (0)	62 (80)	78	64.9 (13.2)	SR	All (stents)	91.1	92.0	75.4	97.5	100	81.5	93.6	100
Heuschmid[110] (2007 - Germany)	Suspected or known CAD	51 (0)	64 (73)	75	65 (14)	25% Not SR	All (stents)	96	87	61	99	97	73	90	92
Johnson[111] (2007 - Germany)	Suspected or known CAD	35 (0)	60 (69)	48	Median 68 [52-96]	SR	All (2% + stents)	88 (71-96)	98 (96-99)	78	99	100 (83-100)	89 (65-98)	89	100
Leber[112] (2007 - Germany)	Suspected CAD	88 (2)	58 (63)	23	73 (-)	8% AF	All (1%)	90	98	81	99	95 (76-99)	90 (80-95)	74 (58-89)	99 (91-99)
Leschka[119] (2009 - Switzerland)	Suspected or known CAD	35 (0)	62 (80)	_	≤ 60	_	All (0)	94	96	80	99	100	91	88	100
Meng[121] (2009 - China)	Suspected CAD	109 (0)	63 (62)	78	71.8 (13.2)	SR	≥ 15mm	95	91	65	99	98	79	94	91
Oncel[113] (2007 - Turkey)	AF and Suspected CAD	15 (0)	58.5 (60)	67	83.7 (8.9)	AF	All (6%)	80 (60-100)	99 (97-100)	80 (60-100)	99 (97-100)	100	75 (50-100	78 (50-100)	100

HR = heart rate, SR = sinus rhythm, AF = atrial fibrillation, Sn = sensitivity, Sp = specificity,

Table 3.2 Studies of dual source CT-CA accuracy in comparison to I-CA contd.

Author[Ref] (Year - County)	Patient Group	Patients (Excluded)	Mean Age (% Male)	Patient Prev. CAD %	Mean HR (SD) bpm	SR or AF?	Segment Inclusion (% excluded)	Per Segment Sn % (95% CI)	Per Segment Sp % (95% CI)	Per Segment PPV % (95% CI)	Per Segment NPV % (95% CI)	Per Patient Sn % (95% CI)	Per Patient Sp % (95% CI)	Per Patient PPV % (95% CI)	Per Patient NPV % (95% CI)
Plass[120] (2009 - Switzerland)	Valvular disease	40 (0)	_ (75)	53	_	SR	12 Seg Model (1)	91	99	92	99	_	_	_	_
Ropers[114] (2007 - Italy)	Suspected CAD	100 (0)	61 (63)	41	64 (13)	SR	≥1.5mm (0)	92 (86-96)	97 (95-97)	68 (60-75)	99 (99-100)	98 (88-100)	81 (69-89)	79 (66-88)	98 (89-100)
Scheffel[115] (2006 - Switzerland)	Suspected CAD	30 (0)	63.1 (80)	50	70.3 (14.2)	SR	≥1.5mm (2)	96.4 (87.7-99.6)	97.5 (95.4-98.9)	85.7 (74.6-93.3)	99.4 (98.0-99.9)	93.3 (68.1-99.8)	100 (78.2-100)	100 (76.8-100)	93.8 (69.8-99.8)
Tsiflikas[116] (2009 - Germany)	Suspected or known CAD	170 (0)	64 (73)	82	64 (9)	26% Not SR	All (stents)	92	93	75	98	94	79	88	90
Tsiflikas[117] (2009 - Germany)	Suspected or known CAD	44 (0)	67.5 (71)	68	69 (14)	"Not SR" 57% AF	All (stents)	73 (63-83)	91 (88-93)	63 (53-72)	94 (91-96)	81 (63-93)	54 (52-81)	81 (63-93)	54 (25-81)
Weustink[118] (2007 - Netherlands)	Suspected or known CAD	100 (0)	61 (79)	77	68 (11)	SR	All (0)	95 (90-97)	95 (93-96)	75 (69-80)	99 (98-99)	99 (92-100)	87 (65-97)	96 (89-99)	95 (74-100)

HR = heart rate, SR = sinus rhythm, AF = atrial fibrillation, Sn = sensitivity, Sp = specificify

3.6 128-, 256- and 320-slice MSCT-CA

The production of DSCT-CA focused on improvements in temporal resolution. Research in a different direction has focused on substantially reducing scan length. By increasing the number of slices, a greater volume can be scanned with each rotation of the gantry and so the MSCT-CA is performed over fewer cardiac cycles. 128-slice, 256-slice and 320-slice MSCT scanners have recently become commercially available. The 256-slice and 320-slice scanners are capable of completing MSCT-CA within one or two cardiac cycles. Firstly, this has the potential to considerably reduce motion artefact. The detrimental effects of cardiac arrhythmia and heart rate variation on image reconstruction are virtually eliminated. Furthermore, the required breath hold becomes negligible. Secondly, these scanners should markedly reduce effective radiation dose. Such dose reduction is in part due to the reduction in scan length but also to more reliable use of prospective gating.

Despite the commercial availability of 128-, 256- and 320-slice scanners, few studies have published data on clinical accuracy. Two small studies have evaluated 128-slice MSCT-CA.[122,123] The first was a feasibility study and included 20 patients who were scanned with a 128-slice scanner with a temporal resolution of 150ms.[122] The authors reported that five out of 20 patients had non-diagnostic scans which were mostly due to vessel calcifications but some motion artefact was also noted. Mean effective radiation dose in this study was 3.6mSv. The authors concluded that in selected patients with effective heart rate control and thorough instruction for breath hold compliance the 128-slice MSCT-CA was technically feasible. The second study included 78 patients with suspected or known CAD.[123] In this study 7% of segments were not assessable due to motion artefact or vessel calcification. The 128-slice MSCT-CA reports were compared to subsequent I-CA in all patients. After exclusion of the unevaluable segments, sensitivity, specificity, PPV and NPV for MSCT-CA on a per segment analysis were 87%, 97%, 83% and 97% respectively. The first study to evaluate the diagnostic accuracy of 256-slice MSCT-CA

included 104 patients with a high pre-test probability of CAD and subsequently a high prevalence determined by I-CA of 83%. On the clinically relevant per patient basis sensitivity, specificity, PPV and NPV were 99%, 50%, 92% and 88% respectively.[107] A later study compared prospectively gated 256-slice MSCT-CA to 64-slice MSCT-CA in terms of image quality and radiation dose.[124] This study demonstrated a significant increase in the proportion of assessable segments from 95.6% in the 64-slice group to 98.9% in the 256-slice group, $p< 0.05$. There was no significant difference in radiation dose between the two groups.

Image quality for 320-slice MSCT-CA was initially evaluated retrospectively in 40 patients.[125] The authors reported that using a 15-segment model, 89% of segments had excellent image quality with the most common reason for image degradation being cardiac motion. Only one segment in one patient was deemed unevaluable. However, the MSCT-CA results were compared with the gold standard I-CA in only four patients. In terms of radiation exposure, effective doses were higher when retrospective ECG gating was used, in larger patients and in those where imaging required two cardiac cycles. A subsequent study of clinical accuracy included 64 patients and reported per patient sensitivity, specificity, PPV and NPV to be 100%, 81%, 88% and 100% respectively.[126]

The potential benefits of 128- to 320-slice MSCT-CA in terms of radiation effective dose reduction are evident but it is not yet clear to what extent additional slices will improve the diagnostic accuracy of MSCT-CA and whether these improvements will be significant enough to justify increased expenditure on more sophisticated scanners. It is likely, however, that irrespective of whether or not 320-slice MSCT-CA is utilised for determining the presence and extent of CAD, it will have a role to play in the more novel applications of cardiac CT such as plaque characterisation, in addition to myocardial viability and perfusion imaging.

3.7 The role of MSCT-CA in evaluating patients with coronary artery bypass grafts

There is potential for MSCT-CA to be very useful in symptomatic patients with previous coronary artery bypass grafting (CABG). Selective injection of saphenous vein grafts can be technically challenging at I-CA and this can lead to prolonged studies with substantial contrast loads and greater radiation exposure for both the patient and the catheterisation laboratory staff. Conversely, the larger diameter of saphenous vein grafts and their relative lesser mobility makes them easier to visualise than native vessels on MSCT-CA. MSCT-CA in the post-CABG patient is also valuable in its ability to define the anatomical positions of grafts where the previous surgical history is incomplete and in particular its ability to identify the course of grafts which could be subject to iatrogenic damage in the context of repeat sternotomy.

Eight small studies have evaluated the diagnostic accuracy of 64-slice MSCT-CA[127-133] or 64-slice DSCT-CA[134] in the examination of patients with previous coronary artery bypass grafting (Table 3.3). Sensitivity, specificity and PPV and NPV for the detection of graft stenosis ≥ 50% is uniformly high. However, assessment of symptomatic patients with previous CABG must also consider the severity of disease in the native circulation and in particular in coronary segments distal to graft anastomoses (distal run-off arteries). Only a few studies have evaluated this and have demonstrated reduced diagnostic accuracy in comparison to graft assessment.[127,130,132,134] In particular the native coronary arteries were commonly heavily calcified, leading to overestimation of the severity of stenosis due to bloom artefact.[127,129,133] Additionally, in two studies a high prevalence of previous percutaneous intervention with intra-coronary stents was reported.[127,133] The latter of these studies reported that 54% of native coronary arteries and 18% of grafts in their patient population of 50 had previously been stented.[133] As a result, segment evaluation was compromised by the presence of bloom and beam hardening artefact. A further issue was the presence of artefact from metal vascular clips at the distal anastomoses. Arterial grafts

(left and right internal mammary artery grafts) tend to require more clips and as such were most commonly affected in some studies.[130,133] Clearly the most clinically relevant analysis when assessing a symptomatic patient with previous CABG is the per patient analysis where evaluation of severity of disease in native and grafted coronary arteries in addition to the grafts themselves is considered. Only one study has specifically reported this.[129,130] The study found that only two thirds of the 50 patients in their study were fully evaluable. While sensitivity was high at 97%, specificity was reduced to 86% most likely secondary to false positive assessments secondary to native coronary calcification and metal clip artefact at distal anastomoses.

In conclusion, it would seem appropriate for MSCT-CA to be performed in a post-CABG patient in circumstances where the native circulation is of minimal clinical relevance or where I-CA is contraindicated. Additionally it would be valuable prior to further cardiothoracic surgery in order to accurately define retrosternal graft position.

Table 3.3 The accuracy of MSCT-CA in patients with previous CABG

Author[Ref] (Year - Country)	Patients (excluded)	No. Grafts (excluded)	Graft Sn (95% CI)	Graft Sp (95% CI)	Graft PPV (95% CI)	Graft NPV (95% CI)	No. non-grafted Native Segments (excluded)	Native Sn (95% CI)	Native Sp (95% CI)	Native PPV (95% CI)	Native NPV (95% CI)
Malagutti[127] (2007 - Netherlands)	52 (0)	109 (0)	100 (90.9-100)	98.3 (89.9-99.9)	98.0 (88.0-99.9)	100 (92.4-100)	288 (0)	96.9 (88.2-99.5)	85.7 (80.3-89.9)	66.0 (55.4-75.2)	99.0 (95.9-99.8)
Meyer[128] (2006 - Germany)	138 (0)	397 (9)	97 (92-99)	97 (96-99)	93 (87-97)	99 (96-99)	–	–	–	–	–
Pache[129] (2006 - Germany)	31 (0)	93 (3)	97.8 (88.5-99.9)	89.3 (76.9-96.5)	90 (78.2-96.7)	97.7 (87.7-99.9)	–	–	–	–	–
Ropers[130] (2006 - Germany)	50 (0)	138 (0)	100	94	92	100	566 (55)	86	76	44	96
Feuchtner[131] (2007 - Austria)	41 (0)	71 (0)	85	95	80	96	–	–	–	–	–
Dikkers[132] (2007 - Netherlands)	34 (0)	69 (0)	100	98.7	–	–	–	80.0	90.8	–	–
Jabara[133] (2007 - U.S.A.)	50 (0)	145 (2)	100 (76.8-100)	100 (96.5-1000	100 (76.8-100)	100 (96.5-100)	–	–	–	–	–
Weustink[134] (2009 - Netherlands)	52 (0)	152 (0)	100	100	100	100	118 (0)	97 (83-100)	92 (83-96)	83 (67-92)	99 (92-100)

Sn = sensitivity, Sp = specificity

3.8 The role of MSCT-CA in evaluating patients with intra-coronary stents

The potential capability of MSCT-CA to determine intra-coronary stent patency has also been studied. MSCT-CA analysis of stented segments in the early 16-slice studies was difficult due to the dense stent material promoting bloom artefact that degraded image quality.[135] Nevertheless, MSCT-CA was capable of ruling out in-stent restenosis in larger stents, particularly in those situated in the left main stem.[136] Clinical applicability was limited, however, due to numerous false positive assessments in smaller stents and a high number of unevaluable stents.[137]

A recently published meta-analysis confirmed much improved diagnostic accuracy for 64-slice MSCT-CA in the detection of in-stent restenosis.[138] The authors reviewed 14 studies where 64-slice MSCT-CA or, in two studies, 64-slice DSCT-CA were evaluated for their value in detecting stent patency. Pooled sensitivity and specificity were 90% (95% CI 86-94) and 91% (95% CI 90-93) respectively for detection of re-stenosis in stents considered evaluable by MSCT-CA. However, the mean percentage of unevaluable stents across the studies was 11% and when these were included in calculation of accuracy parameters (in five studies only) sensitivity and specificity were reduced to 79% (95% CI 68-88) and 81% (95% CI 77-84) respectively. The major issue with stent evaluation was the presence of metal causing artefact. In recognition of this the majority of studies included in the meta-analysis utilised a dedicated sharp, edge enhancing convolution kernel to limit the severity of high attenuation artefacts.[139] Stent diameter proved to be important in terms of evaluability and diagnostic accuracy. The authors concluded that 64-slice MSCT-CA could be considered reliable in the detection of in-stent restenosis in stents with diameter greater than 3mm. Of note, the two DSCT-CA studies included in the meta-analysis had fewer unevaluable stents than the MSCT-CA studies.[140,141] Despite this, it remained evident that stent diameter was very relevant in terms of accuracy with one study reporting a significant increase in false positive evaluations with diameter $\leq$ 2.75mm.[140]

To date there has been only one published study of 320-slice MSCT-CA in the detection of in-stent restenosis.[142] In this study of 53 patients with a total of 89 stents, 92% of stents were evaluable and the per stent prevalence of restenosis was 13%. Considering the unevaluable stents to have significant disease, sensitivity, specificity, PPV and NPV on a per stent basis were 92%, 83%, 46% and 98% respectively while on a per patient basis the corresponding accuracy parameters were 100%, 81%, 58% and 100%. Clearly, while sensitivity and NPV are impressive, the contribution of bloom artefact to false positive assessments is evident with reduced specificity and PPV. Similar to previous 64-slice MSCT-CA studies, a stent diameter of less than 3mm was associated with a reduction in diagnostic accuracy. In addition, reduced image quality and accuracy were apparent with increasing strut thickness.

In conclusion, 64-slice MSCT-CA may have a role in excluding in-stent re-stenosis in stents with a diameter > 3mm but the clinical applicability of this is questionable given its inability to reliably evaluate smaller stents. Currently there is no evidence for DSCT-CA or 320-slice MSCT-CA overcoming this difficulty but further studies are required.

3.9 International and national guidelines

The most recent international guideline concerning MSCT-CA was in the form of a scientific statement from the AHA Committee published in 2008.[102] This group recommended implementation of MSCT-CA for the evaluation of symptomatic patients with an intermediate pre-test likelihood of coronary artery stenoses after initial risk stratification including patients with equivocal stress tests. This was a Class IIa recommendation based on level B evidence. It was highlighted that high risk patients with a low pre-test likelihood should not proceed to MSCT-CA in view of the associated radiation dose and that patients with a high pre-test likelihood of significant disease should have I-CA rather than MSCT-CA as these patients are more likely to require

revascularisation and hence definitive evaluation of their coronary anatomy. The guidelines stated that while MSCT-CA was capable of evaluating patients with suspected anomalous coronary arteries, due to radiation protection concerns, magnetic resonance angiography (MRA) was preferable if available. These recommendations are similar to those from the AHA in 2006 except that MSCT-CA is no longer considered appropriate in high risk patients with a low pre-test likelihood of disease following stress testing.

The ESC also published updated guidelines on the implementation of MSCT-CA in 2008.[103] Again, MSCT-CA was considered appropriate for symptomatic patients with an intermediate pre-test risk of CAD but with the proviso that it be restricted to patients in whom diagnostic image quality could be expected and that it would be expertly performed and reported. Routine use of MSCT-CA to evaluate the presence or absence of re-stenosis of intra-coronary stents was not recommended although it was stated that this may be possible in certain, carefully selected cases e.g. a large stent in a proximal artery. Despite the evidence supporting MSCT-CA evaluation of coronary artery bypass grafts (CABG), this was not recommended by the ESC due to the inability of MSCT-CA to reliably visualise the native coronary arteries in these patients or to accurately assess distal vessel run-off. It was, however, considered that CABG assessment by MSCT-CA may occasionally be appropriate e.g. when I-CA has failed to visualise a graft. The use of MSCT-CA was advocated as a first-line investigation for the assessment of patients with suspected anomalous coronary arteries. MSCT-CA was also considered to have a role in delineating the anatomy of the coronary veins to facilitate biventricular pacing. Use of MSCT-CA was also recommended for the evaluation of complex congenital heart disease, particularly in the context of patients with permanent pacemaker systems where MRA would not be appropriate.

The National Institute for Health and Clinical Excellence (NICE) published guidelines in March 2010 for the investigation of patients with chest pain of recent onset.[143] These guidelines advocate the use of coronary artery calcium scoring in patients presenting with stable chest pain and a low estimated likelihood of underlying CAD of 10-29%. Thereafter, if the Agatston calcium score is greater than 0 but less than 400, 64-slice MSCT-CA is recommended for detection and evaluation of coronary artery disease. In the context of a calcium score of 0, consideration of other non-cardiac causes of chest pain is recommended while if the calcium score is greater than 400, I-CA rather than MSCT-CA is recommended. The guidelines go on to state that patients with an intermediate estimated likelihood of CAD of 30-60% should undergo investigation by way of functional imaging and proceed to I-CA if appropriate while patients with a high estimated likelihood of more than 60% should proceed directly to I-CA without prior MSCT-CA or functional testing.

CHAPTER 4

ACCURACY OF MSCT-CA IN COMPARISON TO I-CA FOR DETECTING SIGNIFICANT CAD - A PATIENT-BASED ANALYSIS

4.1 Introduction

The primary analysis of this study sought to determine the accuracy parameters (sensitivity, specificity, positive (PPV) and negative (NPV) predictive values) for MSCT-CA in comparison to I-CA on a per patient basis. If MSCT-CA is to replace the gold standard investigation of I-CA in select patient groups then its accuracy in comparison to the reference standard must first be evaluated in clinical context. Whether or not it can accurately determine the extent of stenoses in specific coronary artery segments is irrelevant if it cannot safely distinguish between patients with and without significant CAD. Therefore, in this patient-based analysis, any coronary segment that was deemed unevaluable by the MSCT-CA reporters was subsequently considered to represent a stenosis ≥ 50%. This strategy seemed to best represent clinical practice where patients whose MSCT-CAs were not fully evaluable would be referred for I-CA for a definitive diagnosis. This analytical protocol ensured the accuracy of MSCT-CA was not being over-estimated by the discounting of unevaluable segments.

A stenosis of ≥ 50% was considered to represent significant CAD. This threshold was selected to permit direct comparisons with previous MSCT-CA vs I-CA studies. However, a secondary analysis was performed to determine the accuracy of MSCT-CA in detecting stenoses ≥ 70% on a per patient basis. Stenoses at this level have conventionally been considered to represent obstructive CAD which will induce functional cardiac ischaemia.[144]

4.2 Statistical analysis

Statistical analysis was performed using statistical software: R Version 2.9.1. Quantifiable variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR). Sensitivity, specificity, PPV and NPV were calculated for MSCT-CA in comparison to I-CA for the detection of stenosis ≥ 50% on a per patient basis with 95%

confidence intervals (CI) calculated from binomial expression. Receiver operating characteristics (ROC) curves were created to determine the optimal threshold of coronary artery stenosis on MSCT-CA that would predict stenoses of ≥ 50% and ≥ 70% on I-CA. Categorical variables were compared between groups using exact Fisher tests and continuous variables were compared between groups using t-tests or Wilcoxon tests as appropriate. The estimated effective radiation dose in mSv was estimated from the product of the dose-length product and a conversion coefficient for the chest as the investigated anatomic region ($k = 0.017$ mSv x mGy^{-1} cm^{-1}) averaged between male and female models.[145]

4.3 Results

4.3.1 Patient baseline characteristics

The sample size calculation (detailed in chapter 2.1.4) had estimated that, with the previously suggested sensitivity and specificity of MSCT-CA and the expected prevalence of CAD in our population, 204 patients would be required to accurately estimate the NPV of MSCT-CA with an acceptable lower confidence limit. However, an interim analysis of the first 90 patients demonstrated the actual sensitivity and specificity of MSCT-CA and the study population prevalence of CAD to be so different from the anticipated values that the sample size calculation was effectively invalidated. Following expert statistical advice it was determined that continuing to pursue a sample size of 204 patients would not have enhanced achievement of the original study objectives and was hence potentially unethical. For this reason, following approval of the funding body, recruitment was stopped at a total of 100 patients.

Over 17 months a total of 100 patients (55 male, 45 female, mean (SD) age 58.0 (10.7)) were recruited. Just over half the patient population were hypertensive (defined as BP ≥ 140/90 mmHg[87] or current antihypertensive therapy) and / or were previous or current

smokers. Almost 90% had hypercholesterolaemia (defined as total cholesterol > 5 mmol/l[87]) or were on statin therapy. Forty per cent had a family history of premature CAD (defined as angina or myocardial infarction in a male relative age < 55 years or a female relative age < 65 years)[87] and 11% were diabetic. Employing the Duke Clinical Score,[88] the percentage of patients considered to have low (0-24%), intermediate (25-74%) and high (>75%) pre-test probabilities of significant CAD were 19%, 40% and 41% respectively. Mean (SD) body mass index (BMI) was 28.6 (5.2) kg/m^2 with no significant difference between males and females; 28.0 (4.9) and 29.3 (5.6) respectively, $p = 0.226$. Seventy-five per cent of patients had a BMI ≥ 25 and 35% had a BMI ≥ 30. Ninety-four per cent of patients described chest pain with 56% describing chest pain entirely consistent with angina and 38% describing atypical pain. Mean (SD) duration of symptoms prior to entry to the study was 12 (18) months with median (IQR) duration of symptoms 5 (2-13) months. Almost all patients, 91%, had had an exercise tolerance test prior to referral for I-CA. Almost one third of patients had had a thallium perfusion scan. Significantly more men than women described chest pain typical of angina; 67.3% and 42.2% respectively, $p=0.022$ and significantly more men than women were in the high pre-test probability group; 70.9% and 4.4% respectively, $p<0.001$. Otherwise, there were no significant differences in baseline patient characteristics between men and women. Patient characteristics are summarised in Table 4.1.

Table 4.1 Patient characteristics (N=100)

Mean Age Years (SD)	58.0 (10.7)
Hypertension*	54%
Hypercholesterolaemia*	87%
Smoking (Current)	25%
Smoking (Previous)	32%
Family History CAD*	40%
Diabetes Mellitus	11%
Mean BMI kg/m^2 (SD) BMI ≥ 30 kg/m^2 BMI < 30 kg/m^2	28.6 (5.2) 35% 65%
Chest Pain	94%
Typical Angina	56%
Median Symptom Duration - months (IQR)	5.0 (2.0-13.0)
Low Pre-Test Probability†	19%
Intermediate Pre-Test Probability†	40%
High Pre-Test Probability†	41%
Previous Exercise Tolerance Test	92%
Previous Myocardial Perfusion Imaging	29%
Beta-Blocker Therapy	66%
Rate-Limiting Calcium Channel Blocker Therapy	24%
Mean Heart Rate during MSCT-CA (SD)	68.8 (9.0)
Mean Radiation Dose mSv (SD)	15.6 (3.0)
Moderate Coronary Calcification on MSCT-CA	22%
Heavy Coronary Calcification on MSCT-CA	35%
No Significant Coronary Artery Disease (No stenosis ≥ 50%)‡	62.9%
Single Vessel Disease (1 vessel with stenosis ≥ 50%)‡	11.3%
Two Vessel Disease (2 vessels with stenoses ≥ 50%)‡	11.3%
Triple Vessel Disease (3 vessels with stenoses ≥ 50%)‡	14.4%

**Hypertension, hypercholesterolaemia and family history of CAD were defined respectively by the Joint British Societies' Guidelines 2005[87] as BP ≥ 140/90 (or current antihypertensive medication), cholesterol > 5mmol/l (or current statin medication) and angina or myocardial infarction in a male relative < 55 years or a female relative < 65 years*

† Pre-test Probability was determined utilising the Duke Clinical Score[88]

‡ Based on I-CA of 97 patients as in each of 3 patients 1 vessel was considered unevaluable on I-CA

4.3.2 MSCT-CA - patient characteristics

Mean (SD) heart rate during MSCT-CA was 68.8 (9.0) beats per minute. Almost all (90%) patients were taking regular rate limiting medication; 66% beta-blocker therapy and 24% rate limiting channel blockers. One patient was on ivabradine. There was no significant difference in mean heart rate between male and female patients. A considerable proportion of patients had moderate or heavy coronary artery calcification on MSCT-CA (57%). Arterial calcification was more common in men than women; 74% vs 36%, p<0.001. The calculated radiation dose from MSCT-CA ranged from 477.1mGy (approximately 8mSv) to 1338.9mGy (approximately 23mSv). Mean (SD) radiation dose

for MSCT-CA in men was 974.6 (166.1) (approximately 16.6mSv) and in women was 851.6 (173.4) (approximately 14.4mSv). This difference was statistically significant p=0.001. The time taken to report an individual MSCT-CA varied from 8 minutes to 40 minutes with a mean (SD) time of 22.6 (6.6) minutes.

4.3.3 I-CA - patient characteristics

Using the 15 segment model of the AHA,[89] the mean (SD) number of evaluable segments on I-CA per patient was 14.4 (1.3). The overall prevalence of significant CAD (at least one stenosis ≥ 50% on I-CA) was 38.4%. The prevalence of single, double and triple vessel disease was 11.3%, 11.3% and 14.4%. The prevalence of CAD with at least one stenosis ≥ 70% on I-CA was 32.7%. When minor CAD was included i.e. any stenosis ≥ 10%, the overall prevalence of CAD was 68%. Thirty-two per cent of patients were considered to have entirely normal coronary arteries on I-CA.

4.3.4 Accuracy parameters of MSCT-CA in comparison to I-CA for the detection of significant CAD ≥ 50% on a patient-based analysis

Table 4.2 demonstrates sensitivity, specificity, PPV and NPV with 95% confidence intervals for MSCT-CA in comparison to I-CA for the detection of stenoses ≥ 50% on a per patient basis.

Table 4.2 The accuracy of MSCT-CA for detecting stenoses ≥ 50% - patient- based analysis

ICA Stenosis ≥ 50%	MSCT Stenosis ≥ 50%			Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
	No	Yes	UE*				
No	29	8	24	92.1% (79.2%, 97.3%)	47.5% (35.5%, 59.8%)	90.6% (75.8%, 96.8%)	52.2% (40.5%, 63.7%)
Yes	3	27	8				
UE*	1	0	0				

**UE = Unevaluable - studies considered unevaluable overall due to one or more segments of a major artery being considered unevaluable and no significant disease being identified in the evaluable segments*

This analysis considered 99 of 100 patients with one patient excluded due to the I-CA being considered not fully evaluable and this patient having no stenosis ≥ 50% in the evaluable arteries. The MSCT-CAs of 32 patients were considered not fully evaluable due to there being at least one unevaluable segment of a major artery. To permit a clinically relevant patient-based analysis these patients were all considered to have significant CAD, subsequently generating 8 true positives and 24 false positives. Of 38 patients identified on I-CA as having at least one stenosis ≥ 50%, MSCT-CA correctly identified 35 patients (92%). In the three patients where MSCT-CA failed to detect CAD diagnosed on I-CA, a 70% distal circumflex lesion, an 80% left ventricular branch lesion, a 70% obtuse marginal vessel lesion and a 60% proximal right coronary artery lesion in the presence of moderate arterial calcification were missed.

4.3.5 Accuracy parameters of MSCT-CA in comparison to I-CA for the detection of significant CAD ≥ 70% on a patient-based analysis

Traditionally, a stenosis on I-CA of ≥ 70% was considered likely to be functionally significant and there was some evidence from intravascular ultrasound and fractional flow reserve studies to support this.[144] For this reason the patient-based analysis was repeated to determine the accuracy of MSCT-CA in the detection of stenoses ≥ 70%. The results are demonstrated in Table 4.3. This analysis included 98 of 100 patients with two patients excluded because their I-CAs were not fully evaluable and these patients had no stenoses ≥ 70% in their evaluable arteries.

Table 4.3 The accuracy of MSCT-CA for detecting stenoses ≥ 70% - patient-based analysis

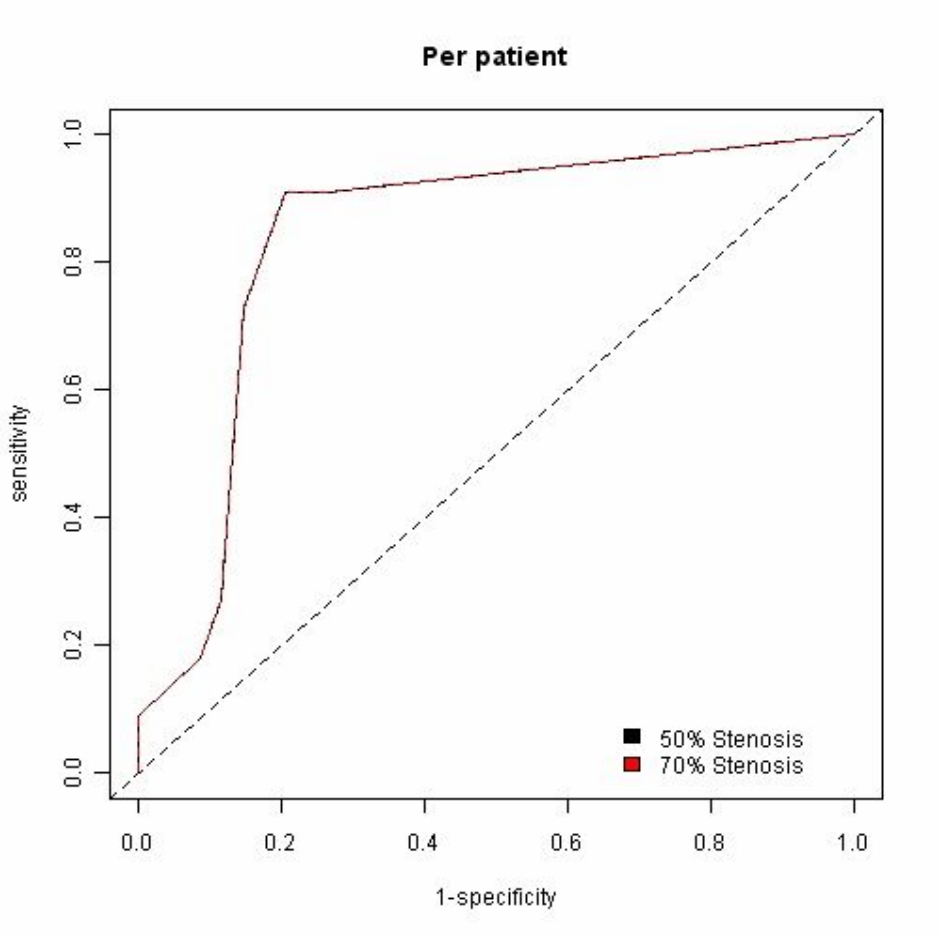
ICA Stenosis ≥ 70%	MSCT Stenosis ≥ 70%			Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
	No	Yes	UE*				
No	31	6	29	71.9% (54.6%, 84.4%)	47.0% (35.4%, 58.8%)	77.5% (62.5%, 87.7%)	39.7% (28.1%, 52.5%)
Yes	9	11	12				
UE*	1	1	0				

**UE = Unevaluable - studies considered unevaluable overall due to one or more segments of a major artery being considered unevaluable and no significant disease being identified in the evaluable segments*

4.3.6 ROC/AUC analysis of MSCT-CA in comparison to I-CA for the detection of significant CAD at the ≥ 50% and ≥ 70% levels

ROC analysis was performed on a per patient basis to determine the optimal threshold of coronary artery stenosis on MSCT-CA to maximise sensitivity and specificity for the detection of CAD identified as being ≥ 50% on I-CA. For this analysis, patients with one or more arteries that were not fully evaluable were excluded. For the detection of CAD determined ≥ 50% on I-CA, a cut-off level of ≥ 40% stenosis identified on MSCT-CA was appropriate, generating an AUC of 0.837. The AUC at the ≥ 70% stenosis level on I-CA was identical. This is explained by there only being 5 patients with I-CA identified stenoses ≥ 50% without any stenoses ≥ 70% and these 5 patients were all excluded from the ROC analysis on the basis that each had at least one artery that was not fully evaluable. These ROC curves are illustrated in Figure 4.1.

Figure 4.1 Patient-based analysis ROC curve



4.4 Discussion

The population examined in this study was representative of the Scottish population as a whole with multiple risk factors for CAD. Notably 40% had a family history of premature CAD. A quarter of patients were smokers with almost 1/3 having previously smoked. Similarly, a recent publication from the British Heart Foundation (BHF) reported that around 24% of Scottish men and women are smokers.[146] A considerable proportion (75%) of our study population were overweight with a BMI ≥ 25 while over one third were obese with a BMI ≥ 30. This is comparable to the recent report from the BHF which found that around 75% of the Scottish population between the ages of 65 and 74 years have a BMI of ≥ 25 while 22% of Scottish men and 26% of Scottish women have a BMI of ≥ 30.[146] The patients in our study had a higher prevalence of diabetes (11%) than the general Scottish population with the recent BHF report suggesting a prevalence of diabetes in Scotland of 4%.[146]

This is the first UK study comparing MSCT-CA to I-CA for the detection of significant CAD in a district general hospital setting. Only two previous studies (both Scandinavian) have reported 40-64-slice MSCT-CA accuracy explicitly in routine clinical practice.[147,148] In a per patient analysis, this study demonstrated that sensitivity, specificity, PPV and NPV for 40-slice MSCT-CA in the detection of CAD ≥ 50% were 92%, 48%, 52% and 91% respectively. These results are at variance with recently published meta-analyses of 64-slice MSCT-CA accuracy where sensitivity, specificity, PPV and NPV were 98-99%, 89-91%, 93-94% and 97-100% respectively.[90,91] Our results are, however, comparable to those of CATSCAN the first multi-centre study of MSCT-CA accuracy and to a Scandinavian study of 16-slice MSCT-CA in a community hospital setting.[57,70] In these studies specificity and PPV were reported to be 54% and 50%; and 29% and 57% respectively. Similarly the two previous district hospital studies evaluating the accuracy of 64-slice MSCT-CA or DSCT-CA demonstrated poor specificity and PPV in comparison to

tertiary centre studies.[147,148] In the first of these studies, despite 15% of patients being excluded altogether due to either high calcium scores or "technically unsuccessful" imaging and despite only segments ≥ 2mm in diameter being evaluated, overall specificity and PPV were only 78% and 77% respectively.[147] The even lower specificity and PPV in our study may have been due to all patients being included irrespective of calcium scoring or technical issues with scanning and to all segments being considered regardless of diameter.

In the per patient analysis for the accuracy of MSCT-CA in the detection of stenoses ≥ 70%, sensitivity, specificity, PPV and NPV were 72%, 47%, 40% and 78%. Few other studies have evaluated MSCT-CA accuracy at the ≥ 70% threshold. One 64-slice study reported patient-based sensitivity, specificity, PPV and NPV of 98%, 50%, 94% and 75%.[149] However valid comparisons with our study cannot be made for various reasons. In the aforementioned 64-slice study there was a very high prevalence of CAD of 88% and a strategy of excluding unevaluable segments. Furthermore, MSCT-CA accuracy was only considered at the ≥ 70% level and analysis at ≥ 50% was not performed. The multi-centre study ACCURACY[100] reported accuracy parameters for thresholds of both ≥ 50% and ≥ 70%. Sensitivity, specificity and NPV were effectively identical for both thresholds but PPV was higher at the ≥ 50% threshold; 64% compared to 48%. The authors reported that this likely reflected the tendency of MSCT-CA to over-estimate the severity of stenoses. Conversely, it would seem that in our study, MSCT-CA had a tendency to underestimate the severity of stenoses with sensitivity and NPV being lower at the ≥ 70% threshold at 72% and 75% respectively.

The low specificity and PPV in our study is certainly to some extent the consequence of our strategy for dealing with unevaluable segments. In the per patient analysis all MSCT-CAs that were not fully evaluable were considered positive for significant CAD. This

approach increased the number of false positive scans and hence reduced specificity and PPV, whilst falsely inflating sensitivity. It is, however, clearly the only clinically relevant strategy, as in practice, a patient with a partially unevaluable MSCT-CA would need to proceed to I-CA for a definitive diagnosis. This analytical approach was not adopted by all authors of previous studies with many discounting unevaluable segments in the per patient analysis.

The accuracy of MSCT-CA in our study may have been adversely affected by the characteristics of the patient population studied. A considerable proportion of our patients were overweight or obese and/or had at least moderate coronary artery calcification. Furthermore, despite 90% of our patients taking regular heart rate controlling medication, the mean (SD) heart rate during MSCT-CA was relatively high at 68.8 (9.0) in comparison to previous studies. The significance of each of these factors in terms of MSCT-CA evaluability and diagnostic accuracy is specifically discussed in Chapter 5.

Appropriate patient selection is imperative in order to emulate the high accuracy of MSCT-CA demonstrated in studies from large, academic centres in routine practice. The training and experience of those involved in performing and reporting the scans is equally important. The need for radiologists and cardiologists to undergo appropriate training and to achieve accreditation in MSCT-CA prior to independent reporting is recognised in international guidelines.[103,150] It is likely that the relative inexperience of our centre in terms of performing and reporting MSCT-CA adversely affected diagnostic accuracy. Notably, one previous district hospital study of MSCT-CA accuracy demonstrated a statistically significant improvement in diagnostic specificity with increasing reporter experience as their study progressed.[148] The technical aspects of performing MSCT-CA including ensuring appropriate patient pre-medication may have reduced accuracy in published multi-centre studies.[57,99,100] Accuracy of MSCT-CA in these studies may have

been further reduced had the MSCT-CAs been reported at the individual hospitals by local cardiology and radiology staff rather than by experts in core laboratories in specialist centres.

A further limitation of our study was our use of a 40-slice MSCT scanner rather than the now widely distributed 64-slice scanner. There have been few studies assessing MSCT-CA accuracy with 40-slice scanners but it is not considered to be significantly inferior to its 64-slice counterpart.[74,93-96] The development of the now commercially available dual source and 320-slice scanners will likely overcome many of the technical difficulties of 40-64-slice scanning presented above but until NHS funding is sufficient to install these scanners in multiple sites, 40-64-slice scanners and even 16-slice scanners will continue to be used and so the findings of our work retain clinical relevance.

4.5 Conclusion

This study evaluated the diagnostic accuracy of 40-slice MSCT-CA in a district general hospital in the west of Scotland. The per patient analysis demonstrated a high sensitivity and NPV for the detection of CAD $\geq$ 50%. ROC analysis demonstrated a tendency for MSCT-CA to underestimate severity of CAD and suggested a cut off of stenosis $\geq$ 40% on MSCT-CA as indicative of I-CA stenosis $\geq$ 50%. The specificity and PPV of MSCT-CA were compromised by a high number of unevaluable scans. Unevaluable scans occurred secondary to a number of factors including various patient characteristics (discussed further in chapter 6).

It would seem that the high accuracy of MSCT-CA alluded to in the studies published from large academic centres with substantial experience in MSCT-CA is not directly transferable to routine clinical practice in a district general hospital in Scotland. Implementation of MSCT-CA as a gate-keeper to I-CA in the patient population studied

here would have avoided a proportion of I-CAs following negative MSCT-CAs but many unnecessary I-CAs would have been performed following unevaluable MSCT-CAs. The high negative predictive value demonstrated (91%) and the prevalence of CAD in the population studied (38%) would suggest that the strength of MSCT-CA in this setting is the exclusion of significant CAD without requiring I-CA. However, care must be taken to ensure MSCT-CAs are sufficiently evaluable and MSCT-CA may be less appropriate in patients with certain characteristics. This will be considered further in chapter 6.

CHAPTER 5

VARIATIONS IN MSCT-CA ACCURACY FOR DETECTING CAD BY ARTERY AND BY SEGMENT

5.1 Introduction

In terms of clinical relevance the per patient analysis detailed in chapter 4 is of greatest importance. However, the potential for variation in accuracy of MSCT-CA in detecting significant stenoses in specific coronary segments or arteries is interesting and may provide insight into some of the technical constraints of the procedure. This chapter will first present the accuracy parameters of MSCT-CA in comparison to I-CA for the detection of significant CAD on a per segment basis and then on a per artery basis. Discussion of the potential reasons for variability in image quality and diagnostic accuracy will follow.

5.2 Statistical analysis

Segments were defined on I-CA and MSCT-CA by the 15-Segment Model of the AHA.[89] Nominally the following segments were assessed: left main stem (LMS), proximal left anterior descending artery (LAD), mid LAD, distal LAD, first diagonal artery (D1), second diagonal artery (D2), proximal circumflex artery (Cx), distal Cx, first obtuse marginal artery (OM1), second obtuse marginal artery (OM2), proximal right coronary artery (RCA), mid RCA, distal RCA, posterior descending artery (PDA) and left ventricular branch (LV branch). The LV branch was defined as the branch supplying the inferior surface of the heart. This was an extension of the Cx in left system dominant circulations and of the RCA in right system dominant circulations. Segments considered absent or unevaluable on I-CA or MSCT-CA were excluded from the per segment analysis.

In the per artery analysis individual segments were analysed together in groups. The LAD artery comprised proximal, mid and distal LAD segments in addition to the LAD branches (D1 and D2). The Cx artery comprised the proximal and distal Cx segments in addition to the Cx branches (OM1 and OM2). The RCA comprised the proximal, mid and distal RCA segments in addition to the PDA and the LV branch. The LMS was considered separately. In the per artery analysis, segments deemed unevaluable by MSCT-CA were considered to

represent significant stenoses unless the unevaluable segment was in a branch (D1, D2, OM1, OM2, PDA, LV branch) in which case it was ignored. An artery was therefore considered to have a significant stenosis if any of its segments contained significant stenoses or if any of the individual major arterial segments were considered unevaluable.

Statistical analysis was performed using statistical software: R Version 2.9.1. Quantifiable variables were expressed as mean and standard deviation (SD) or median and interquartile range. Sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values were calculated for MSCT-CA in comparison to I-CA for the detection of stenosis ≥ 50% on a per segment and per artery basis with 95% confidence intervals (CI) calculated from binomial expression. Receiver operating characteristics curves were created to determine, per artery, the optimal threshold of coronary artery stenosis on MSCT-CA that would predict stenoses of ≥ 50% and ≥ 70% on I-CA. Inter-modality agreement data for MSCT-CA and I-CA for the detection of CAD ≥ 50% data were expressed as Cohen's kappa statistics (κ) with bootstrap confidence intervals (1000 replicates) on a per segment and a per artery basis. Interpretation was facilitated by the guidelines of Landis and Koch[151] where $\kappa < 0$, 0.0-0.20, 0.21-0.40, 0.41-0.60, 0.61-0.80, 0.81-100 represent "no agreement", "slight agreement", "fair agreement", "moderate agreement", "substantial agreement" and "almost perfect agreement" respectively.

5.3 Results

5.3.1 Accuracy parameters of MSCT-CA in comparison to I-CA for the detection of significant CAD at the ≥ 50% and ≥ 70% levels - A segment-based analysis

Accuracy parameters for MSCT-CA on a per segment basis were determined following exclusion of segments deemed unevaluable by MSCT-CA reporters. Segments considered unevaluable or absent by I-CA reporters were also excluded. Using the 15-Segment model of the AHA[89] the mean (SD) percentage of MSCT-CA evaluable segments per patient was

64.2% (22.9) with the mean number of evaluable segments per patient being 9.6 (3.4). In comparison, the mean (SD) number of segments per patient identified on I-CA was 14.4 (1.3). The mean (SD) percentage of evaluable segments considered to have good image quality on MSCT-CA was 45.5 (29.5)% while the mean (SD) percentage with only adequate quality was 54.2 (29.5%). On MSCT-CA distal segments were more often excluded than proximal segments. For example 8 LMSs, 10 proximal LADs, 11 proximal Cxs and 5 proximal RCAs were considered unevaluable in comparison to 70 D2s, 79 OM2s and 42 PDAs.

After excluding all unevaluable segments (34%), the per segment prevalence of significant CAD was 9.5% and 5.9% for stenoses ≥ 50% and ≥ 70% respectively. Table 5.1 demonstrates sensitivity, specificity, NPV and PPV for MSCT-CA for the detection of stenoses ≥ 50% on a per segment basis. Overall per segment sensitivity was poor at 36.3%. Sensitivity was highest for the proximal and mid LAD and RCA and the proximal Cx. Sensitivity was lowest for detection of CAD in branch vessels although the very small number of branches where I-CA identified disease means the confidence intervals are very wide. Sensitivity for the detection of LMS stenosis ≥ 50% was surprising low at 14.3%. I-CA detected eight LMS lesions ≥ 50% and MSCT-CA identified only one. Of those missed by MSCT-CA, one LMS was unevaluable due to heavy calcification, two LMS lesions were underestimated (both considered by MSCT-CA reporters to be 40%), three were missed in the context of a heavily calcified LMS or proximal LAD and one was missed despite reported good image quality (Figure 5.1 (a-c)). The sensitivity of MSCT-CA for the detection of significant stenoses ≥ 70% on a per segment basis was also poor at 21.4% (Table 5.2). Again, sensitivity for the detection of stenoses in more proximal segments was marginally better.

Figure 5.1 (a) False negative LMS assessment despite "good" image quality

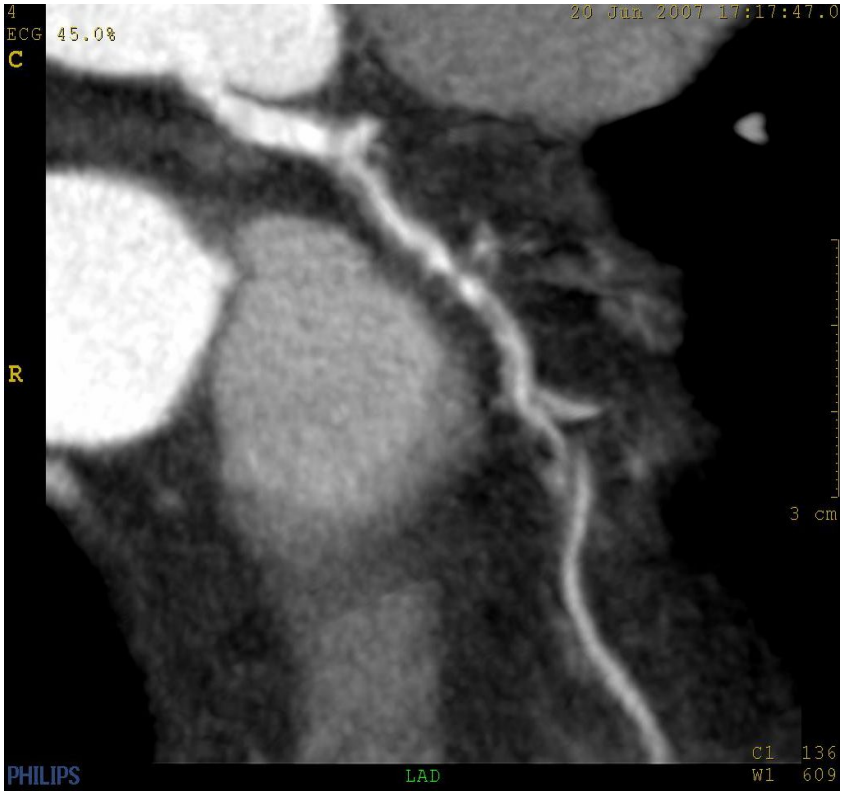


Figure 5.1 (b) False negative LMS assessment in the context of calcification

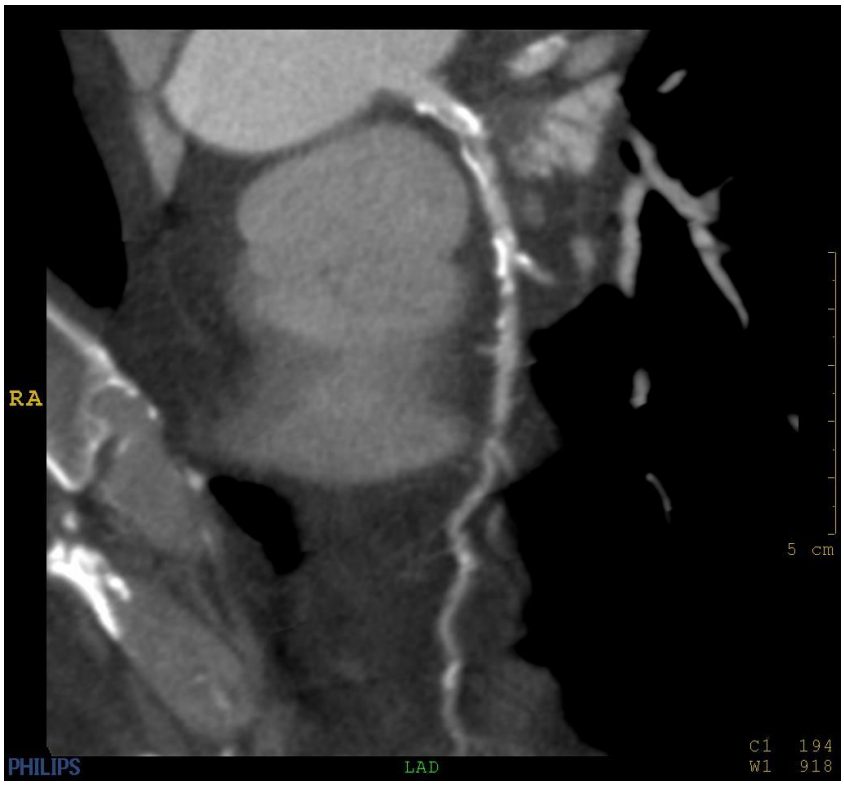


Figure 5.1 (c)i Curved multiplanar reformation of significant LMS lesion underestimated by MSCT-CA as 40% luminal stenosis

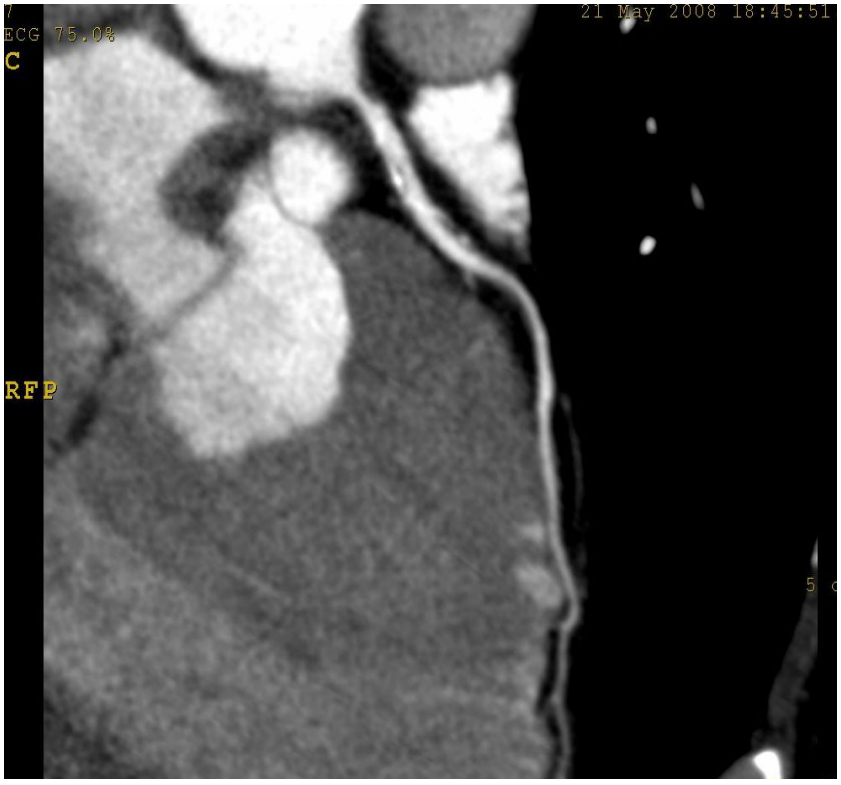
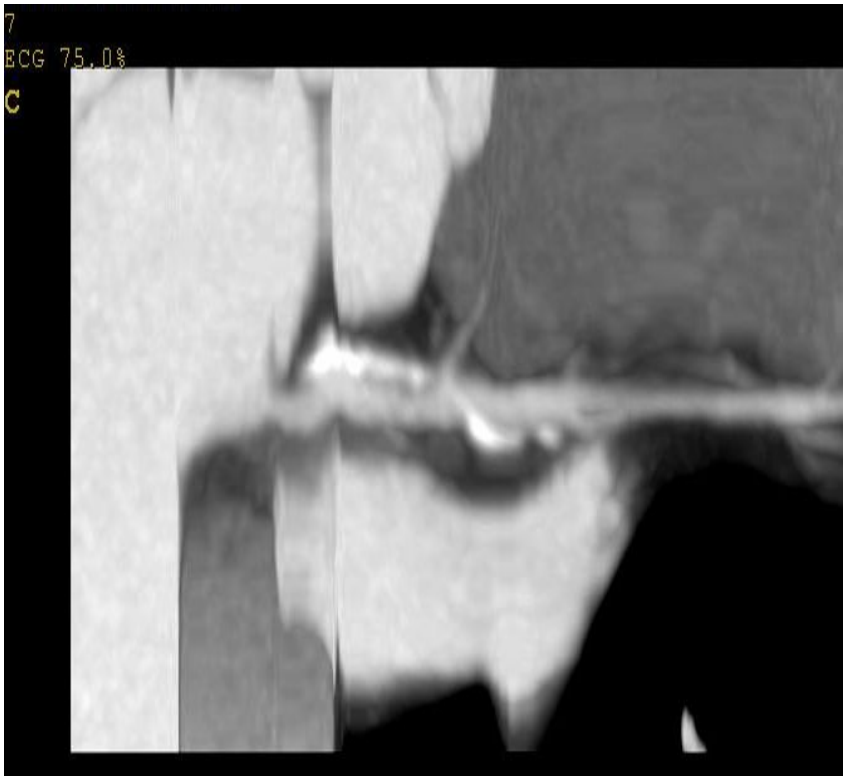


Figure 5.1 (c)ii Straight multiplanar reformation of the significant LMS lesion in Figure 5.1 (c) i



Per segment specificity of MSCT-CA was generally high, ranging from 87.0% to 100% with averages of 96.6% and 98.7% for identifying the absence of stenoses ≥ 50% and ≥ 70% respectively. Similarly NPV for MSCT-CA correctly ruling out stenoses was high at 93.5% and 95.3% for stenoses ≥ 50% and ≥ 70% respectively.

Analysis of agreement between I-CA and MSCT-CA for the detection of CAD ≥ 50% on a per segment basis demonstrated $\kappa = 0.384$ (95% CI 0.267, 0.485). Agreement between the two modalities was greatest for detection of disease in the proximal LAD, $\kappa = 0.713$ (95% CI 0.472, 0.893) followed by the mid RCA, $\kappa = 0.582$ (95% CI 0.187, 0.882) and then the mid LAD, $\kappa = 0.460$ (95% CI 0.198, 0.688).

Table 5.1 Accuracy of MSCT-CA for detecting stenoses ≥ 50% - a segment based analysis

Segment	ICA stenosis ≥ 50%	MSCT Stenosis ≥ 50%			Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
		No	Yes	UE*				
LMS	No Yes UE*	84 6 0	1 1 0	7 1 0	14.3% (0.7, 51.3)	98.8% (93.6, 99.9)	93.3% (86.2, 96.9)	50.0% (2.6, 97.4)
Proximal LAD	No Yes UE*	72 2 0	5 11 0	7 3 0	84.6% (57.8, 95.7)	93.5% (85.7, 97.2)	97.3% (90.7, 99.3)	68.8% (44.4, 85.8)
Mid LAD	No Yes UE*	60 5 0	9 9 0	14 3 0	64.3% (38.8, 83.7)	87.0% (77.0, 93.0)	92.3% (83.2, 96.7)	50.0% (29.0, 71.0)
Distal LAD	No Yes UE*	69 5 2	1 0 0	23 0 0	0.0% (0.0, 43.3)	98.6% (92.3, 99.9)	93.2% (85.1, 97.1)	0.0% (0.0, 94.9)
Diagonal 1	No Yes UE*	54 6 0	0 1 1	31 7 0	14.3% (0.7, 51.3)	100.0% (93.4, 100)	90.0% (79.9, 95.3)	100.0% (5.1, 100)
Diagonal 2	No Yes UE*	22 1 0	0 0 1	68 2 6	0.0% (0.0, 94.9)	100.0% (85.1, 100)	95.7% (79.0, 99.8)	–
Proximal Cx	No Yes UE*	79 3 0	3 3 0	9 2 1	50.0% (18.8, 81.2)	96.3% (89.8, 98.7)	96.3% (89.8, 98.7)	50.0% (18.8, 81.2)
Distal Cx	No Yes UE*	60 7 0	0 1 0	23 7 2	12.5% (0.6, 47.1)	100.0% (94.0, 100)	89.6% (80.0, 94.8)	100.0% (5.1, 100)
Obtuse Marginal 1	No Yes UE*	40 7 0	1 0 0	41 9 2	0.0% (0.0, 35.4)	97.6% (87.4, 99.9)	85.1% (72.3, 92.6)	0.0% (0.0, 94.9)
Obtuse Marginal 2	No Yes UE*	7 2 0	1 0 0	75 4 11	0.0% (0.0, 65.8)	87.5% (52.9, 99.4)	77.8% (45.3, 93.7)	0.0% (0.0, 94.9)
Proximal RCA	No Yes UE*	80 6 1	5 3 0	3 2 0	33.3% (12.1, 64.6)	94.1% (87.0, 97.5)	93.0% (85.6, 96.8)	37.5% (13.7, 69.4)
Mid RCA	No Yes UE*	73 2 1	3 4 0	10 6 1	66.7% (30.0, 90.3)	96.1% (89.0, 98.6)	97.3% (90.8, 99.3)	57.1% (25.0, 84.2)
Distal RCA	No Yes UE*	67 3 1	0 0 0	21 1 7	0.0% (0.0, 56.1)	100.0% (94.6, 100)	95.7% (88.1, 98.5)	–
PDA	No Yes UE*	46 3 1	0 0 0	41 1 8	0.0% (0.0, 56.1)	100.0% (92.3, 100)	93.9% (83.5, 97.9)	–
LV Branch	No Yes UE*	20 0 2	0 0 0	67 2 9	–	100.0% (83.9, 100)	100.0% (83.9, 100)	–
Any Segment	No Yes Unevaluable*	833 58 8	29 33 2	440 50 47	36.3% (27.1, 46.5)	96.6% (95.2, 97.6)	93.5% (91.7, 94.9)	53.2% (41.0, 65.1)

* *UE = Unevaluable - refers to segments either unevaluable on MSCT-CA or absent on I-CA*

Table 5.2 Accuracy of MSCT-CA for detecting stenoses ≥ 70% - a segment-based analysis

Segment	ICA stenosis ≥ 70%	MSCT Stenosis ≥ 70%			Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
		No	Yes	UE				
LMS	No Yes UE	88 3 0	0 1 0	8 0 0	25.0% (1.3, 69.9	100.0% (95.8, 100)	96.7% (90.8, 98.9)	100.0% (5.1, 100)
Proximal LAD	No Yes UE	78 6 0	3 3 0	7 3 0	33.3% (12.1, 64.6)	96.3% (89.7, 98.7)	92.9% (85.3, 96.7)	50.0% (18.8, 81.2)
Mid LAD	No Yes UE	69 7 0	4 3 0	15 2 0	30.0% (10.8, 60.3)	94.5% (86.7, 97.8)	90.8% (82.2, 95.5)	42.9% (15.8, 75.0)
Distal LAD	No Yes UE	70 5 2	0 0 0	23 0 0	0.0% (0.0, 43.4)	100.0% 94.8, 100)	93.3% (85.3, 97.1)	–
Diagonal 1	No Yes UE	56 4 1	0 1 0	33 5 0	20.0% (1.0, 62.4)	100.0% (93.6, 100)	93.3% (84.1, 97.4)	100.0% (5.1, 100)
Diagonal 2	No Yes UE	23 0 1	0 0 0	69 1 6	–	100.0% (85.7, 100)	100.0% (85.7, 100)	–
Proximal Cx	No Yes UE	84 2 0	0 2 0	10 1 1	50.0% (15.0, 85.0)	100.0% (95.6, 100)	97.7% (91.9, 99.4)	100.0% (34.2, 100)
Distal Cx	No Yes UE	62 6 0	0 0 0	25 5 2	0.0% (0.0, 56.1)	100.0% (94.2, 100)	91.2% (82.1, 95.9)	–
Obtuse Marginal 1	No Yes UE	44 3 0	1 0 0	44 6 2	0.0% (0.0, 56.1)	97.8% (88.4, 99.9)	93.6% (82.8, 97.8)	0.0% (0.0, 94.9)
Obtuse Marginal 2	No Yes UE	9 1 0	0 0 0	76 3 11	0.0% (0.0, 94.9)	100.0% (70.1, 100)	90.0% (59.6, 99.5)	–
Proximal RCA	No Yes UE	87 4 1	3 0 0	3 2 0	0.0% (0.0, 49.0)	96.7% (90.7, 98.9)	95.6% (89.2, 98.3)	0.0% (0.0, 56.1)
Mid RCA	No Yes UE	79 0 1	1 2 0	10 6 1	100.0% (34.2, 100)	98.8% (93.3, 99.9)	100.0% (95.4, 100)	66.7% (20.8, 98.3)
Distal RCA	No Yes UE	69 1 1	0 0 0	21 1 7	0.0% (0.0, 94.9)	100.0% (94.7, 100)	98.6% (92.3, 99.9)	–
PDA	No Yes UE	47 2 1	0 0 0	41 1 8	0.0% (0.0, 65.8)	100.0% (92.4, 100)	95.9% (86.3, 98.9)	–
LV Branch	No Yes UE	20 0 2	0 0 0	68 1 9	–	100.0% (83.9, 100)	100.0% (83.9, 100)	–
Any Segment	No Yes UE	885 44 10	12 12 0	453 37 47	21.4% (12.7, 33.8)	98.7% (97.7, 99.2)	95.3% (93.7, 96.5)	50.0% (31.4, 68.6)

[*] *UE = Unevaluable - refers to segments either unevaluable on MSCT-CA or absent on I-CA*

5.3.2 Accuracy parameters of MSCT-CA in comparison to I-CA for the detection of significant CAD at the ≥ 50% and ≥ 70% levels - An artery-based analysis

Of 397 arteries identified on I-CA, 316 (80.0%) were evaluable on MSCT-CA. The percentage of LMSs, LADs, Cxs and RCAs considered unevaluable on MSCT-CA was 8.0%, 18.0%, 29.2% and 26.5% respectively. The per artery prevalence of CAD ≥ 50% and ≥ 70% was 21.4% and 15.4% respectively. Considering unevaluable arteries to have significant stenoses ≥ 50%, the overall per artery sensitivity, specificity, NPV and PPV were 71.8%, 76.6%, 90.9% and 45.5% respectively. This is demonstrated in Table 5.3 along with the accuracy parameters for MSCT-CA in determining stenoses in each individual artery. Sensitivity was highest for LAD assessment. NPV was generally high while specificity and PPV were both low on a per artery basis.

Analysis of agreement between I-CA and MSCT-CA for the detection of CAD ≥ 50% on a per artery basis demonstrated $\kappa = 0.559$ (95% CI 0.427, 0.672). Agreement between the two modalities was greatest for the LAD, $\kappa = 0.729$ (95% CI 0.566, 0.862) followed by the RCA, $\kappa = 0.499$ (95% CI 0.230, 0.728) and the Cx artery, $\kappa = 0.279$ (95% CI 0.002, 0.536).

Table 5.3 Accuracy of MSCT-CA for detecting stenoses ≥ 50% and ≥ 70% - an artery-based analysis

% stenosis	Artery	ICA	MSCT stenosis			Sn	Sp	NPV	PPV
			No	Yes	UE*	(95% CI)	(95% CI)	(95% CI)	(95% CI)
≥ 50%	LMS	No	84	1	7	25.0% (7.1,59.1)	91.3% (83.8,95.5)	93.3% (86.2, 96.9)	20.0% (5.7, 51.0)
		Yes	6	1	1				
		UE*	0	0	0				
	LAD	No	49	6	13	87.5% (71.9, 95.0)	72.1% (60.4, 81.3)	92.5% (82.1, 97.0)	59.6% (45.3, 72.4)
		Yes	4	23	5				
		UE*	0	0	0				
	Cx	No	53	4	17	64.0% (44.5, 79.8)	71.6% (60.5, 80.6)	85.5% (74.7, 92.2)	43.2% (28.7, 59.1)
		Yes	9	4	12				
		UE*	0	0	1				
	RCA	No	53	6	19	75.0% (53.1, 88.8)	67.9% (57.0, 77.3)	91.4% (81.4, 96.3)	37.5% (24.2, 53.0)
		Yes	5	8	7				
		UE*	2	0	0				
	Any Artery	No	23	17	56	71.8% (61.4, 80.2)	76.6% (71.6, 81.0)	90.9% (86.8, 93.8)	45.5% (37.3, 54.0)
		Yes	9	36	25				
		UE*	24	0	1				
			2						
≥ 70%	LMS	No	88	0	8	25.0% (1.3, 69.9)	91.7% (84.4, 95.7)	96.7% (90.8, 98.9)	11.1% (0.6, 43.5)
		Yes	3	1	0				
		UE*	0	0	0				
	LAD	No	54	4	20	63.6% (43.0, 80.3)	69.2% (58.3, 78.4)	87.1% (76.6, 93.3)	36.8% (23.4, 52.7)
		Yes	8	10	4				
		UE*	0	0	0				
	Cx	No	57	1	21	55.0% (34.2, 74.2)	72.2% (61.4, 80.8)	86.4% (76.1, 92.7)	33.3% (19.8, 50.4)
		Yes	9	2	9				
		UE*	0	0	1				
	RCA	No	58	3	21	66.7% (41.7, 84.8)	70.7% (60.1, 79.5)	92.1% (82.7, 96.6)	29.4% (16.8, 46.2)
		Yes	5	2	8				
		UE*	2	1	0				
	Any Artery	No	25	8	70	59.0% (46.5, 70.5)	76.7% (71.9, 80.9)	91.1% (87.2, 93.9)	31.6% (23.8, 40.6)
		Yes	7	15	21				
		UE*	25	1	1				
			2						

**UE = Unevaluable - refers to all arteries not fully evaluable by MSCT-CA or I-CA due to at least one major segment being unevaluable and no significant disease being identified in evaluable segments, Sn = sensitivity, Sp = specificity*

5.3.3 ROC analysis for MSCT-CA accuracy in comparison to I-CA for detecting s significant CAD on a per artery basis

Table 5.4 demonstrates the most appropriate cut-off values for MSCT-CA in the detection of CAD ≥ 50% and ≥ 70% by I-CA on a per artery basis.

Table 5.4 ROC analysis for MSCT-CA accuracy in comparison to I-CA for detecting significant CAD on a per artery basis

Artery	MSCT-CA Stenosis Cut-off	**50% Stenosis (I-CA)**			MSCT-CA Stenosis Cut-off	**70% Stenosis (I-CA)**		
		Sn	Sp	AUC		Sn	Sp	AUC
LMS	≥ 40%	0.429	0.976	0.703	≥ 40%	0.750	0.997	0.864
LAD	≥ 40%	0.842	0.849	0.895	≥ 40%	0.929	0.897	0.933
Cx	≥ 20%	0.727	0.857	0.774	≥ 20%	0.700	0.842	0.757
RCA	≥ 40%	0.700	0.911	0.807	≥ 40%	0.833	0.883	0.851

LMS = left main stem, LAD = left anterior descending, Cx = circumflex, RCA = right coronary artery, Sn = sensitivity, Sp = specificity, AUC = area under curve

This analysis demonstrates that the AUC for the prediction of I-CA stenoses ≥ 50% or ≥ 70% in the LMS, LAD or RCA is greatest when a MSCT-CA stenosis of ≥ 40% is used as a cut-off. For Cx stenosis the AUC is greatest when a MSCT-CA stenosis of ≥ 20% is used as cut-off. The ROC curves for each artery are illustrated in Figure 5.2 (a-d).

Figure 5.2 (a) Left main stem

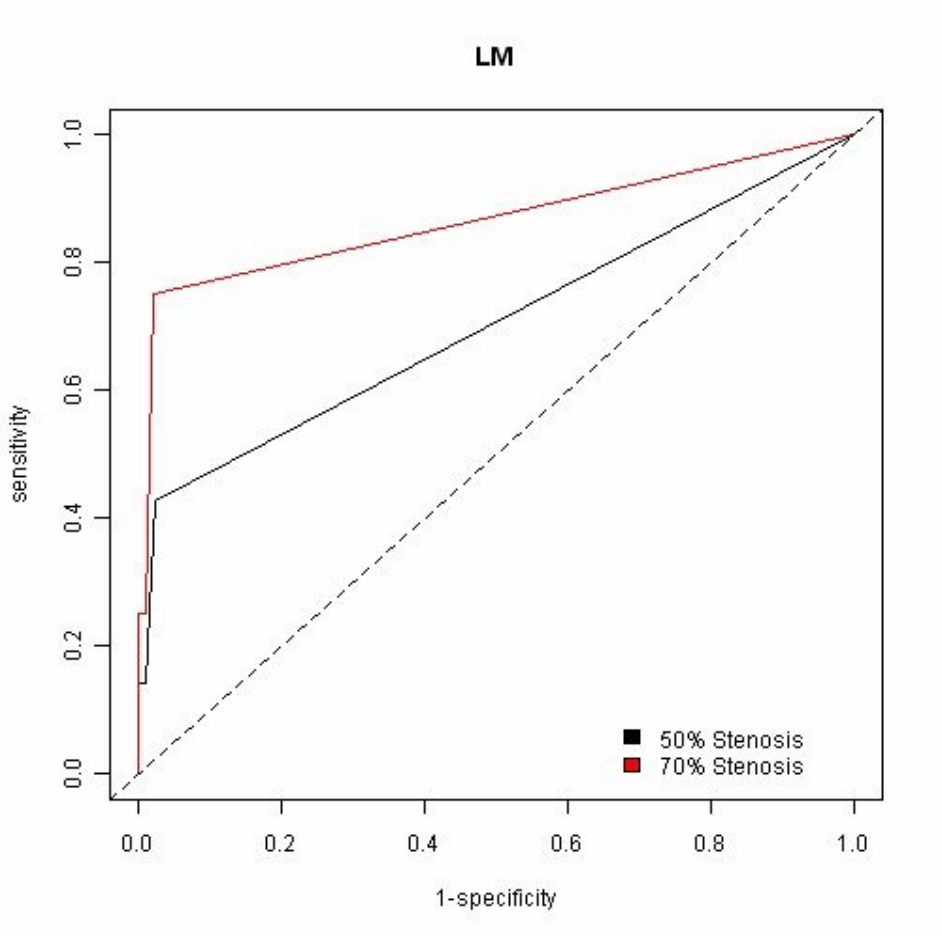


Figure 5.2 (b) Left anterior descending artery

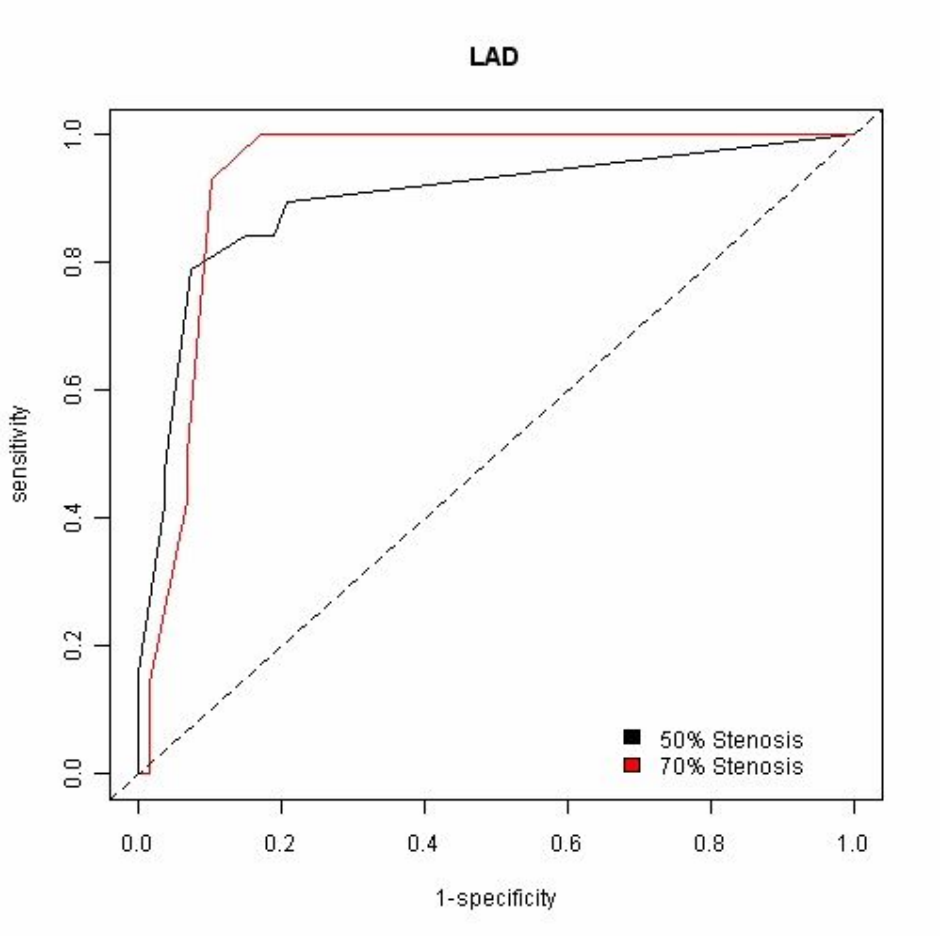


Figure 5.2 (c) Circumflex artery

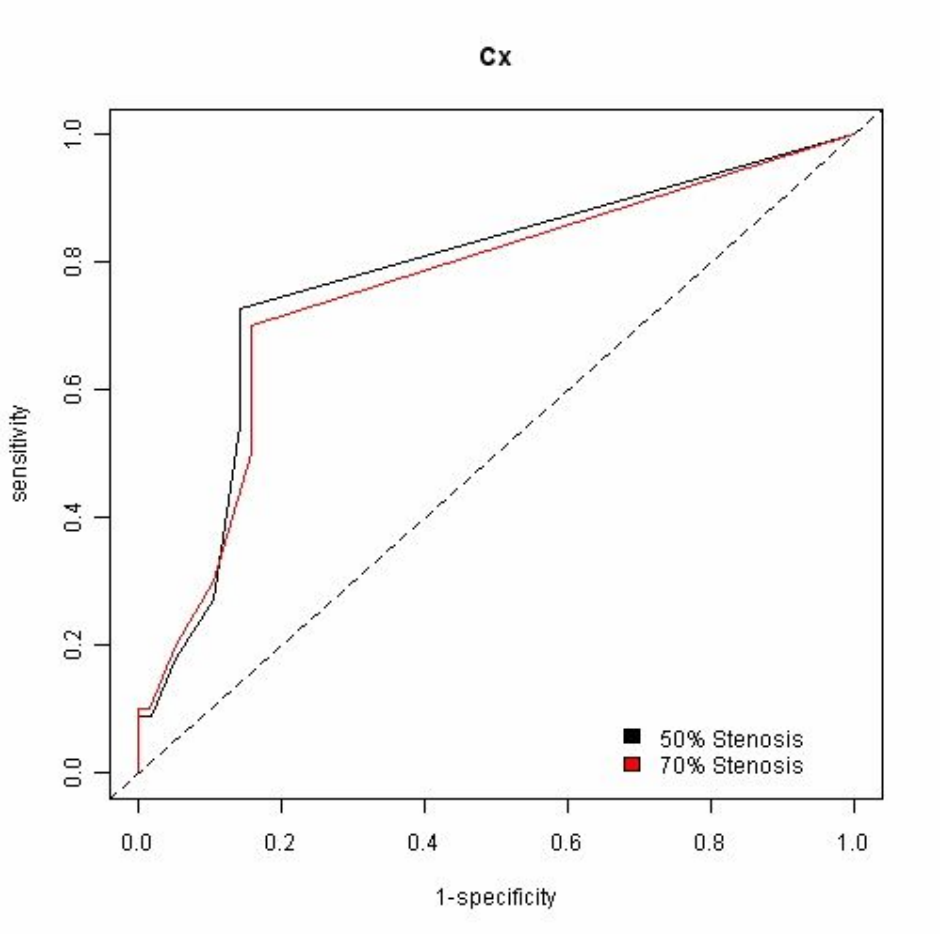
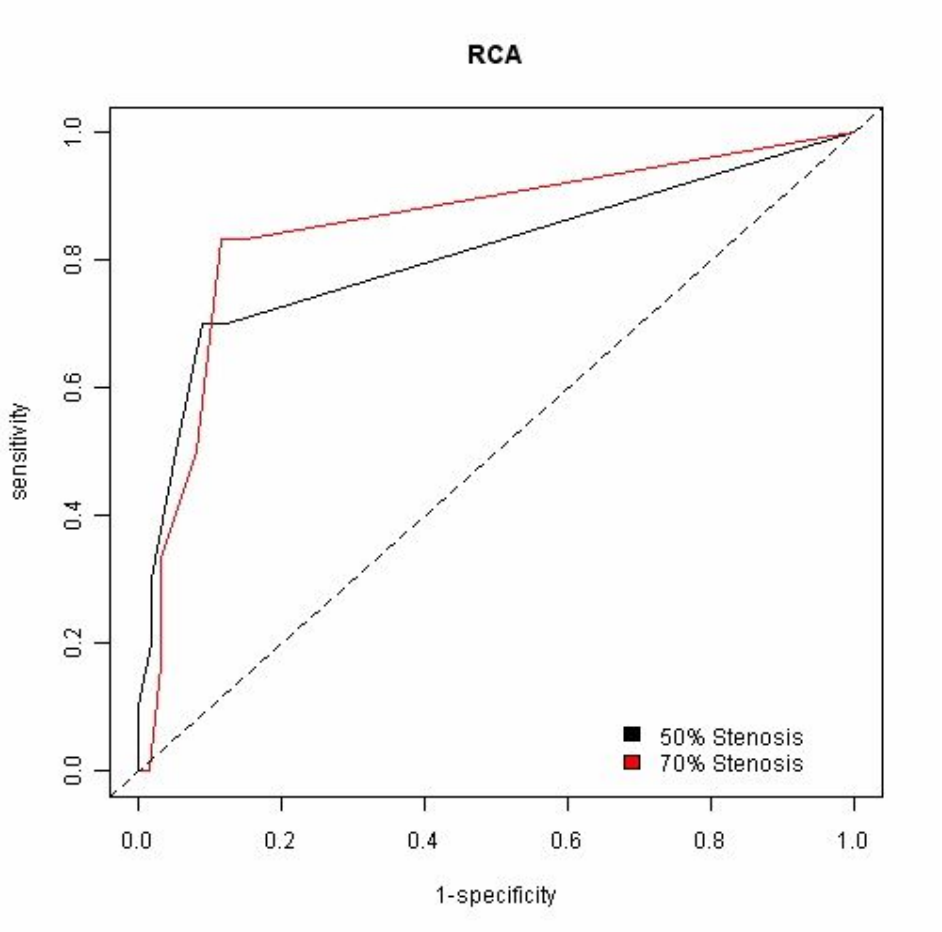


Figure 5.2 (d) Right coronary artery



5.4 Discussion

In this study, 34% of all coronary artery segments were considered unevaluable on MSCT-CA and for the purpose of the per segment analysis were excluded. This is in contrast to previous studies where reported segment exclusion rates generally did not exceed 10%.[90,91] However, many previous studies explicitly only attempted to analyse segments "down to 1.5mm in diameter" and hence the segment exclusion rate reported in these studies included only unevaluable segments with a diameter ≥ 1.5mm.[51,73,77,79] In our study all unevaluable segments were included in the segment exclusion rate irrespective of diameter.

It is well recognised that distal segments are smaller and more often unevaluable on MSCT-CA.[103] In one previous 16-slice study it was reported that while 11% of all segments identified on I-CA were not visualised on MSCT-CA, only 3% of I-CA segments > 2mm diameter were not seen on MSCT-CA.[53] In our study distal segments were more often unevaluable than proximal segments. This is consistent with a previous 64-slice study where the percentage of evaluable segments was reported for each individual segment as per the 15-segment model of the AHA.[76] The authors reported that 100% of proximal and mid RCA and LAD segments in addition to LMS and proximal Cx segments were evaluable by MSCT-CA. In comparison, 91% , 93% and 84% of distal RCA, LAD, and Cx segments respectively were evaluable and only 78% of PDAs, 76% of D2s and 82% of OM2s were evaluable. It is likely that the primary reason for distal segments being poorly visualised is their small size but reducing contrast opacification towards the more distal segments may also play a part.[51] A further difficulty is that with a fixed spatial resolution smaller segments are more prone to partial volume effects and hence even mild calcification may render the segment unevaluable. In any case, small segments < 1.5mm in diameter are unlikely to be clinically important.

Most notably, MSCT-CA sensitivity on a per segment basis was very low in our study at 36.3%. This is in stark contrast to the per segment sensitivity reported in a recent meta-analysis.[90] This meta-analysis included nineteen 64-slice studies reporting per segment accuracy, and calculated a sensitivity of 86%. One reason for the poor per segment sensitivity in our study was segment mis-naming, i.e. MSCT-CA reporters incorrectly classifying lesions to be in proximal or distal segments rather than mid segments or vice versa. This may have been a particular problem in our study as reasonable visibility of side branches is a requirement to nominally determine the major artery segments and many of the side branches in this study were unevaluable. This concept is validated by the significant improvement in MSCT-CA sensitivity in our study when assessed on a per artery basis, 71.8%. Sensitivity on a per segment basis in this study was also reduced by a considerable number of segments being affected by motion artefact or calcification. Indeed, less than half of evaluable segments were considered to have "good" image quality. The high per segment specificity and NPV in our study were comparable to previous meta-analyses where specificity and NPV were 96% and 97% and 97% and 99% respectively.[90,91]

In this study the LAD artery was most often evaluable and sensitivity on a per artery basis was highest for the detection of LAD disease at 87.5% in comparison to per artery sensitivities of 75.0% and 64.0% for the RCA and Cx artery respectively. This finding is consistent with previous studies including the large multicentre study CorE-64.[99] In CorE-64 the per artery sensitivity of MSCT-CA was 80% for the LMS/LAD arteries but only 73% and 71% for the Cx artery and RCA respectively. The technical difficulties with MSCT-CA analysis of the RCA and Cx arteries in particular are well recognised. Studies of coronary artery motion have demonstrated that the RCA is most mobile followed by the Cx artery and then the LAD artery.[152,153] This appears to translate into clinical studies that report RCA and Cx artery segments to be most often affected by motion artefact.[51,53,73,154]

Motion artefact has the effect of increasing the likelihood of a segment being deemed unevaluable and it is likely that the "evaluable" segments affected by motion artefact will be more prone to erroneous reporting. One study found that residual coronary motion either resulted in the impression of lumen obstruction or in blurred vessel walls preventing plaque detection.[59] This resulted in false positive and false negative assessments respectively. Difficulties in evaluating the Cx artery have also been attributed to its tortuous course and difficulties distinguishing it from adjacent contrast-filled structures such as the great cardiac vein and the left atrium.[66,154]

5.5 Conclusion

In this study 34% of all segments were unevaluable which was in part due to the attempted inclusion of segments < 1.5mm. Distal segments were more often unevaluable than larger more proximal segments. Sensitivity of MSCT-CA on a per segment basis was poor, and to some extent, the result of segment misnaming. Specificity and NPV were high and comparable to previous studies. On the per artery analysis the RCA and Cx artery were most often unevaluable and sensitivity of MSCT-CA was reduced in these arteries. This is consistent with previous studies where RCA and Cx artery evaluability was reduced by motion artefact due to the higher mobilities of these vessels.

CHAPTER 6

THE INFLUENCE OF GENDER, BMI, PRE-TEST PROBABILITY, HEART RATE AND CORONARY ARTERY CALCIFICATION ON THE ACCURACY OF MSCT-CA

6.1 Introduction to chapter

The diagnostic performance of an investigation is not uniform but rather fluctuates depending on the characteristics of the population being studied. An understanding of this concept is key to permitting appropriate utilisation of an investigation and to maximise accuracy. Several patient characteristics have been considered to adversely affect the efficacy of MSCT-CA for the detection of significant CAD. This chapter will, therefore, consider the performance of MSCT-CA in terms of coronary artery segment evaluability and diagnostic accuracy with respect to various patient subgroups. As such, following the statement of statistical methods in section 6.2, the remainder of the chapter will be divided into five sections: Gender; BMI; Pre-test probability; Heart rate; and Calcification.

6.2 Statistical analysis

Coronary artery segment definition as per the 15-Segment model of the AHA[89] and strategies for dealing with segments considered unevaluable or absent on MSCT-CA or I-CA have been described previously in chapter 5.2. Statistical analysis was performed using R version 2.9.1. Quantifiable variables were expressed as mean and standard deviation (SD) or median and interquartile range. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were calculated for MSCT-CA in comparison to I-CA for the detection of stenosis $\geq$ 50% on a per patient, per artery and per segment basis with 95% confidence intervals (CI) calculated from binomial expression. Categorical variables were compared between groups using exact Fisher tests and continuous variables were compared between groups using t-tests or Wilcoxon tests as appropriate. Categorical measures with more than two categories were compared using χ^2-tests. Continuous measures between two groups were compared using t-tests or Wilcoxon-Mann-Whitney tests as appropriate. Continuous measures between more than two groups were compared using ANOVA or Kruskal-Wallis-tests as appropriate.

6.3 Gender

6.3.1 Introduction

Determining the presence or absence of CAD without I-CA is more challenging in women than in men. Non-invasive investigations for cardiac ischaemia including exercise tolerance testing (ETT), myocardial perfusion imaging and stress echocardiography have all been shown to be less accurate in women.[155] Female sex is an independent factor in reducing the sensitivity of ETT for detecting obstructive CAD.[156] A recent meta-analysis including 19 studies comparing ETT to I-CA demonstrated a mean sensitivity for ETT in women of 61%.[155] Specificity of ETT was also shown to be diminished in women: 70% in comparison to 77% in men. This meta-analysis included five studies of thallium myocardial perfusion imaging and reported a mean sensitivity of 78% and a mean specificity of 64%. One study demonstrated convincingly that diagnostic accuracy was lower in women and postulated this may be due to smaller left ventricles being more prone to image blurring.[157] When stress cardiac magnetic resonance imaging was evaluated in women, sensitivity and specificity were comparatively high at 84% and 88% respectively.[158] However, sensitivity was significantly reduced in women with single vessel disease and women with small left ventricles to 71% and 69% respectively.

It is likely that multiple factors contribute to the lower accuracy of non-invasive testing for cardiac ischaemia in women including variations in exercise and coronary physiology, body habitus and the prevalence of CAD between men and women.[159] It is important, therefore, to validate the accuracy of MSCT-CA in women. It may be that diagnostic accuracy is adversely affected by similar factors to those reducing sensitivity and specificity of the investigations for cardiac ischaemia in women. Alternatively, it may prove to be a more precise means of investigating women with suspected underlying CAD.

This section will consider the performance of MSCT-CA in men in comparison to women in terms of segment evaluability and diagnostic accuracy.

6.3.2 Gender differences in patient characteristics

The present study recruited 55 men and 45 women. Table 6.1 illustrates patient characteristics by gender. There were no statistically significant differences in risk factors for CAD. In terms of symptoms, men were significantly more likely to describe chest pain typically consistent with angina. A higher percentage of women than men had previously been investigated by myocardial perfusion imaging rather than ETT, perhaps reflecting physician knowledge of the reduced accuracy of ETT in women. This difference, however, did not reach statistical significance. As expected, mean pre-test probability was significantly higher in men. Accordingly, arterial calcification was present more commonly in men.

Table 6.1 Gender differences in patient characteristics

	Male	Female	p value
Mean (SD) Age (years)	57.3 (10.8)	58.8 (10.7)	p=0.486
Hypertension	26 (47.3%)	28 (62.2%)	p=0.161
Hypercholesterolaemia	50 (90.9%)	37 (82.2%)	p=0.240
Previous or Current Smoking	41 (74.5%)	26 (57.7%)	p=1.000
Family History CAD	20 (36.4%)	20 (44.4%)	p=0.421
Diabetes	7 (12.7%)	4 (8.9%)	p=0.864
Median [IQR] Duration of Symptoms (months)	5.5 [2.0 - 11.0]	5.0 [2.0 - 18.0]	p=0.641
Chest Pain	54 (98.2%)	40 (88.9%)	p=0.088
Typical Pain	37 (67.3%)	19 (42.2%)	**p=0.022**
ETT	53 (96.4%)	39 (86.6%)	p=0.098
Th^{201} Scan	14 (25.5%)	15 (33.3%)	p=0.507
Mean (SD) Pre-test Probability	77.5 (22.4)	37.8 (23.4)	**p<0.001**
Mean (SD) BMI (kg/m^2)	28.0 (4.9)	29.3 (5.6)	p=0.226
Beta-Blockers	35 (63.6%)	31 (68.9%)	p=0.673
Mean (SD) Heart Rate (bpm)	67.6 (8.5)	70.3 (9.4)	p=0.134
Artery Calcification	41 (74.6%)	16 (35.6%)	**p<0.001**

ETT = exercise tolerance test, Th^{201} Scan = Thallium perfusion scan, BMI = body mass index

6.3.3 The effect of gender on MSCT-CA evaluability

There was no significant difference between the mean (SD) number of evaluable segments per MSCT-CA in women compared to men: 9.7 (3.1) vs 9.5 (3.7), p=0.783 (Table 6.2). There was also no significant difference in the percentage of evaluable segments considered to be of good, as opposed to adequate, image quality between men and women: 43% vs 49%, p=0.269. In the per patient analysis 38% of female MSCT-CAs were considered unevaluable overall in comparison to 27% of male MSCT-CAs.

6.3.4 The effect of gender on MSCT-CA accuracy for the detection of significant CAD

In this study the prevalence of significant CAD (at least one stenosis ≥ 50%) was significantly higher in men than in women: 56% vs 16%, p<0.001. In the per patient analysis sensitivity, specificity and PPV were reduced in women while NPV was higher in women than in men. Table 6.3 illustrates the gender differences in accuracy parameters for MSCT-CA in the detection of CAD in per segment, per artery and per patient analyses. Due to the small number of women with significant CAD the confidence intervals for these accuracy parameters are wide.

Table 6.2 The effect of gender on segment evaluability

	Subgroup (No. of patients)	Mean (SD) no. of evaluable segments per patient on MSCT-CA	p Value
Gender	**Male** (55)	9.5 (3.7)	p = 0.783
	Female (45)	9.7 (3.1)	

Table 6.3 Gender differences in MSCT-CA accuracy

Gender	Analysis	ICA ≥ 50%	MSCT ≥ 50%			Sn (95%CI)	Sp (95%CI)	NPV (95%CI)	PPV (95%CI)
			No	Yes	UE*				
Men	**Segment**	No Yes UE*	418 49 6	20 30 2	218 46 36	38.0% (28.1, 49.0)	95.4% (93.1, 97.0)	89.5% (86.4, 92.0)	60.0% (46.2, 72.4)
	Artery	No Yes UE*	110 19 1	9 32 0	28 21 0	73.6% (62.4, 82.4)	74.8% (67.2, 81.2)	85.3% (78.1, 90.4)	58.9% (48.6, 68.5)
	Patient	No Yes UE*	12 2 0	3 23 0	9 6 0	93.5% (79.3, 98.2)	50.0% (31.4, 68.6)	85.7% (60.1, 96.0)	70.7% (55.5, 82.4)
Women	**Segment**	No Yes UE*	415 9 2	9 3 0	222 4 11	25.0% (8.9, 53.2)	97.9% (96.0, 98.9)	97.9% (96.0, 98.9)	25.0% (8.9, 53.2)
	Artery	No Yes UE*	129 5 1	8 4 0	28 4 1	61.5% (35.3, 82.3)	78.2% (71.3,83.8)	96.3% (91.6, 98.4)	18.2% (9.5, 32.0)
	Patient	No Yes UE*	17 1 1	5 4 0	15 2 0	85.7% (48.7, 99.3)	45.9% (31.0, 61.6)	94.4% (74.2, 99.7)	23.1% (11.0, 42.1)

**UE - Unevaluable - Refers to segments considered unevaluable by MSCT-CA or absent on I-CA, arteries considered unevaluable by MSCT-CA or I-CA due to at least one major segment being unevaluable and no significant disease in the evaluable segments of that artery and patients considered unevaluable by MSCT-CA or I-CA due to one or more major segments being unevaluable and no significant disease in the evaluable segments. Sn = sensitivity, Sp = specificity*

6.3.5 Discussion

In this study, while there was no significant difference in the mean number of evaluable segments per MSCT-CA between men and women, overall a higher percentage of female MSCT-CAs were unevaluable. A possible explanation is that as the prevalence of CAD was higher in men than in women, partially evaluable MSCT-CAs of male patients were more likely to have at least one significant stenosis and so less likely to be considered unevaluable overall in the per patient analysis. Another possible explanation is that females may have been more likely to have a segment of a major artery considered unevaluable whereas the unevaluable segments in men may have been more commonly in small branches and hence did not result in the MSCT-CA being considered unevaluable overall. As described previously, patients' MSCT-CAs that were not fully evaluable (due to at least one segment of a major artery being considered unevaluable and the absence of any stenosis ≥ 50% in any evaluable segments) were considered positive for significant CAD. This strategy, while clinically relevant, meant that there were a high number of false positives which adversely affected MSCT-CA accuracy profiles in low CAD prevalence subgroups. Due to the high prevalence of CAD in the male subgroup, this had the effect of falsely inflating sensitivity as many of the unevaluable scans generated true positives. There was, however, the opposite effect in the female group where a low prevalence of CAD meant that the unevaluable scans mostly generated false positives which reduced specificity and PPV.

Several published studies have evaluated gender differences in MSCT-CA accuracy.[93,160-162] The results of our study are comparable to those of a 16-slice study of 95 men and 52 women with prevalence of CAD of 62% and 20% respectively where all MSCT-CA accuracy parameters were reduced in women and in particular sensitivity (70% vs 95%) and PPV (64% vs 93%).[160] Similarly to our study, the authors noted a significantly higher rate of non-diagnostic MSCT-CAs in women in comparison to men: 14% vs 4%, $p<0.05$.

In this study there was no difference in mean heart rate between men and women and while the men had significantly more coronary artery calcification, there was no gender difference in the mis-diagnosed segments due to calcium. The authors here postulated that the reason for the discrepancies in accuracy in men and women could be that women have smaller arteries. Correspondingly they demonstrated that all four coronary arteries were significantly larger in diameter in men than in women. This observation, however, did not persist after correction for body surface area except in the left main stem. It was considered that since smaller arteries are more prone to motion artefact, this could explain the higher percentage of non-diagnostic examinations in women. In addition, in the context of smaller coronary arteries, side branches are more likely to measure < 1.5mm and currently the spatial resolution of MSCT scanners is considered insufficient to accurately evaluate stenoses in such vessels. A subsequent 40-slice study also found that the percentage of unevaluable segments was significantly higher in women and postulated this may be due to women having smaller arteries.[93] The largest study to date evaluating gender differences in MSCT-CA accuracy is a 64-slice study which included 279 men and 123 women with a fairly high prevalence of CAD, 68% and 51% respectively.[161] In a per patient analysis they reported a significant reduction in specificity in women: 75% vs 90%, $p<0.05$. They also found that there was a significant reduction in per segment sensitivity in women which was driven by a significantly lower sensitivity of MSCT-CA for distal segments. Conversely, a smaller 64-slice study of 51 men and 52 women with prevalence of CAD of 64% and 42% respectively reported no gender difference in diagnostic accuracy.[162] Notably, in this study, unevaluable segments were excluded and were more prevalent in women. Only one of the major multi-centre studies of 64-Slice MSCT-CA considered the accuracy by gender.[101] This study demonstrated MSCT-CA to have similar sensitivities and specificities in men and women but reduced PPV and marginally increased NPV in women consistent with their lower prevalence of CAD.

6.3.6 Conclusion

In conclusion, the results of our study and of previous published studies support a reduced accuracy of MSCT-CA for the detection of significant CAD in women in comparison to men. This may be driven by a higher percentage of unevaluable scans in women secondary to smaller coronary arteries. The actual reported sensitivities and specificities in these studies vary with different strategies for dealing with unevaluable segments while PPV and NPV vary with the prevalence of CAD in the male and female subgroups.

6.4 BMI

6.4.1 Introduction

Obesity is associated with hypertension, hypercholesterolaemia and type 2 diabetes and as a consequence patients with elevated BMI are potentially at greater risk for developing CAD.[87] The prevalence of obesity in Scotland is increasing rapidly, particularly amongst older patients.[146] Currently, around 60% of men and 65% of women are overweight or obese (BMI $\geq$ 25 kg/m^2) and 22% of men and 26% of women are obese (BMI $\geq$ 30 kg/m^2).[146] In view of the high prevalence of obesity in Scotland and the propensity for these patients to develop CAD, consideration of the performance of MSCT-CA in the context of elevated BMI is very relevant. This section will consider the effect of an elevated BMI on segment evaluability and on the diagnostic accuracy of MSCT-CA for the detection of significant CAD.

6.4.2 The effect of BMI on MSCT-CA evaluability

In this study mean (SD) body mass index (BMI) was 28.6 (5.2) kg/m^2 with no significant difference between males and females. 75% of patients had a BMI $\geq$ 25 kg/m^2 and 35% had a BMI $\geq$ 30 kg/m^2. Segment evaluability was considered in four BMI groups: < 25 kg/m^2; $\geq$ 25 kg/m^2; < 30 kg/m^2; and $\geq$ 30 kg/m^2. Segment exclusion rates for these groups were 30%, 32%, 35% and 37% respectively. Table 6.4 illustrates the mean (SD) number of evaluable segments per patient in each of the BMI groups. While the average number of evaluable segments appeared higher in the lower BMI groups this perceived difference did not reach statistical significance. In terms of image quality (assessed as good, adequate or non-diagnostic) the mean (SD) percentage of segments per patient considered to have adequate image quality was significantly higher in the < 30 kg/m^2 group in comparison to the $\geq$ 30 kg/m^2 group, 40.2% (17.9) vs 30.6% (12.2), p = 0.004. There was, however, no significant difference in the percentage of segments per patient considered to have good

image quality between the BMI groups. There were no significant differences between the BMI groups in terms of mean heart rates or extent of arterial calcification.

Table 6.4 The effect of BMI on segment evaluability

	Subgroup (No. of patients)	**Mean (SD) no. of evaluable segments per patient on MSCT-CA**	**p Value**
BMI (kg / m^2)	**< 25** (25)	10.1 (3.4)	p = 0.352
	≥ 25 (75)	9.5 (3.5)	
	< 30 (65)	9.9 (3.4)	p = 0.271
	≥ 30 (35)	9.2 (3.4)	

6.4.3 The effect of BMI on MSCT-CA accuracy for the detection of significant CAD

The accuracy parameters of MSCT-CA for the detection of significant CAD with respect to the different BMI groups are illustrated in Table 6.5. It should be remembered that the per segment analysis was performed after exclusion of those segments considered unevaluable and therefore does not fully represent the accuracy of MSCT-CA in the different BMI groups. Nevertheless, it seemed that sensitivity was lower in patients with BMI ≥ 30 kg/m^2 than in those with BMI < 30 kg/m^2: 26% and 41% respectively. Specificity and NPV were uniformly high across the groups. PPV appeared higher in patients with BMI < 25 kg/m^2 than in those with BMI ≥ 30 kg/m^2: 60% and 50% respectively. Similarly, in the per artery analysis PPV was higher in the BMI < 25 kg/m^2 group than in the ≥ 25 kg/m^2 group: 57% vs 42%. It should be noted, however, that due to the relatively few segments with significant stenoses in each BMI group, the 95% confidence intervals for sensitivity and PPV are wide.

In the per patient analysis (where unevaluable segments were included and each considered to represent a significant stenosis) sensitivity and NPV were high across the different BMI

groups. Specificity was generally poor, likely due to the high number of false positives generated by the strategy for dealing with unevaluable segments. PPV appeared higher in the < 25 kg/m^2 group than the others but the confidence interval was wide due to only a small number of patients in this group having significant CAD.

Table 6.5 The effect of BMI on MSCT-CA accuracy

BMI (kg/m^2)	Analysis	ICA ≥ 50%	MSCT ≥ 50%			Sn (95%CI)	Sp (95%CI)	NPV (95%CI)	PPV (95%CI)
			No	Yes	UE*				
≥ 30 (35 patients)	Segment	No	287	7	173	25.9% (13.2, 44.7)	97.6% (95.2, 98.8)	93.5% (90.2, 95.7)	50.0% (26.8, 73.2)
		Yes	20	7	18				
		UE*	0	1	12				
	Artery	No	87	5	19	69.0% (50.8, 82.7)	78.4% (69.8, 85.0)	90.6% (83.1, 95.0)	45.5% (31.7, 59.9)
		Yes	9	8	12				
		UE*	0	0	0				
	Patient	No	13	2	8	91.7% (64.6, 99.6)	56.5% (36.8, 74.4)	92.9% (68.5, 99.6)	52.4% (32.4, 71.7)
		Yes	1	7	4				
		UE*	0	0	0				
< 30 (65 patients)	Segment	No	546	22	267	40.6% (29.5, 52.9)	96.1% (94.2, 97.4)	93.5% (91.2, 95.2)	54.2% (40.3, 67.4)
		Yes	38	26	32				
		UE*	8	1	35				
	Artery	No	152	12	37	73.2% (60.4, 83.0)	75.6% (69.2, 81.0)	91.0% (85.7, 94.5)	45.6% (35.7, 55.8)
		Yes	15	28	13				
		UE*	2	0	1				
	Patient	No	16	6	16	92.3% (75.9-97.9)	42.1% (27.9, 57.8)	88.9% (67.2, 96.9)	52.2% (38.1, 65.9)
		Yes	2	20	4				
		UE*	1	0	0				
≥ 25 (75 patients)	Segment	No	618	23	343	39.3% (28.1-51.9)	96.4% (94.7-97.6)	94.4% (92.3-95.9)	51.1% (37.2-64.7)
		Yes	37	24	38				
		UE*	7	2	33				
	Artery	No	179	14	46	74.6% (62.2-83.9)	74.9% (69.0-80.0)	92.3% (87.6-95.3)	42.3% (33.3-51.9)
		Yes	15	27	17				
		UE*	2	0	0				
	Patient	No	22	7	19	92.3% (75.9-97.9)	45.8% (32.6-59.7)	91.7% (74.2-97.7)	48.0% (34.8-61.5)
		Yes	2	19	5				
		UE*	1	0	0				
< 25 (25 patients)	Segment	No	215	6	97	30.0% (16.7-47.9)	97.3% (94.2-98.7)	91.1% (86.6-94.1)	60.0% (35.7-80.2)
		Yes	21	9	12				
		UE*	1	0	14				
	Artery	No	60	3	10	65.4% (46.2-80.6)	82.2% (71.9-89.3)	87.0% (77.0-93.0)	56.7% (39.2-72.6)
		Yes	9	9	8				
		UE*	0	0	1				
	Patient	No	7	1	5	91.7% (64.6-99.6)	53.8% (29.1-76.8)	87.5% (52.9-99.4)	64.7% (41.3-82.7)
		Yes	1	8	3				
		UE*	0	0	0				

**UE - Unevaluable - Refers to segments considered unevaluable by MSCT-CA or absent on I-CA, arteries considered unevaluable by MSCT-CA or I-CA due to at least one major segment being unevaluable and no significant disease in the evaluable segments of that artery and patients considered unevaluable by MSCT-CA or I-CA due to one or more major segments being unevaluable and no significant disease in the evaluable segments. Sn = sensitivity, Sp = specificity*

6.4.4 Discussion

Several previous studies have documented reduced image quality of MSCT-CA in patients with elevated BMI.[15,25,108] Specifically, elevated BMI has been shown to increase MSCT image noise and to significantly reduce the contrast to noise ratio in the coronary arteries.[163,164] It has also been demonstrated that vessel contrast opacification is poor in obese compared to non-obese patients.[165] While there was no significant difference in the rates of unevaluable segments between BMI groups, our study found "adequate" image quality to be significantly less common in the ≥ 30 kg/m^2 group. This did not, however, appear to translate to a significant deterioration in diagnostic accuracy. These findings are consistent with the most recent published study to specifically address the effect of elevated BMI on MSCT-CA accuracy.[107] In this study 150 patients underwent 64-Slice dual source CT-CA followed by I-CA and the rate of non-evaluable segments in the ≥ 26 kg/m^2 BMI group was almost double that of the < 26 kg/m^2 group. The authors also reported minor reductions in specificity and PPV in the higher BMI group which was not statistically significant. Similarly, ACCURACY, the largest multi-centre study of MSCT-CA accuracy to date included 320 patients with a mean (SD) BMI of 31.4 (6.2) kg/m^2 and demonstrated similar sensitivity and specificity in obese and non-obese patient groups. It is interesting that while an elevated BMI results in a significant degradation in image quality, even in studies with the newest generation of dual source scanners, it does not appear to adversely affect the accuracy of evaluation of CAD. It could be postulated that patients with an elevated BMI have larger arteries making visual assessment of luminal stenosis more accurate in the context of the fixed spatial resolution of MSCT-CA. This phenomenon has been demonstrated before in a gender comparison of MSCT-CA accuracy as described earlier in 6.3.4.[160] In any case, it is fortunate that elevated BMI does not appear to significantly compromise diagnostic accuracy as the mean BMI in our study was 28.6 kg/m^2 and this is consistent with most other studies of MSCT-CA for the detection of significant CAD in which the majority of patients are overweight or obese.

6.4.5 Conclusion

Elevated BMI was common in our study population with more than one third of patients being clinically obese. A non-significant trend of reduced segment evaluability in the higher BMI groups was observed and this was consistent with previous studies. This did not, however, appear to translate to any significant reduction in diagnostic accuracy. This may be due to better visual assessment of luminal stenosis in larger arteries in the context of the fixed spatial resolution of MSCT-CA.

6.5 Pre-test Probability

6.5.1 Introduction

In order to elucidate further the precise patient population in whom MSCT-CA is most appropriate for the evaluation of suspected CAD, subgroup analysis of patients assigned to pre-test probability groups was performed. This chapter describes the clinical scoring system utilised to estimate risk, the characteristics of the different groups and the effect of pre-test probability on diagnostic accuracy of MSCT-CA for the detection of significant CAD. Comparisons with similar studies are made.

6.5.2 Determining pre-test probability by the Duke Clinical Score

Several algorithms for estimating CAD risk prior to non-invasive or invasive investigation have been developed.[88,166,167] While both of the most recently published international guidelines for the use of MSCT-CA in suspected CAD refer to patients considered to be in low, intermediate, or high pre-test probability groups, neither specifically advocate the use of a particular score.[102,103] Previous American guidelines have referred to a modification of the Diamond and Forrester algorithm which is based on age, gender and the typicality or otherwise of symptoms.[81,166] The recently published NICE Guidelines for the assessment of chest pain suggest the use of the Diamond Forrester score with adaptations from the Duke Clinical Score adding consideration of risk factors for CAD.[88,143,166]

In this study pre-test probability was estimated and pre-test probability groups assigned utilising the Duke Clinical Score.[88] This score was derived from data stored on the Duke Database for Cardiovascular Disease with information on risk factors, presentation and non-invasive investigations of all patients referred for I-CA at Duke over a number of years. Statistical models were developed to determine a clinical risk score capable of estimating the anatomical severity of CAD at I-CA. Consideration was given to various

factors and logistical regression analysis demonstrated that the type of chest pain was most characteristic for the prediction of CAD (>75% stenosis), followed by prior myocardial infarction, male sex, age, smoking, hyperlipidaemia, ST-T changes on ECG and diabetes mellitus. The effect of increasing age was more important in terms of elevating risk in men whilst the effect of smoking was more damaging in women.[168] The Duke Clinical Score was chosen for determining pre-test probability groups in this study as it was considered accessible and uncomplicated and would permit comparisons with a previous study of MSCT-CA in different pre-test probability groups where the same score was utilised.[169] The Duke Clinical Score as used in this study is illustrated in Appendix v. A score of 0-24% was considered low pre-test probability, a score of 25-74% was considered intermediate pre-test probability and a score of >75% was considered high pre-test probability for the patient having significant CAD defined as > 75% stenosis of at least one major artery.

6.5.3 Pre-test probability groups

In this study of 100 patients, mean (SD) pre-test probability was 59.6% (30.2). There was a significant difference between mean pre-test probability of males and females: 77.5% (22.4) and 37.8% (23.4) respectively, $p < 0.001$. Of all patients, 19% were in the low pre-test probability group, 40% were in the intermediate pre-test probability group and 41% were in the high pre-test probability group for the presence of significant underlying CAD. Significantly more males than females had a high pre-test probability: 39 and 2 respectively, $p < 0.001$. There were no significant differences in BMI or mean heart rate between the pre-test probability groups but arterial calcification was present more frequently in the high pre-test probability group: 87.8% vs 35.6%, $p < 0.001$.

The overall prevalence of significant coronary artery disease defined as at least one stenosis ≥ 50% was 38%. The overall prevalence of significant CAD where at least one

stenosis was ≥ 70% was 33%. 30 patients (73%) in the high pre-test probability group had at least one stenosis ≥ 50% on I-CA while 27 patients (66%) in the high pre-test probability group had at least one stenosis ≥ 70%. Six patients (15%) in the intermediate pre-test probability group had at least one stenosis ≥ 50% on I-CA while four patients (10%) had at least one stenosis ≥ 70%. Two patients (11%) in the low pre-test probability group had at least one stenosis ≥ 50% on I-CA while one patient (6%) had at least one stenosis ≥ 70%.

Of the 30 patients in the high pre-test probability group with significant CAD ≥ 50%, 14 (47%) had triple vessel disease, and a further nine patients (30%) had two vessel disease. Eight patients (27%) had significant LMS disease. Of the six patients in the intermediate pre-test probability group with significant CAD ≥ 50%, four had single vessel disease while one had two vessel disease and one had triple vessel disease. None had significant LMS disease. Of the two patients with significant CAD ≥ 50% in the low pre-test probability group one had single vessel disease and the other two vessel disease.

6.5.4 The effect of pre-test probability on accuracy of MSCT-CA

Table 6.6 demonstrates the effect of pre-test probability on diagnostic accuracy of MSCT-CA in the detection of significant CAD ≥ 50%. This was determined separately on a per segment, per artery and per patient basis. For the purpose of this analysis, given the relatively small number patients in the low pre-test probability subgroup, the groups considered were low-intermediate pre-test probability, (59 patients) and high pre-test probability, (41 patients).

On per segment analysis, sensitivity and PPV appeared higher in the high pre-test probability group while NPV was lower. On per artery analysis, sensitivity and PPV again appeared higher in the high pre-test probability group while specificity and NPV were substantially lower. Most relevant in this context is the per patient analysis where again

sensitivity and positive predictive value were higher in the high pre-test probability group while specificity and NPV were lower at 27.3% and 75.0% respectively.

Table 6.6 The effect of pre-test probability on MSCT-CA accuracy

Pre-test Probability	Analysis	ICA ≥ 50%	MSCT ≥ 50%			Sn (95%CI)	Sp (95%CI)	NPV (95%CI)	PPV (95%CI)
			No	Yes	UE*				
Low to Inter-mediate (0-74%)	Segment	No Yes UE*	579 8 2	12 3 0	262 6 13	27.3% (9.7, 56.6)	98.0% (96.5, 98.8)	98.6% (97.3, 99.3)	20.0% (7.0, 45.2)
	Artery	No Yes UE*	180 5 1	10 5 0	32 2 1	58.3% (32.0, 80.7)	81.1% (75.4, 85.7)	97.3% (93.8, 98.8)	14.3% (7.1, 26.7)
	Patient	No Yes UE*	26 2 1	6 4 0	18 2 0	75.0% (40.9-92.9)	52.0% (38.5, 65.2)	92.9% (77.4, 98.0)	20.0% (9.5, 37.3)
High (≥ 75%)	Segment	No Yes UE*	254 50 6	17 30 2	178 44 34	37.5% (27.7, 48.5)	93.7% (90.2, 96.0)	83.6% (79.0, 87.3)	63.8% (49.5, 76.0)
	Artery	No Yes UE*	59 19 1	7 31 0	24 23 0	74.0% (62.9, 82.7)	65.6% (55.3, 74.6)	75.6% (65.1, 83.8)	63.5% (52.9, 73.0)
	Patient	No Yes UE*	3 1 0	2 23 0	6 6 0	96.7% (83.3, 99.8)	27.3% (9.7, 56.6)	75.0% (30.1, 98.7)	78.4% (62.8, 88.6)

**UE - Unevaluable - Refers to segments considered unevaluable by MSCT-CA or absent on I-CA, arteries considered unevaluable by MSCT-CA or I-CA due to at least one major segment being unevaluable and no significant disease in the evaluable segments of that artery and patients considered unevaluable by MSCT-CA or I-CA due to one or more major segments being unevaluable and no significant disease in the evaluable segments. Sn = sensitivity, Sp = specificity*

6.5.5 Discussion

Our study demonstrated sensitivity and PPV of MSCT-CA for the detection of significant CAD on a per patient basis to be increased in the high pre-test probability group while specificity and NPV were substantially reduced. Only two previous studies have specifically assessed MSCT-CA accuracy in patients separated into different pre-test probability groups.[169,170] In the former of these, as in our study, patients with suspected CAD were divided into pre-test probability groups using the Duke Clinical Score.[88,169] Similarly to our study, patients in the high pre-test probability group were more likely to be

male, to have an elevated calcium score and to have significant underlying CAD on I-CA. The authors reported sensitivity to be uniformly high on the per patient analysis across the groups while NPV was reduced in the high pre-test probability group and PPV increased. Most notably, specificity fell from 93% in the low pre-test probability group to 74% in the high pre-test probability group and this trend was found to be significant, ($p < 0.05$). Similarly in our study, specificity was reduced by almost 50% from the low-intermediate to the high pre-test probability group. In the second study where pre-test probability was directly considered, patients were separated into high and low pre-test probability groups based on a modification of the Diamond and Forrester algorithm.[166,170] Again, patients in the high pre-test probability group were significantly more likely to have a high calcium score and underlying CAD. As before, the major finding was a reduction in specificity of MSCT-CA on a per patient basis from 88% in the low pre-test probability group to 58% in the high pre-test probability group. Any change in specificity can be explained in terms of an alteration of the false positive to true negative ratio. In the case of lowering of specificity of MSCT-CA in the high pre-test probability group it is likely that false positives were more common as calcification was significantly more common in the high pre-test probability groups and MSCT-CA has a recognised tendency to over-estimate the extent of a stenosis in the presence of calcification. Furthermore, the percentage of true negatives will be reduced in the high pre-test probability groups as a function of the significantly higher prevalence of CAD in these cohorts.

The results of our study and of previous studies identify the low-intermediate pre-test probability group as being the group most appropriately assessed by MSCT-CA.[169,170] The high NPV of MSCT-CA in this context means that unnecessary I-CA can often be avoided in this population. Correspondingly national and international guidelines for MSCT-CA advocate the use of MSCT-CA in these patients.[102,103,143] However, in the high pre-test probability group, the lower specificity would result in unnecessary I-CAs for patients with

false positive scans, perhaps due to coronary artery calcifications, and the poor NPV, 75% in our study, would risk patients being falsely reassured. Indeed, one study where post-test probability was determined reported that in the high pre-test probability group a post-test probability of 17% would be assigned to a patient with a negative MSCT-CA and as such any symptomatic patient in this circumstance would be likely to proceed to I-CA. It was concluded that MSCT-CA was of limited clinical value in this group.[169]

6.5.6 Conclusion

In conclusion, MSCT-CA is most appropriately utilised in assessment of patients with suspected CAD who are at low to intermediate risk. In these patients, the high negative predictive value of MSCT-CA can reliably exclude CAD where appropriate. In the high pre-test probability group both specificity and NPV were notably reduced likely due to the higher prevalence of coronary artery calcification and CAD in this group. The Duke Clinical Score appeared a reliable method for defining pre-test probability groups in our population with 73% of patients in the high pre-test probability group having significant CAD identified on I-CA in comparison to only 10.5% in the low pre-test probability group. Recent national guidelines suggest the use of a combination score with features of the Diamond and Forrester algorithm and the Duke Clinical Score.[143] However, these guidelines also suggest that a national registry of patients undergoing assessment for suspected CAD should be established to permit further research aimed at developing and validating a new score for estimating pre-test probability with particular consideration given to ongoing uncertainties of current risk estimation.

6.6 Heart Rate

6.6.1 Introduction

This section considers the importance of heart rate control during MSCT-CA in terms of temporal resolution and reconstruction protocols and the consequent effects on image quality and diagnostic accuracy.

6.6.2 The importance of heart rate control

Coronary arteries are highly mobile due to cardiac contraction and as such avoiding motion artefact in MSCT-CA is challenging. Maximal coronary motion occurs at early to mid systole and during rapid filling in early diastole. Data for MSCT-CA are, therefore, generally acquired in a reconstruction window at end diastole as this represents the phase in the cardiac cycle with least motion.

Intuitively, a low heart rate during MSCT-CA data acquisition would be desirable as the length of diastole is increased at lower heart rates and so the risk of movement and subsequent misalignment of data acquired during the reconstruction window is reduced. A further important concept to consider is heart rate variability. If the heart rate is irregular, for example due to ectopic activity, then the length of diastole varies from one cycle to the next. This affects the time for diastolic filling and therefore the extent of ventricular expansion which directly influences coronary artery motion. Since variations in heart rate are unpredictable, prospective ECG gating in particular, becomes very difficult. Furthermore, in the context of a variable heart rate, the use of multi-segment reconstruction protocols (designed to improve temporal resolution at higher heart rates) result in data averaging of non-identical cardiac cycles and image blurring due to spatial inconsistencies. Previous studies have confirmed the need for careful control of heart rate and heart rate

variability to reduce motion artefact and avoid detrimental effects on image quality.[27,34,59,109,171]

As would be expected, the extent to which heart rate needs to be reduced for MSCT-CA is dependent on the defined temporal resolution of the scanner. Using the early scanners with effective temporal resolution of ≥ 250ms, a heart rate of < 60 bpm was required to minimise coronary motion artefact.[172] Subsequent improvements in temporal resolution to 165ms permitted satisfactory image quality at heart rates up to 75 bpm.[173] The new dual source scanners with a temporal resolution of 83ms have been demonstrated capable of achieving diagnostic image quality at even higher heart rates.[104,106,109,115,174]

One method of increasing temporal resolution in MSCT-CA is the utilisation of multi-segment reconstruction protocols. Using this technique data for one image are acquired over two or more consecutive cycles, hence shortening the reconstruction window for each cycle. This technique is favoured particularly in patients with higher heart rates and many centres employ a protocol that automatically initiates multi-segment reconstruction in patients with higher heart rates. In our study a half-sector acquisition protocol was used with multi-segment reconstruction permitting an effective temporal resolution of between 50 and 200ms depending on patient heart rate. Previous studies have demonstrated an improvement in image quality with multi-segment as opposed to single-segment reconstruction.[19,21,175] Indeed, one of these studies found multi-segment reconstruction improved the average vessel length free of motion artefacts by 56% in comparison to a standard reconstruction protocol[19] and two studies demonstrated a corresponding improvement in diagnostic accuracy.[19,175] There are, however, two major recognised disadvantages of multi-segment reconstruction protocols. The first is that due to inconsistencies in consecutive cardiac cycles, data acquired over several heart beats will be derived from slightly different cardiac phases. While in single segment reconstruction this

would result in stair-step artefact, in multi-segment reconstruction averaging of signals occurs which effects blurring within the images.[176] The second issue is the higher radiation dose associated with multi-segment reconstruction.[177] This is a result of the requisite reduction in pitch to permit data acquisition and the corresponding increase in scan length. In addition, the efficacy of ECG gated tube modulation is reduced at higher heart rates due to the period of reduced tube output becoming shorter relative to the length of the cardiac cycle.

6.6.3 Considerations in method of heart rate control for this study

At the time of protocol development for this study, several studies of 40-64-slice MSCT-CA accuracy had been published and these investigators' methods of patient heart rate control during MSCT-CA were considered. The majority administered oral beta-blockade prior to commencement of MSCT-CA and achieved mean heart rates between 58 beats per minute and 72 beats per minute.[18,28,33,51,74,75,78,80] Other studies utilised intravenous beta-blockade achieving mean heart rates between 59 beats per minute and 65 beats per minute.[15,73,76,79]

All patients recruited to this study had symptoms suggestive of angina and underlying CAD was suspected. Correspondingly the majority of patients were appropriately commenced on rate-limiting anti-angina medication and beta-blockers were utilised as first line treatment. It was considered that oral beta-blockers, or in the case of contraindications oral rate-limiting calcium channel blockers, would be sufficient to achieve satisfactory heart rate control for MSCT-CA in line with the previous studies documented above. A second consideration was the improved temporal resolution of our 40-slice MSCT scanner: 200ms with half sector acquisition in comparison to 250ms with previous 16-slice scanners. Furthermore, the capacity of our scanner to utilise the multi-segment reconstruction facility, permitting temporal resolutions as low as 50ms in some cases, was

considered sufficient to negate any requirement for rate control with intravenous beta-blockade.[175]

6.6.4 Heart rate control achieved in this study

Mean (SD) heart rate during MSCT-CA was 68.8 (9.0) beats per minute. Thirty-five patients had a mean heart rate of less than 65 beats per minute and 54 patients had a heart rate of less than 70 beats per minute. Rate-limiting medication was prescribed to 90% of patients (66% beta-blockers, 24% calcium channel blockers). There was no significant difference between the mean heart rates of males and females ($p = 0.134$), or between patients in the different pre-test probability groups ($p = 0.259$) or between different BMI groups ($p = 0.313$) but the mean (SD) heart rate of patients 51-100 was significantly lower than that of patients 1-50: 66.8 bpm (8.1) for the second 50 patients vs 70.9 bpm (9.4) for the first 50 patients, $p = 0.023$. As such, significantly more of patients 51-100 fell into the mean heart rate < 65 bpm category: 24 patients vs 11 patients, $p = 0.011$.

Despite 90% of patients in our study taking rate controlling medication, just over half had heart rates < 70 bpm and only a third had heart rates < 65 bpm. This is in contrast to the previous studies where oral beta-blockers were administered for rate control.[18,28,33,51,74,75,78,80] However, in the majority of these studies a large dose of short-acting beta-blocker was given shortly before the MSCT-CA while in our study patients simply took their regular beta-blocker or alternative rate-limiter on the morning of the study (generally about nine hours before MSCT-CA). In addition, while the importance of continuing rate limiting medication up to and including the day of MSCT-CA was emphasized, there was no way of ensuring patient compliance. The AHA, ESC and NICE guidelines all recognise the importance of heart rate control during MSCT-CA in order to optimise image quality and generally recommend a mean heart rate of < 60 beats per minute.[102,103,143] However, none of these guidelines specifically advocate a regime of

either oral or intravenous beta-blockade in order to achieve satisfactory heart rate control. Of note several studies where a mean heart rate of < 60 bpm was achieved, used a combination of oral beta-blockade one or two hours prior to MSCT-CA with additional intravenous beta-blockade at the time of the study if required.[52,70,178]

6.6.5 The effect of heart rate during MSCT-CA on study evaluability

Table 6.7 demonstrates the average number of evaluable segments per patient in each of the mean heart rate groups. Significantly more segments per patient were evaluable in the heart rate < 65 bpm group in comparison to the ≥ 65 bpm group and in the < 70 bpm group in comparison to the ≥ 70 bpm group (p = 0.005 and p = 0.019 respectively).

In the ≥ 65 bpm group the percentage of LAD segments (including branches), Cx segments (including branches) and RCA segments (including PDA and LV branch where appropriate) that were unevaluable were 32.1%, 51.0% and 36.8% respectively. The corresponding percentages of unevaluable segments in the < 65 bpm group were 21.0%, 32.4% and 24.2% respectively. The greatest improvement in percentage of evaluable segments with reduced heart rate was for the Cx artery where a further 19% of Cx segments were evaluable.

Table 6.7 The effect of heart rate control on segment evaluability

	Subgroup (No. of patients)	**Mean (SD) no. of evaluable segments per patient on MSCT-CA**	**p Value**
Heart Rate (beats per minute)	**< 65** (35)	10.9 (2.7)	**p = 0.005**
	≥ 65 (65)	9.0 (3.6)	
	< 70 (54)	10.3 (3.1)	**p = 0.019**
	≥ 70 (46)	8.8 (3.6)	

6.6.6 The effect of heart rate on MSCT-CA accuracy for detecting significant CAD

Table 6.8 illustrates the accuracy parameters of MSCT-CA in comparison to I-CA for the detection of significant CAD in different heart rate groups at the per segment, per artery and per patient levels.

On a per segment basis, following exclusion of unevaluable segments, the accuracy parameters of MSCT-CA in heart rate groups revealed sensitivity and PPV to be highest for patients with the lowest mean heart rates. Specificity and NPV of MSCT-CA were high across all heart rate groups on per segment analysis. It should be noted that the exclusion of unevaluable segments in this analysis, particularly in the higher heart rate groups where the prevalence of unevaluable segments was higher, means that accuracy was, in general, over-estimated.

In contrast to the per segment analysis, at the per artery level, sensitivity appeared highest for patients with higher heart rates. The likely reason for this was that unevaluable segments in the per artery analysis were considered to represent significant disease and so fewer diseased segments would have been missed due to being "unevaluable". Correspondingly, specificity and PPV were lower in the higher heart rate groups.

On the per patient analysis the sensitivity of MSCT-CA again appeared better in the higher heart rate groups while specificity and PPV were lower. As for the per artery analysis, this was likely related to our strategy for dealing with unevaluable segments. Surprisingly, NPV seemed to be lowest in the < 65 bpm heart rate group but given the very small numbers involved the confidence intervals for this observation are wide.

Table 6.8 The effect of heart rate control on MSCT-CA accuracy

Heart Rate (bpm)	Analysis	ICA ≥ 50%	MSCT ≥ 50%			Sn (95%CI)	Sp (95%CI)	NPV (95%CI)	PPV (95%CI)
			No	Yes	UE*				
< 65 (35 patients)	Segment	No	328	11	111	44.1% (28.9, 60.5)	96.8% (94.3, 98.2)	94.5% (91.6, 96.5)	57.7% (38.9, 74.5)
		Yes	19	15	17				
		UE*	6	2	16				
	Artery	No	90	6	11	64.5% (46.9, 78.9)	84.1% (76.0, 89.8)	89.1% (81.5, 93.8)	54.1% (38.4, 69.0)
		Yes	11	17	3				
		UE*	2	0	0				
	Patient	No	11	1	6	87.5% (64.0, 96.5)	61.1% (38.6, 79.7)	84.6% (57.8, 95.7)	66.7% (45.4, 82.8)
		Yes	2	12	2				
		UE*	1	0	0				
≥ 65 (65 patients)	Segment	No	541	10	340	17.2% (7.6, 34.5)	98.2% (96.7, 99.0)	95.8% (93.8, 97.1)	33.3% (15.2, 58.3)
		Yes	24	5	22				
		UE*	2	0	31				
	Artery	No	149	11	45	75.9% (63.1, 85.4)	72.7% (66.2, 78.3)	92.0% (86.8, 95.3)	42.3% (32.9, 52.2)
		Yes	13	19	22				
		?	0	0	1				
		UE*							
	Patient	No	18	7	18	95.5% (78.2, 99.8)	41.9% (28.4, 56.7)	94.7% (75.4, 99.7)	45.7% (32.2, 59.8)
		Yes	1	15	6				
		UE*	0	0	0				
< 70 (54 patients)	Segment	No	469	18	198	37.1% (26.2, 49.5)	96.3% (94.2, 97.6)	92.3% (89.7, 94.3)	56.1% (41.0, 70.1)
		Yes	39	23	25				
		UE*	7	2	29				
	Artery	No	130	9	21	66.0% (52.6, 77.3)	81.2% (74.5, 86.5)	87.8% (81.6, 92.2)	53.8% (41.9, 65.4)
		Yes	18	25	10				
		UE*	2	0	1				
	Patient	No	16	2	10	92.0% (75.0, 97.8)	57.1% (39.1, 73.5)	88.9% (67.2, 96.9)	65.7% (49.2, 79.2)
		Yes	2	18	5				
		UE*	1	0	0				
≥ 70 (46 patients)	Segment	No	364	11	242	34.5% (19.9, 52.7)	97.1% (94.8, 98.4)	95.0% (92.4, 96.8)	47.6% (28.3, 67.6)
		Yes	19	10	25				
		UE*	1	0	18				
	Artery	No	109	8	35	81.2% (64.7, 91.1)	71.7% (64.1, 78.3)	94.7% (89.1, 97.6)	37.7% (27.2, 49.5)
		Yes	6	11	15				
		UE*	0	0	0				
	Patient	No	13	6	14	92.3% (66.7, 99.6)	39.4% (24.7, 56.3)	92.9% (68.5, 99.6)	37.5% (22.9, 54.7)
		Yes	1	9	3				
		UE*	0	0	0				

**UE - Unevaluable - Refers to segments considered unevaluable by MSCT-CA or absent on I-CA, arteries considered unevaluable by MSCT-CA or I-CA due to at least one major segment being unevaluable and no significant disease in the evaluable segments of that artery and patients considered unevaluable by MSCT-CA or I-CA due to one or more major segments being unevaluable and no significant disease in the evaluable segments. Sn = sensitivity, Sp = specificity*

6.6.7 Discussion

Our results confirm those of previous studies where increased heart rate significantly reduced image quality.[34,37] In one study, global image quality of all segments was found to be significantly better in patients with heart rates ≤ 65 bpm when compared with those exceeding heart rates of 75 bpm.[37] These studies also demonstrated, as we did, that the Cx artery and RCA were worst visualised. In one study it was noted that the image quality of the RCA was particularly degraded in the > 75 bpm group in comparison to the ≤ 65 bpm groups.[37] In our study, however, the Cx artery appeared most sensitive to increased heart rate in terms of evaluability. This is consistent with previous consideration of coronary artery mobility which has demonstrated that velocity of motion of the LAD is significantly lower than that of the RCA or Cx artery.[152] Studies of optimal reconstruction intervals for the major arteries have demonstrated that the Cx artery is least mobile in mid-diastole while the RCA is least mobile in late systole and early diastole.[152] It follows that the Cx artery motion would be affected more at higher heart rates as diastole shortens more than systole.[27]

Heart rate variability was not measured in our study. Previous studies, however, have demonstrated the importance of minimising heart rate variability in terms of improving image quality.[27,37,109] The latter study specifically showed that heart rate was less variable and image quality was better in patients receiving beta-blockers.[27]

In this study the accuracy parameters for MSCT-CA in comparison to I-CA when considered in different heart rate groups were inextricably linked to the strategies used for dealing with unevaluable segments. This was a particular issue as such a high percentage of segments were reported as unevaluable and as there were significantly fewer evaluable segments per patient in the higher heart rate groups. Nevertheless, there was some evidence from the per segment analysis that sensitivity and specificity of MSCT-CA were

reduced at higher heart rates. Specificity, in particular, may have been reduced as the result of motion artefact in arteries perhaps incorrectly considered "evaluable", contributing to false positive assessments of normal arteries.

One previous 16-slice study of the effect of heart rate control on diagnostic accuracy, similarly found sensitivity and specificity on a per segment basis to be significantly improved at lower heart rates[34] while a previous 64-slice study found all accuracy parameters on a per patient basis to be reduced at higher heart rates.[15] However, a further study demonstrated that despite a deterioration in image quality with higher heart rates, this did not translate into a reduction in diagnostic accuracy.[37] The authors of this study considered the likely explanation for this to be that while image quality was reduced from "excellent" to "good" or "moderate" at higher heart rates, the actual percentage of "non-diagnostic" segments did not differ significantly between heart rate groups. Furthermore, in the context of segments with sub-optimal image quality, additional post-processing reconstruction techniques were utilised in order to improve segment assessment. These techniques were not employed in our study which might explain to an extent why a much higher percentage of segments were unevaluable and why diagnostic accuracy was adversely affected.

6.6.8 Conclusion

This study confirmed the results of some previous studies that MSCT-CA image quality is reduced at heart rates ≥ 65 bpm and that this may result in a deterioration in diagnostic accuracy on a per segment basis if additional post-processing reconstruction techniques are not utilised.[15,34,37] Image quality of the Cx artery in particular was adversely affected by higher heart rates which is consistent with previous studies of coronary artery motion.[27,152] While heart rate variability was not assessed in this study, there is evidence from previous studies that it may significantly reduce image quality perhaps to a greater extent than

elevated heart rate alone.[27,37] Continuation of daily oral beta-blockers or calcium channel blockers in this study appeared less successful in lowering heart rate during MSCT-CA than protocols in previous studies where oral beta-blockers were given an hour before the scan and intravenous beta-blockade was administered subsequently if required.[52,70,178] Current national and international guidelines suggest lowering heart rate to < 60 bpm is most appropriate although they do not advocate a specific regime.[102,103,143] The need for careful heart rate control may be less pressing as dual source scanners become more widely available and even less important with the advent of the 320-slice scanner where imaging of the entire heart in a single cardiac cycle is possible.[109,125,179]

6.7 Coronary Artery Calcification

6.7.1 Introduction

The presence and extent of coronary artery calcification in MSCT-CA is important for several reasons.

Firstly, coronary calcification is considered to be a surrogate for the presence of atherosclerosis and is thought to represent the healing mechanism induced by subclinical plaque rupture.[180] Whilst not all atherosclerotic plaque is calcified, the extent of coronary calcium has been shown to correlate with overall plaque burden.[181] Indeed, a recent study of coronary calcium scores in a subgroup of patients from CorE-64 demonstrated that the presence of any coronary calcium significantly increased the likelihood of a patient having a significant coronary artery stenosis (OR 8.1, $p < 0.001$) whilst the absence of coronary calcium significantly increased the likelihood of a patient being free of significant coronary disease (OR 8.8, $p < 0.001$).[182] In both cases this was true after adjusting for the effects of traditional risk factors for coronary disease including age and gender.

Second, the presence or absence of calcification in certain patient groups has been shown to have prognostic significance. Specifically, the presence of coronary artery calcium has an incremental prognostic value in the prediction of coronary events in asymptomatic patients.[44] Moreover, there is evidence that in asymptomatic patients with a Framingham 10-20% ten year risk of a coronary event, a coronary artery calcium score of > 100 Agatston units transforms the moderately high risk patient to a higher risk status where more aggressive primary prevention is appropriate.[183] In contrast, the absence of any calcification in low and intermediate risk patient populations has been shown to have a high negative predictive value for ruling out significant coronary disease.[43,184] On the basis of this the ACC/AHA Expert Consensus Document published in 2007 stated that "for the

symptomatic patient, exclusion of measurable coronary calcium may be an effective filter before undertaking invasive diagnostic procedures or hospital admissions. Scores < 100 are typically associated with a < 3% probability of significant obstruction (> 50% stenosis) on cardiac catheterisation".[185]

Finally, and most relevant to the present study, coronary arterial calcification has been shown to degrade image quality due to partial volume effects and bloom artefacts. Consequently, previous studies of MSCT-CA accuracy have commonly excluded patients with high Agatston calcium scores. In this study the degree of calcification of each segment's vessel wall was assessed subjectively as heavy (indicating high density lesions extending longitudinally along the vessel wall, resulting in beam hardening and partial volume artefact), moderate (indicating small, isolated eccentric high density lesions in the vessel wall), or none.[66] All patients were included in analysis regardless of extent of calcification.

This section will consider the prevalence and demographics of coronary artery calcification within the study population and then discuss the impact of this on MSCT-CA image quality and diagnostic accuracy. A brief discussion of the utility of the presence or absence of coronary calcification as a gatekeeper for further investigations will follow.

6.7.2 The prevalence of calcification in our study

Calcification was common in our study population. Of 100 patients, 22 patients had moderate calcification and 35 patients had heavy calcification on MSCT-CA. Calcification was significantly more common in males than females: 74.5% vs 35.6%, $p < 0.001$, and with increasing age ($p < 0.001$). Heavy calcification was significantly more prevalent in the high pre-test probability group than the low pre-test probability group: 63.4% vs

10.5%, $p < 0.001$. There was no significant difference in percentage of calcified segments between different BMI groups.

6.7.3 The effect of calcification on MSCT-CA segment evaluability

The mean number of MSCT-CA evaluable segments per patient with no or only moderate arterial calcification was 10.0 (3.1) while the mean number of evaluable segments in the presence of heavy calcification was 8.9 (3.9) (Table 6.9). This difference was not statistically significant. However, there was a significant reduction in the percentage of evaluable segments in the context of heavy calcification in comparison to those with moderate calcification: 59.6% vs 71.5%, p=0.002.

Table 6.9 The effect of calcification on segment evaluability

	Subgroup (No. of patients)	**Mean (SD) no. of evaluable segments per patient on MSCT-CA**	**p Value**
Calcification	**None** (43)	9.6 (3.2)	p = 0.176
	Moderate (22)	10.7 (2.7)	
	Heavy (35)	8.9 (3.9)	

6.7.4 The effect of calcification on MSCT-CA accuracy for detecting significant CAD

The effect of the presence of calcification on the accuracy of MSCT-CA for the detection of significant CAD was considered at the per segment, per artery and per patient levels (Table 6.10). On a per segment level the presence of moderate or heavy calcification appeared to increase sensitivity and PPV for MSCT-CA for identifying stenoses ≥ 50% while reducing NPV. However, only six MSCT-CA evaluable segments with no calcium present had a stenosis ≥ 50% and so it is difficult to draw any significant conclusions. Similarly, at the per artery level only two MSCT-CA evaluable arteries with no calcification had significant CAD. When the presence of moderate calcification was

compared to the presence of heavy calcification in terms of MSCT-CA accuracy at the per artery level, heavy calcification increased sensitivity: 45.0% (95% CI 25.8-65.8) vs 80.6% (95% CI 69.1-88.6) and PPV: 42.9% (95% CI 24.5-63.5) vs 67.6% (56.3-77.1) while reducing specificity: 82.1% (95% CI 71.3-89.4) vs 68.8% (95% CI 57.8-78.1). On the per patient analysis, most notably it appears that moderate-heavy calcification in comparison to no calcification reduced NPV from 100.0% to 75.0% while increasing PPV from 4.5% to 75.6%. It should be noted however that only one patient with any stenoses ≥ 50% had no calcification.

Table 6.10 The effect of arterial calcification on MSCT-CA accuracy

Arterial Ca^{2+}	Analysis	ICA ≥ 50%	MSCT ≥ 50%			Sn (95%CI)	Sp (95%CI)	NPV (95%CI)	PPV (95%CI)
			No	Yes	UE*				
No Arterial Ca^{2+}	Segment	No Yes UE*	404 5 1	3 1 0	222 1 8	16.7% (0.9, 56.4)	99.3% (97.9, 99.7)	98.8% (97.2, 99.5)	25.0% (1.3, 69.9)
	Artery	No Yes UE*	131 1 1	3 1 0	34 1 0	66.7% (20.8, 98.3)	78.0% (71.1, 83.6)	99.2% (95.8, 100)	5.1% (1.4, 16.9)
	Patient	No Yes UE*	20 0 1	2 1 0	19 0 0	100.0% (5.1, 100)	48.8% (34.3, 63.5)	100.0% (83.9, 100)	4.5% (0.2, 21.8)
Moderate or Heavy Arterial Ca^{2+}	Segment	No Yes UE*	429 53 7	26 32 2	218 49 39	37.6% (28.1, 48.3)	94.3% (91.8, 96.1)	89.0% (85.9, 91.5)	55.2% (42.5, 67.3)
	Artery	No Yes UE*	108 23 1	14 35 0	22 24 1	72.0% (61.4, 80.5)	75.0% (67.3, 81.4)	82.4% (75.0, 88.0)	62.1% (52.1, 71.2)
	Patient	No Yes UE*	9 3 0	6 26 0	5 8 0	91.9% (78.7, 97.2)	45.0% (25.8, 65.8)	75.0% (46.8, 91.1)	75.6% (61.3, 85.8)

**UE - Unevaluable - Refers to segments considered unevaluable by MSCT-CA or absent on I-CA, arteries considered unevaluable by MSCT-CA or I-CA due to at least one major segment being unevaluable and no significant disease in the evaluable segments of that artery and patients considered unevaluable by MSCT-CA or I-CA due to one or more major segments being unevaluable and no significant disease in the evaluable segments. Sn = sensitivity, Sp = specificity*

6.7.5 Discussion

It had been postulated that coronary artery calcification may be more common in our West of Scotland population than in some of the European populations of previous studies. Since Agatston scores were not calculated in our study a direct comparison is difficult. No previous studies have reported the percentage of study patients with moderate or heavy calcification. Studies providing more information on extent of calcification than a mean Agatston score for the population have done so on a per segment basis. One multi-centre study reported that 68.7% of all segments were free from calcification.[101] One more historical study, where extent of calcification was defined in the same way as in our study, reported that almost half of all segments had no calcification.[66] Both these studies were performed in the Netherlands. Our study, in comparison, had fewer segments affected by calcification with 80.9% of all segments being calcium free. However, given that 57% of the patients in our study had some calcification it may be that while fewer coronary segments were calcified, a similar number of patients were affected as in the studies above.

The presence of coronary arterial calcification results in artefactual changes on MSCT-CA which adversely affect segment evaluability. Three specific issues have been identified: bloom artefact; partial volume artefact; and beam hardening artefact. Bloom artefact or "blooming" occurs when excess optical signal from calcification of one voxel affects neighbouring voxels and hence overestimates the size of the calcified lesion, seemingly reducing lumen diameter. The partial volume effect occurs when the degree of calcification is overestimated by automatic averaging of all tissue densities within a voxel, i.e. the presence of one small speck of calcium results in the whole voxel being depicted as white. Beam hardening is probably most relevant in terms of causing a segment to be "unevaluable" rather than merely resulting in an over-estimate of degree of stenosis. Beam hardening refers to the reconstruction algorithm failing to correctly interpret high or low attenuation rays emanating from the calcification which results in dark bands or streaks

which impair segment visualisation. The presence of heavy calcification, in particular, adversely affected segment evaluability in this study. This occurred due to a variety of the artefacts described above. Previous studies of 64-slice MSCT-CA and DSCT-CA have reported similar findings.[37,45,107] One study demonstrated an increase in the rate of unevaluable segments from 2.7% to 13.1% with increasing calcium scores.[45] Another study determined that calcification was the only predictor variable with a statistically significant effect on the number of non-diagnostic segments.[37] Even more recent studies utilising state of the art dual source technology have found calcification to reduce segment evaluability. One such study found that of all unevaluable segments, 38.5% were unevaluable due to extensive arterial wall calcification with beam hardening artefacts impairing arterial lumen assessment.[107] It is perhaps not surprising that simply increasing the temporal resolution of CT-CA does not reduce the artefact produced by calcification. What is really required is an improvement in the spatial resolution which must come from technological advances in the production of x-ray detectors and will be unaffected by merely increasing the speed of gantry rotation or the number of slices.

As would be expected, the reduction in image quality and segment evaluability due to coronary arterial calcification translated into a reduction in diagnostic accuracy in this study. It was difficult to evaluate the extent of this effect at the per segment or per artery level due to only a small number of evaluable segments and arteries having significant disease. However, it seemed that sensitivity and PPV increased with the presence of calcification. Such an observation is fairly intuitive given that the MSCT-CA reporter will be less likely to report a calcified segment as normal considering calcification is directly associated with atherosclerotic burden and the presence of bloom artefact will tend to over-estimate rather than underestimate the extent of any stenoses. In particular, on the per artery analysis, PPV was likely to be higher in the presence of calcification as calcified arteries reported unevaluable were considered to represent significant stenoses and the

majority of these did have significant disease. Previous studies have reported an increase in MSCT-CA sensitivity with higher degrees of calcification.[15,66,101,186] None of these studies, however, noted a corresponding increase in PPV. In the present study, on the per patient analysis, PPV was higher in patients with calcification while NPV was lower. One large 64-slice study reported similar results where on a per patient basis NPV markedly declined in the group with the most severe coronary calcification.[15] Several studies have reported that the presence of calcification resulted in over-estimation of the severity of stenoses and hence an increase in false positives.[15,51,68,78] Correspondingly they noted a reduction in specificity on per segment analyses. This was not a feature in our study probably because a large number of calcified segments were considered unevaluable and hence excluded from the per segment analysis rather than being over-reported.

Whether or not the presence of coronary artery calcification can be utilised as a gate-keeper to further investigation either by MSCT-CA or I-CA in asymptomatic or symptomatic patients is currently a point of controversy. As discussed previously, the absence of any calcification in low and intermediate risk patients has been shown to have a high NPV for ruling out significant coronary disease[43,184] and in recognising this the ACC/AHA recommended the use of exclusion of measurable calcification as a "filter" prior to undertaking invasive diagnostic procedures or hospital admissions.[185] Similarly the recently published NICE guidelines 2010 recommend a diagnostic pathway that excludes CAD in patients with a low pre-test probability of CAD (10-29% by modified Diamond Forrester Score) and an Agatston calcium score of 0 without the patient undergoing either MSCT-CA or I-CA.[143]

However, more recently, a large study of calcium scoring in patients with symptoms suggestive of underlying CAD, demonstrated that of 72 patients with no coronary artery calcification, 14 patients (19%) had at least one stenosis $\geq$ 50%.[182] Correspondingly the

authors concluded that in patients with a clinical indication for coronary angiography, a calcium score of 0 could not be used as a gatekeeper as it could not reliably rule out underlying significant CAD. In sub-group analysis, where pre-test probability (Morise score[167]) was considered, it was shown that for patients with a calcium score of 0, of those with a low pre-test probability, none had significant stenoses. Twenty-one per cent of patients with a calcium score of 0 and an intermediate pre-test probability had significant CAD while 29% of those with calcium score 0 and a high pre-test probability had significant disease.

In our study, of the 43 patients with no coronary artery calcification only one patient had significant CAD (stenosis $\geq$ 50%). This patient was a middle-aged, hypertensive, hypercholesterolaemic, male smoker and therefore in the high pre-test probability group. Of the 22 patients with moderate calcification, 10 patients (45.4%) had significant CAD and of the 35 patients with heavy calcification, 27 (77.1%) had significant CAD.

In total, five patients with no coronary artery calcification were in the high pre-test probability group while 26 and 12 were in the intermediate pre-test probability and low pre-test probability groups respectively. If the presence of coronary artery calcification had been used as a gate-keeper for MSCT-CA in patients with low-intermediate pre-test probability (as per the ACC/AHA guidelines[185] or the NICE guidelines[143]) then no patients with significant CAD would have been missed and 38 of 43 patients (39% of the total study population) would potentially have avoided MSCT-CA and/or I-CA. However, four patients (a 64 year-old hypertensive, hypercholesterolaemic, diabetic woman, a 57 year-old diabetic man, a 55 year-old hypercholesterolaemic, male smoker and a 67 year-old man with no risk factors for CAD) would have undergone MSCT-CA unnecessarily and two of these patients would have subsequently undergone unnecessary I-CA due to unevaluable MSCT-CAs.

6.7.6 Conclusion

In conclusion, the extent of coronary artery calcification corresponds with atherosclerotic plaque burden and its presence increases the likelihood of underlying CAD. The absence of coronary artery calcification in an asymptomatic patient carries prognostic significance in terms of a reduced risk of future coronary events. Calcification in the context of MSCT-CA produces bloom, partial volume and beam hardening artefact and adversely affects image quality. This translates to a reduction in diagnostic accuracy. Overcoming the challenges of coronary calcification on MSCT-CA will involve technological advances aimed at improving spatial resolution of MSCT scanners in addition to the routine utilisation of sharp-tissue convolution kernels to compensate for bloom artefacts. Patients with high calcium scores should proceed directly to I-CA. Whether or not the absence of coronary artery calcium can be used as a gatekeeper for further investigations by way of MSCT-CA or I-CA is controversial. This study suggests that such a strategy, in patients with a low-intermediate pre-test probability of underlying CAD, may be safe.

6.8 Conclusion of chapter

This chapter has presented variations in the performance of MSCT-CA for the detection of CAD in different patient subgroups. More specifically, female gender, elevated BMI, sub-optimal heart rate control and coronary artery calcification have been identified as factors likely to increase the percentage of unevaluable coronary artery segments. In the case of female gender, sub-optimal heart rate control and coronary artery calcification this appeared to translate to a reduction in diagnostic accuracy. The major strength of MSCT-CA was its high NPV in patients with a low-intermediate pre-test probability of underlying CAD. The Duke Clinical Score appeared a reliable method of identifying these patients. Notably, this study suggested that patients with no coronary artery calcification and a low-intermediate pre-test probability of CAD could potentially safely avoid further investigation with MSCT-CA or I-CA.

CHAPTER 7

INTER-OBSERVER AGREEMENT AND THE LEARNING CURVE EFFECT

7.1 Introduction

In this chapter inter-observer agreement data for I-CA reporters and MSCT-CA reporters are presented. Thereafter, consideration is given to the possibility of a learning curve effect on MSCT-CA reporting during the study. A discussion of competence in MSCT-CA reporting and required training and accreditation follows.

7.2 Statistical analysis

Inter-observer agreement data for ICA reporters and for MSCT-CA reporters for the detection of CAD ≥ 50% were expressed as Cohen's kappa statistics (κ) with bootstrap confidence intervals (1000 replicates) on a per segment, per artery and per patient basis. Interpretation was facilitated by the guidelines of Landis and Koch[151] where $\kappa < 0$, 0.0-0.20, 0.21-0.40, 0.41-0.60, 0.61-0.80, 0.81-100 represent "no agreement", "slight agreement", "fair agreement", "moderate agreement", "substantial agreement" and "almost perfect agreement" respectively. For the purpose of these analyses, only segments, arteries and patients considered evaluable by both I-CA reporters or both MSCT-CA reporters were included. The accuracy parameters of MSCT-CA in comparison to I-CA for the detection of stenoses ≥ 50% on a per segment, per artery and per patient basis and 95% confidence intervals were calculated separately for patients 1 - 50 and patients 51 - 100 to determine if, with respect to MSCT-CA reporting, a learning curve effect was apparent. Accuracy parameters were subsequently calculated on a per MSCT-CA reporter basis to further assess whether or not reporter inexperience was likely to have degraded accuracy.

7.3 Inter-observer agreement for I-CA and MSCT-CA

7.3.1 Inter-observer agreement for I-CA

7.3.1.1 Results

Table 7.1 illustrates analysis of agreement between I-CA reporters for the detection of significant CAD on a per segment, per artery and per patient basis. According to the guidelines of Landis and Koch there was substantial agreement between I-CA reporters at the per artery and per patient levels and almost perfect agreement for the detection of stenoses ≥ 70% on a per patient basis. Overall inter-observer agreement (κ) on a per segment basis was high at 0.624 (95% CI 0.542, 0.679). When individual segments were considered, inter-observer agreement was highest for the mid RCA, proximal Cx and LMS where κ was 0.777, 0.755 and 0.753 respectively.

Table 7.1 Analysis of agreement between I-CA reporters

Segment, Artery or Patient			Reporter 2			Kappa (95% CI)
			No	Yes	Unevaluable*	
Segments (50%)	**Reporter 1**	No	1225	52	33	0.624 (0.542, 0.679)
		Yes	36	85	15	
		Unevaluable*	36	5	13	
LMS (50%)	**Reporter 1**	No	90	2	1	0.753 (0.328, 1.000)
		Yes	1	5	1	
		Unevaluable*	0	0	0	
LAD (50%)	**Reporter 1**	No	59	7	1	0.761 (0.574, 0.875)
		Yes	3	26	2	
		Unevaluable*	0	1	1	
Cx (50%)	**Reporter 1**	No	71	5	0	0.684 (0.452, 0.829)
		Yes	5	15	2	
		Unevaluable*	0	1	1	
RCA (50%)	**Reporter 1**	No	73	5	0	0.675 (0.267, 0.717)
		Yes	2	9	3	
		Unevaluable*	2	6	0	
Artery (50%)	**Reporter 1**	No	293	19	2	0.737 (0.588, 0.774)
		Yes	11	55	8	
		Unevaluable*	2	8	2	
Patient (50%)	**Reporter 1**	No	51	8	0	0.741 (0.582, 0.873)
		Yes	4	33	2	
		Unevaluable*	1	0	1	
Patient (70%)	**Reporter 1**	No	63	3	0	0.839 (0.600, 0.886)
		Yes	3	23	3	
		Unevaluable*	1	3	1	

**Unevaluable - Refers to segments considered unevaluable or absent on I-CA, arteries considered unevaluable by I-CA due to at least one major segment being unevaluable and no significant disease in the evaluable segments of that artery and patients considered unevaluable by I-CA due to one or more major segments being unevaluable and no significant disease in the evaluable segments*

7.3.1.2 Discussion

Despite I-CA being the widely accepted gold standard investigation for the detection of CAD, there are very few reports in the literature documenting inter-observer agreement. Early studies suggested that inter-observer agreement was poor,[187,188] while more recent work found that although levels of agreement did not appear to improve with reporter experience, there was an improvement when quantitative I-CA was employed or when decisions regarding stenosis severity were made by a panel of I-CA reporters.[189] In our study we did not perform quantitative I-CA as this would be contrary to our routine clinical practice. Despite that our inter-observer agreement data for I-CA were excellent and similar to that of a recent study of 320-slice MSCT-CA accuracy in comparison to I-CA where I-CA inter-observer agreement (κ) was 0.78 (95% CI 0.69, 0.85) and 0.87 (95% CI 0.73, 0.99) on a per patient basis and per artery basis respectively, corresponding to substantial and almost perfect agreement.[151,190]

7.3.2 Interobserver agreement for MSCT-CA

7.3.2.1 Results

Table 7.2 illustrates analysis of agreement between MSCT-CA reporters for the detection of significant CAD on a per segment, per artery and per patient basis. Level of agreement was fair to moderate on a per segment and per artery basis with $\kappa = 0.370$ and 0.479 respectively. The Cx artery appeared most difficult to evaluate with only slight inter-observer agreement. However, on a per patient basis, inter-observer agreement was substantial and almost perfect at the $\geq 50\%$ and $\geq 70\%$ levels where $\kappa = 0.611$ and 0.832 respectively.

Table 7.2 Analysis of agreement between MSCT-CA reporters

Segment, Artery or Patient			Reporter 2			Kappa (95% CI)
			No	Yes	Unevaluable*	
Segment (50%)	**Reporter 1**	No	694	20	147	0.370 (0.249, 0.474)
		Yes	48	24	43	
		Unevaluable*	150	2	372	
LMS	**Reporter 1**	No	82	1	8	0.655 (-0.017, 1.000)
		Yes	1	2	0	
		Unevaluable*	2	0	4	
LAD (50%)	**Reporter 1**	No	35	1	10	0.476 (0.210, 0.733)
		Yes	9	7	14	
		Unevaluable*	2	0	22	
Cx (50%)	**Reporter 1**	No	40	2	13	0.152 (-0.102, 0.533)
		Yes	5	1	9	
		Unevaluable*	3	0	27	
RCA (50%)	**Reporter 1**	No	38	1	14	0.552 (-0.033, 0.898)
		Yes	3	3	10	
		Unevaluable*	2	0	29	
Artery (50%)	**Reporter 1**	No	195	5	45	0.479 (0.284, 0.654)
		Yes	18	13	33	
		Unevaluable*	9	0	82	
Patient (50%)	**Reporter 1**	No	17	1	7	0.611 (0.380, 0.850)
		Yes	6	12	21	
		Unevaluable*	2	0	34	
Patient (70%)	**Reporter 1**	No	22	0	17	0.832 (0.452, 1.000)
		Yes	2	7	13	
		Unevaluable*	2	1	36	

**Unevaluable - Refers to segments considered unevaluable by MSCT-CA, arteries considered unevaluable by MSCT-CA due to at least one major segment being unevaluable and no significant disease in the evaluable segments of that artery and patients considered unevaluable by MSCT-CA due to one or more major segments being unevaluable and no significant disease in the evaluable segments*

7.3.2.2 Discussion

Inter-observer agreement for MSCT-CA is most often reported in the literature on a per segment basis for the detection of stenoses ≥ 50%. Levels of agreement range from κ = 0.70 to 0.98.[28,48,51,75-78,149,169,191] Notably, in one of these studies a single radiologist performed the reconstruction and post-processing of the MSCT-CA data before presenting the images to two independent reporters.[77] It follows that inter-observer agreement in this study was extremely high with κ = 0.98. These previously reported values are higher than the per segment inter-observer agreement value for MSCT-CA in our study, κ = 0.370. This can be explained, at least in part, by mis-naming of segments by our MSCT-CA reporters, i.e. incorrect classification of lesions to be in proximal or distal segments rather than mid segments or vice versa. As alluded to in section 5.4, this difficulty would have been exacerbated by poorly visible side branches in our study. Accordingly inter-observer

agreement improved at the per artery level with $\kappa = 0.479$. Only a handful of studies of MSCT-CA accuracy have reported inter-observer agreement data on a per patient basis. In these studies the level of agreement ranges from $\kappa = 0.558$ to 0.81.[76,148,149,190] The per patient inter-observer agreement data from our study compares favourably. It should be noted, however, that for this analysis in our study, only patients whose MSCT-CAs were considered evaluable by both MSCT-CA reporters were included. Furthermore, whilst the second reporter had the option of performing further reconstructions and post-processing, in general he reported from the images already reconstructed by the first reporter. As such, the true impact of independent analysis on inter-observer agreement was not evaluated.

7.3.3 Conclusion

In our study MSCT-CA inter-observer agreement was fair to moderate on a per segment basis and per artery basis in comparison to I-CA inter-observer agreement which was considered substantial. This may have been due to the better temporal and spatial resolution of the gold standard I-CA or perhaps just reflects greater experience in I-CA reporting. Importantly, on the clinically relevant patient-based analysis, MSCT-CA inter-observer agreement was substantial and comparable to the corresponding I-CA inter-observer agreement.

7.4 Learning curve analysis

7.4.1 Introduction

It was considered possible that, as this study progressed, the MSCT-CA reporters would become more experienced in reporting MSCT-CA and thus their diagnostic accuracy would improve. It was anticipated that this "learning curve effect" might be demonstrable in terms of higher sensitivity, specificity, PPV or NPV of MSCT-CA or improved inter-observer agreement for the latter patients. Accuracy parameters and inter-observer agreement were, therefore, calculated separately for the first 50 patients and the second 50 patients overall and for each individual MSCT-CA reporter.

7.4.2 The "learning curve effect" with respect to MSCT-CA accuracy on a per patient basis

Table 7.3 illustrates the patient-based analysis of MSCT-CA accuracy for the first 50 patients in comparison to that of the second 50 patients. Overall accuracy parameters are presented in addition to data separated out by MSCT-CA reporter.

Table 7.3 MSCT-CA accuracy per patient for patients 1-50 vs 51-100

Patients and MSCT-CA Reporter	ICA Stenosis ≥ 50%	MSCT Stenosis ≥ 50%			Sensitivity (95%CI)	Specificity (95%CI)	NPV (95%CI)	PPV (95%CI)
		No	Yes	UE*				
Patients 1-50	No Yes UE*	13 1 0	6 12 0	12 6 0	94.7% (75.4-99.7)	41.9% (26.4-59.2)	92.9% (68.5-99.6)	50.0% (34.5-65.5)
Patients 51-100	No Yes UE*	16 2 1	2 15 0	12 2 0	89.5% (68.6-97.1)	53.3% (36.1-69.8)	88.99% (67.2-96.9)	54.8% (37.8-70.8)
Reporter 1 Patients 1-50	No Yes UE*	11 0 0	9 13 0	11 6 0	100.0% (83.2-100.0)	35.5% (21.1-53.1)	100.0% (74.1-100.0)	48.7% (33.9-63.8)
Reporter 1 Patients 51-100	No Yes UE*	13 0 1	4 13 0	13 6 0	100.0% (83.2-100.0)	43.3% (27.4-60.8)	100.0% (77.2-100.0)	52.8% (37.0-68.0)
Reporter 2 Patients 1-50	No Yes UE*	7 0 0	1 8 0	23 11 0	100.0% (83.2-100.0)	22.6% (11.4-39.8)	100.0% (64.6-100.0)	44.2% (30.4-58.9)
Reporter 2 Patients 51-100	No Yes UE*	14 3 1	1 3 0	15 13 0	84.2% (62.4-94.5)	46.7% (30.2-63.9)	82.4% (59.0-93.8)	50.0% (33.6-66.4)

**UE - Unevaluable - Refers to patients considered unevaluable by MSCT-CA or I-CA due to one or more major segments being unevaluable and no significant disease in the evaluable segments*

The specificity of MSCT-CA appeared a little higher for the second 50 patients enrolled in the study than for the first 50 patients, 53.3% and 41.9% respectively. While there was no significant difference in prevalence of CAD, BMI or extent of artery calcification between the two groups, mean heart rate presented a confounding factor. The mean (SD) heart rate of the second 50 patients was significantly lower than that of the first 50 patients, 67(8) vs 71(9), p=0.02. When only patients with heart rates ≥ 70 were considered, specificity still appeared higher in the second group, 53.8% vs 30% (Table 7.4). However, due to the small numbers of patients in these subgroups the confidence intervals are wide and

overlapping making it impossible to determine whether or not there was any significant "learning curve effect" in terms of per patient accuracy.

Table 7.4 MSCT-CA accuracy per patient for patients 1-50 vs 51-100 in mean heart rate groups

Patients and MSCT-CA Reporter	ICA Stenosis ≥ 50%	MSCT Stenosis ≥ 50%			Sensitivity (95%CI)	Specificity (95%CI)	NPV (95%CI)	PPV (95%CI)
		No	Yes	UE*				
Patients 1-50 with HRs ≥70	No Yes UE*	6 0 0	6 5 0	8 2 0	100.0% (64.6-100.0)	30.0% (14.5-51.9)	100.0% (61.0-100.0)	33.3% (17.2-54.6)
Patients 51-100 with HRs ≥70	No Yes UE*	7 1 0	0 4 0	6 1 0	83.3% (43.6-99.1)	53.8% (29.1-76.8)	87.5% (52.9-99.4)	45.5% (21.3-72.0)

**UE - Unevaluable - Refers to patients considered unevaluable by MSCT-CA or I-CA due to one or more major segments being unevaluable and no significant disease in the evaluable segments*

7.4.3 The "learning curve effect" with respect to MSCT-CA accuracy on a per artery and a per segment basis

Table 7.5 illustrates the segment-based and artery-based analyses of the first 50 patients in comparison to that of the second 50 patients. Overall accuracy parameters are presented in addition to data separated out by MSCT-CA reporter. Most notably there appears to have been a small improvement in both specificity and PPV on a per artery basis from 72.8% (95% CI 65.5, 79.1) to 80.7% (95% CI 73.6, 86.2) and from 39.7% (95% CI 29.3, 51.2) to 52.5% (95% CI 40.2, 64.5) respectively. This difference persisted when separated out by MSCT-CA reporter. Due to relatively small numbers in the individual subgroups the 95% CIs for these accuracy parameters are wide and overlapping.

Table 7.5 MSCT-CA accuracy for patients 1-50 vs 51-100 on segment-based and artery-based analyses

Patient Group	Analysis (Segment or Artery)	ICA ≥ 50%	MSCT ≥ 50%			Sensitivity (95%CI)	Specificity (95%CI)	NPV (95%CI)	PPV (95%CI)
			No	Yes	UE*				
Patients 1-50	Segment	No	415	16	221	38.5% (24.9, 54.1)	96.3% (94.1, 97.7)	94.5% (92.0, 96.3)	48.4% (32.0, 65.2)
		Yes	24	15	24				
		UE*	5	1	29				
	Artery	No	118	11	33	78.4% (62.8, 88.6)	72.8% (65.5, 79.1)	93.7% (88.0, 96.7)	39.7% (29.3, 51.2)
		Yes	8	16	13				
		UE*	1	0	0				
Patients 51-100	Segment	No	418	13	219	34.6% (23.2, 48.2)	97.0% (94.9, 98.2)	92.5% (89.7, 94.6)	58.1% (40.8, 73.6)
		Yes	34	18	26				
		UE*	3	1	18				
	Artery	No	121	6	23	66.7% (52.5, 78.3)	80.7% (73.6, 86.2)	88.3% (81.9, 92.7)	52.5% (40.2, 64.5)
		Yes	16	20	12				
		UE*	1	0	1				
Reporter 1 Patients 1-50	Segment	No	400	39	213	41.5% (27.8, 56.6)	91.1% (88.1, 93.4)	94.3% (91.7, 96.2)	30.4% (19.9, 43.3)
		Yes	24	17	22				
		UE*	4	3	28				
	Artery	No	110	22	30	78.4% (62.8, 88.6)	67.9% (60.4, 74.6)	93.2% (87.2, 96.5)	35.8% (26.2, 46.7)
		Yes	8	13	16				
		UE*	0	1	0				
Reporter 1 Patients 51-100	Segment	No	401	31	218	45.3% (32.7, 58.5)	92.8% (90.0, 94.9)	93.3% (90.5, 95.3)	43.6% (31.4, 56.7)
		Yes	29	24	25				
		UE*	3	1	18				
	Artery	No	113	11	26	72.9% (59.0, 83.4)	75.3% (67.9, 81.5)	89.7% (83.1, 93.9)	48.6% (37.4, 59.9)
		Yes	13	17	18				
		UE*	1	0	1				
Reporter 2 Patients 1-50	Segment	No	388	21	243	33.3% (18.0, 53.3)	94.9% (92.3, 96.6)	96.0% (93.7, 97.5)	27.6% (14.7, 45.7)
		Yes	16	8	39				
		UE*	10	0	25				
	Artery	No	93	7	62	89.2% (75.3, 95.7)	57.4% (49.7, 64.8)	95.9% (89.9, 98.4)	32.4% (24.1, 41.9)
		Yes	4	5	28				
		UE*	1	0	0				
Reporter 2 Patients 51-100	Segment	No	447	6	197	33.3% (19.8, 50.4)	98.7% (97.1, 99.4)	95.3% (93.0, 96.9)	64.7% (41.3, 82.7)
		Yes	22	11	45				
		UE*	9	0	13				
	Artery	No	111	1	38	75.0% (61.2, 85.1)	74.0% (66.4, 80.4)	90.2% (83.7, 94.3)	48.0% (37.1, 59.1)
		Yes	12	5	31				
		UE*	1	0	1				

**UE - Unevaluable - Refers to segments considered unevaluable by MSCT-CA or absent on I-CA, arteries considered unevaluable by MSCT-CA or I-CA due to at least one major segment being unevaluable and no significant disease in the evaluable segments of that artery*

7.4.4 The "learning curve effect" in terms of inter-observer agreement

Table 7.6 illustrates inter-observer agreement levels for MSCT-CA reporters for the first 50 patients in comparison to the second 50 patients. As noted before this analysis only included segments, arteries and patients considered evaluable by both MSCT-CA reporters. Due to small numbers, therefore, any suggested differences in inter-observer agreement between the two groups are small and the 95% confidence intervals are wide and overlapping.

Table 7.6 Inter-observer agreement data for MSCT-CA reporters for patients 1-50 and patients 51-100

Analysis	Kappa (95% Confidence Interval)	
	Patients 1-50	**Patients 51-100**
Segment - Stenosis ≥ 50%	0.305 (0.150, 0.463)	0.450 (0.265, 0.603)
Artery - Any Stenosis ≥ 50%	0.462 (0.179, 0.680)	0.492 (0.167, 0.742)
Patient - Any Stenosis ≥ 50%	0.746 (0.323, 1.000)	0.468 (0.142, 0.857)
Patient - Any Stenosis ≥ 70%	0.792 (0.000, 1.000)	0.857 (0.454, 1.000)

7.4.5 Discussion

In this study the specificity of MSCT-CA to detect the absence of significant CAD may have been slightly higher in the second 50 patients. This appeared to be the result of fewer arteries considered unevaluable in the second 50 patients and a corresponding reduction in false positive assessments. This was likely secondary to significantly better heart rate control in the second 50 patients but may also reflect increasing MSCT-CA experience.

To date only two studies have prospectively examined the effect of increasing experience with MSCT-CA on reporters' abilities to evaluate coronary artery stenoses.[148,192] The first of these demonstrated a significant temporal improvement in diagnostic specificity.[148] The two MSCT-CA reporters' diagnostic specificities increased respectively from 68% to 89%,

p = 0,007 and from 71% to 89%, p = 0.01. A significant improvement in inter-observer agreement was also noted during the study period with κ increasing from 0.35 to 0.89, p = 0.01.

In the second study three radiologists and a cardiologist, inexperienced in MSCT-CA, completed a 12 month training fellowship at an academic centre in the Netherlands.[192] Each reporter interpreted 12 - 15 studies each week and sensitivity and specificity for each reporter's evaluation of coronary artery stenoses ≥ 50% (in comparison to I-CA data) was assessed at several points during the year. At baseline sensitivity varied between 33% and 72% and specificity between 70% and 94% in comparison to "expert" reporters who achieved sensitivity and specificity of 95% and 93% respectively. At the end of the 12 month training period sensitivity varied between 66% and 75% while specificity varied between 87% and 92%. In effect, two reporters significantly improved sensitivity of their reporting while one significantly improved specificity. The authors concluded that while increasing experience in MSCT-CA improved diagnostic accuracy, the acquisition of expertise was a gradual process which may take longer than 12 months.

Recently two international societies have published documents presenting guidance on training in MSCT-CA and achieving appropriate competence to permit independent reporting.[103,193] In 2006 the ACC and AHA issued a joint statement concerning competency in MSCT-CA.[193] The minimum requirements for competence were specifically addressed and defined at three different levels. Level 1 competence required only a basic knowledge of MSCT-CA in the context of general adult cardiology or general radiology. Level 2 competence determined the minimum recommended experience prior to independent performing and interpretation of MSCT-CA. This comprised eight weeks of cumulative training in addition to the mentored performance of at least 35 studies and the interpretation of 50 non-contrast and 150 contrast studies. Reference was also made to

the need for physicians with level 2 competence to have knowledge of the potential incidental non-cardiac findings on MSCT-CA and to be able to refer to other specialties as appropriate. Level 3 competence required six months training in total with 100 studies performed and 300 studies interpreted.

Subsequent to the development of the American guidelines above, the ESC published a report documenting recommended training requirements for MSCT-CA reporting.[103] The need for competence on various levels was recognised including: data acquisition with knowledge of appropriate pre-medication and techniques to minimise radiation exposure; image reconstruction and post-processing with adequate comprehension of CT physics, radiology and cardiac physiology; and image interpretation based on knowledge and experience of MSCT-CA in addition to familiarity with normal and variant cardiac and coronary anatomy in the context of clinical assessment for coronary artery disease. The ESC advocated the use of the guidelines for level 1 to level 3 competence published by the ACC/AHA[193] but noted that, in the absence of any specific evidence base, their recommendations were a consensus based on presumed requirements and practicalities.

In our study MSCT-CA reporter 2 and MSCT-CA reporter 3 (who resolved discrepancies between reporters 1 and 2) had achieved level 2 competency in MSCT-CA performance and interpretation prior to the commencement of the study. MSCT-CA reporter 1 was less experienced but achieved level 2 competence during the study. The image reconstruction and post-processing were performed primarily by MSCT-CA reporter 1 so it could be argued that this may have reduced accuracy overall. However, in fact, the accuracy of MSCT-CA reporter 1's study interpretation was equivalent if not superior to that of MSCT-CA reporter 2. In the main patient-based analysis at the $\geq$ 50% level, MSCT-CA reporter 1 achieved sensitivity, specificity, NPV and PPV of 100% (95% CI 90.8, 100.0), 39.3% (95% CI 28.1, 51.9), 100% (95% CI 86.2, 100.0) and 50.7% (95% CI 39.6, 61.7)

respectively. The corresponding sensitivity, specificity, NPV and PPV for MSCT-CA reporter 2 were 92.1% (95% CI 79.2, 97.3), 34.4% (23.7%, 47.0%), 87.5% (95% CI 69.0, 95.7) and 46.7% (95% CI 35.8, 57.8) respectively.

7.4.6 Conclusion

The small increase in MSCT-CA reporter diagnostic specificity in our study was not statistically significant. It may be that a significant learning curve effect would only be apparent after a more substantial period of increasing reporter experience.[192] Careful consideration of the potential difficulties surrounding reporter training is imperative particularly as MSCT-CA is rapidly becoming more and more accessible. Whilst international guidelines state that level 2 competence and level 3 competence for MSCT-CA interpretation can be obtained within eight weeks and six months respectively,[103,193] our study and previous work would suggest that in fact the process of becoming adequately trained in performing and reporting MSCT-CA may be more protracted.[192] Given the potential consequences in terms of patient care if MSCT-CA reporters are inadequately trained prior to establishing MSCT-CA services, consideration should be given to formal accreditation for centres providing diagnostic MSCT-CA.

CHAPTER 8

HEALTH ECONOMIC ANALYSIS

8.1 Introduction

Coronary artery disease (CAD) is the most common cause of mortality in Scotland, accounting for 9,000 deaths each year.[146] This approximates to 1 in 5 deaths in men and 1 in 10 deaths in women. While overall mortality from CAD is falling, the prevalence of CAD in the population, particularly in men aged over 75 years, is rising. As such, the estimated cost of CAD to the UK health care system is currently around £3.2 billion / year.[146]

Accurate diagnosis of the presence and extent of CAD is imperative to permit initiation of appropriate management strategies. Invasive coronary angiography (I-CA) is currently the gold standard investigation providing unrivalled vessel visualisation and lesion definition and the option to perform "same session" therapeutic interventions. Recent publication of coronary heart disease statistics in Scotland have indicated that the number of diagnostic I-CAs performed each year is increasing with 17400 studies performed in 2008 in comparison to 13800 in 2003.[146] This higher volume of diagnostic I-CA in addition to the recent introduction of primary angioplasty for acute myocardial infarction has important implications in terms of time and cost to cardiology services. In addition, the need for cardiac catheterisation laboratories is likely to increase further with the imminent introduction of trans-catheter aortic valve implantation and other therapeutic trans-catheter techniques. With the current government emphasis on waiting time targets, one likely consequence will be increased spending on new laboratories.

In the context of an increasing requirement for diagnosis of CAD and in recognition of the pressures on cardiac catheterisation laboratories in terms of therapeutic interventions and meeting government waiting list targets, the introduction of a new technique for diagnosis of CAD is desirable. Previous studies comparing multi-slice CT coronary angiography (MSCT-CA) to I-CA for the detection of CAD intimated that the major strength of MSCT-

CA appeared to be its high negative predictive value (NPV) for excluding significant disease. The present study confirmed this finding with a NPV of 91% on the patient-based analysis. It would seem reasonable, therefore, that patients with suspected CAD and a negative MSCT-CA would not need to undergo I-CA. Previously, North Glasgow statistics revealed that 60% of I-CAs are performed in patients with suspected rather than known CAD and up to 20% of these studies are entirely normal or demonstrate only plaque disease (North Glasgow Minerva Data). Introducing MSCT-CA for this patient population could clearly markedly curtail referrals for I-CA. Indeed it has been suggested that implementation of such a strategy in routine clinical practice could reduce the number of I-CAs performed for suspected CAD by up to a third.[85] Effective utilisation of MSCT-CA in this clinical context could have a significant impact on NHS Scotland's ability to attain government imposed waiting time targets. Furthermore, while I-CA facilities in the West of Scotland are rapidly becoming centralised, it may be feasible for MSCT-CA to be performed in district general hospitals, thereby maximising patient convenience in addition to potentially eliminating the need for a higher risk, more invasive procedure.

In consideration of the development of a regional or national MSCT-CA service, the potential effects on cardiology and radiology services in NHS Scotland, both in terms of financial burden and waiting list targets, need to be evaluated. This chapter presents a health economic analysis of the implementation of MSCT-CA for the diagnosis of CAD in 100 patients with the characteristics of the present study population in terms of diagnostic accuracy and NHS costs.

8.2 Health economics

An economic evaluation considers two or more strategies in terms of cost and consequences. Health economics is specifically concerned with clinical and cost effectiveness of health care provision in order to optimize population benefit despite

limited resources. Any health economic evaluation must measure both cost and benefits. The costs may be monetary or opportunity costs. The latter considers the cost of any healthcare resource in terms of subsequent unavailability of funding for alternative beneficial services. Benefits are determined in terms of health effect e.g. reductions in morbidity or mortality and may include evaluations of quality of life. A health economic assessment is also required to ensure efficiency of health care provision. This would include consideration of both technical and allocative efficiency. Technical efficiency is concerned with establishing the minimum resources required to achieve a specific outcome while allocative efficiency measures the extent to which resources are appropriately directed to those who will benefit most.

To determine the most appropriate health economic analysis for the present study the four main methods of health economic analysis: cost-effectiveness analysis; cost-utility analysis; cost-benefit analysis; and cost-minimisation analysis were considered.

In a cost-effectiveness analysis the consequences of different strategies are compared in terms of a single outcome defined in "natural units" e.g. deaths avoided, cases detected etc. The cost profile for this analysis can comprise both direct and indirect costs in addition to "intangibles". Direct costs are often monetary e.g. equipment, staff pay, while indirect costs take account of less easily measured losses such as potential other uses of staff time. "Intangibles" are even more difficult to quantify and refer to consequences such as patient anxiety and adverse effects. When comparing two strategies an incremental cost-effectiveness ratio (ICER) is presented where difference in cost is the numerator and difference in outcome the denominator. The quality of a cost-effectiveness analysis is dependent on the quality of the effectiveness data utilised and so analysis should include a detailed sensitivity analysis to evaluate the extent to which alterations in the parameters used would affect the results obtained. Direct comparisons of cost-effectiveness analyses

published from different centres are often difficult due to variations in the outcome measures used.

Theoretically a cost-effectiveness analysis may have been an appropriate strategy for economic analysis of this study. Assuming a protocol where patients undergo MSCT-CA initially and have subsequent I-CA only if the MSCT-CA is either positive for significant disease or unevaluable, a cost-effectiveness analysis would have permitted calculation of the total cost per patient correctly diagnosed. However, it is difficult to know how to interpret such information appropriately i.e. what is an acceptable cost per patient diagnosed?

The theory behind a cost-utility analysis is similar to that of a cost-effectiveness analysis except the outcome measure is the number of quality-adjusted life years (QALY). The QALY is based on a combination of the additional duration of life weighted by the health-related quality of that life. Cost-utility analyses utilise the ICER in the same way as cost-effectiveness analyses with the difference in expected QALYs gained being the denominator. NICE advocate the use of a threshold ICER for cost utility analyses below which a specific intervention is more likely to be funded. The major benefit of a cost-utility analysis is it permits comparison of more than one health benefit with respect to the strategies being evaluated. However, defining quality of life and subsequently determining the "weighted value" associated with a specific health state is extremely difficult and highly controversial.

A cost-utility analysis could have been performed on our data. This, for example, could have taken into consideration the potential clinical and psychological effects on patients of a false negative or false positive MSCT-CA e.g. false reassurance or unnecessary anxiety. However, it was felt that subsequent management and prognosis would not differ with

respect to whether the diagnosis was ascertained by MSCT-CA or I-CA and so the QALY would not be a particularly useful measure. Furthermore, it was assumed that patients with false negative MSCT-CAs would have ongoing symptoms and therefore re-present and undergo I-CA in due course therefore essentially negating the issue of false reassurance.

For a cost benefit analysis the value of the resources used is compared to the value of the benefits in comparable units, usually expressed in terms of financial currency. It permits comparisons between strategies in very different areas both in and outwith healthcare. However, it struggles to measure important benefits that are difficult to express in monetary terms e.g. relief of anxiety. It also requires an explicit value to be placed on life which is difficult and provokes controversy. This type of analysis is not widely accepted in health economics and was not considered suitable for this study due to difficulties in assigning financial values to the multiple benefits of accurate diagnosis of CAD.

The final major method of health economic analysis is termed cost-minimisation. This type of analysis requires evidence of outcome equivalence irrespective of input. As such, the input demonstrated to be less costly is considered more desirable. Cost-minimisation analysis was felt to be most appropriate for this study as the clinical course and management of significant CAD is equivalent regardless of whether diagnosis is made by MSCT-CA or I-CA.

8.3 Method and statistical analysis

A simple model was utilised as a "base case" and added complexity introduced in subsequent one-way sensitivity analyses. The "base case" assumed the accuracy parameters of MSCT-CA for the detection of CAD demonstrated in the present study and the patient prevalence of CAD with stenosis ≥ 50% was also that of the present study population. I-CA was considered, as the gold standard diagnostic investigation, to have

sensitivity and specificity of 100%. The cost of MSCT-CA and I-CA were estimated from recent Scotland specific publications.[194,195] These data inputs are illustrated in Table 8.1.

Table 8.1 Data inputs for health economic analysis

Variable	Value	Source
Prevalence of CAD ≥ 50%	39%	Study Results
MSCT-CA sensitivity	92.1%	Study Results
MSCT-CA specificity	47.5%	Study Results
I-CA sensitivity	100%	Assumed
I-CA specificity	100%	Assumed
MSCT-CA Cost	£206	Estimate from Health Economic Analysis of MSCT-CA at Aberdeen Royal Infirmary[194]
I-CA Cost	£947	Scottish National Tariff Project[195]

It was assumed that if MSCT-CA were the initial diagnostic test performed, a positive test would result in I-CA while a negative result would not require I-CA. It was also assumed that resource use before the choice of diagnostic test was unaffected and that treatment of CAD detected did not depend on whether it was detected by I-CA or MSCT-CA. The "base case" did not take into account the small risk of adverse events of either investigation which in effect favoured I-CA, the higher risk procedure.

A one-way sensitivity analysis was performed in order to determine to what extent selected alterations in "input" e.g. MSCT-CA accuracy parameters, CAD prevalence, MSCT-CA and I-CA cost would effect variations in "output" i.e. cost effectiveness or otherwise of MSCT-CA.

8.4 Results

Using the CAD prevalence and MSCT-CA sensitivity and specificity determined in this study, an "MSCT-CA" first strategy had the effect of saving £7583 per 100 patients (£87,117 for "MSCT-CA" first vs £94,700 for I-CA only). Subsequent one-way sensitivity analysis demonstrated that while keeping all other "base case" assumptions the same, the

"I-CA only strategy" became the cheaper option if any of the following situations occurred:

- Prevalence of CAD > 54%
- MSCT-CA sensitivity < 82% (assuming all false negatives eventually require I-CA)
- MSCT-CA specificity < 36%
- MSCT-CA cost > £281
- I-CA cost < £693

8.5 Discussion

8.5.1 The effect of CAD prevalence on cost effectiveness of MSCT-CA

Sensitivity analysis demonstrated that as the prevalence of CAD in the population increased, any financial savings from an "MSCT-CA first" strategy declined. Specifically, using the accuracy parameters for MSCT-CA determined in our study, from a health economics perspective, I-CA should be the initial investigation in a population where prevalence of CAD exceeded 54%. Intuitively this seems correct as in a higher prevalence population MSCT-CA will more often be positive for CAD and so subsequent I-CA will be required more often, effectively negating the need for an initial MSCT-CA in a larger proportion of patients. Notably, in our study, prevalence of CAD in the high pre-test probability group was 73% while prevalence of CAD in the low-intermediate pre-test probability group was 14%. Had an "MSCT-CA first" strategy been employed in these groups then it would have been at a net cost of £8327 per 100 patients and a net saving of £18492 per 100 patients respectively. The net saving of £18492 from MSCT-CA in the low-intermediate pre-test probability group would be increased further to £21,750 if the slightly higher specificity of MSCT-CA in this group (52%) was used in the calculation in preference to the overall specificity calculated for MSCT-CA (48%). Similarly, the net loss of £8327 from MSCT-CA in the high pre-test probability group would be increased

further to £13696 if the substantially lower specificity of MSCT-CA in this group (27%) was used in the calculation.

The relative benefits of implementing MSCT-CA in low-to intermediate risk patients with a generally lower patient prevalence of significant CAD have been documented in previous health economic analyses.[194,196,197] Two of these studies reported MSCT-CA to be more cost effective than I-CA in patient populations with pre-test likelihoods for CAD of up to 50% and up to 65% respectively.[196,197] Neither study, however, explicitly defined their method of risk stratification. Similarly a UK health economic analysis concluded that only if the prevalence of CAD was relatively high was it likely that the use of MSCT-CA in the diagnostic pathway would result in a higher overall diagnostic cost per patient.[194]

8.5.2 The effect of MSCT-CA accuracy on cost effectiveness

Clearly the accuracy parameters of MSCT-CA for the detection of significant CAD will play an important role in determining the cost-effectiveness of the investigation. In a model where it is assumed that all false negatives will eventually undergo I-CA (subsequent to re-presenting with ongoing symptoms), the sensitivity of MSCT-CA is not relevant. However, the specificity is highly relevant as patients with false positive MSCT-CAs will undergo I-CA whereas patients with true negatives will not. As such, utilising one-way sensitivity analysis, it was demonstrated in the present study that if specificity fell below 36% then the "MSCT-CA first" strategy would cease to be cost-effective. Previous health economic analyses used estimates of MSCT-CA specificity from meta-analytical studies which varied between 89%[194] and 94%[197] which are clearly substantially higher than the specificity found in our study. However, MSCT-CA continued to be cost-effective even at lower specificities with one study reporting preservation of the cost saving even if up to 81.5% of the patient cohort ended up undergoing I-CA.[198]

It was considered in the sensitivity analysis in our study that the accuracy parameters of MSCT-CA might improve over time by way of a "learning curve effect". In particular, comparison of MSCT-CA accuracy in the first 50 patients compared to the second 50 patients in our study suggested a small improvement in specificity (see chapter 7). Even if specificity improved only to the upper 95% confidence limit of 65% in the low-intermediate pre-test probability group, there would be a significant increase in cost saving from £21,750 to £32,337 with the "MSCT-CA first" strategy.

8.5.3 The effect of cost of MSCT-CA and I-CA on cost effectiveness

Clearly the costs of MSCT-CA and I-CA have a major influence on the extent to which MSCT-CA is cost-effective or otherwise. Table 8.2 demonstrates the variability in reported costs for these investigations.

Table 8.2 Varying cost estimates for MSCT-CA and I-CA*

Study (Country)	MSCT-CA	I-CA	Ratio
Our "Base Case" (SCOT)	£206	£947	1:4.6
Amemiya[199] (JAP)	US$1,100	US$7,290	1:6.6
Khare[200] (USA)	US$1,500	US$2,278	1:1.5
Kreisz[197] (AUS)	Aus$ 1,020	Aus$3,035	1:3
Mowatt[194] (UK)	£206	£320	1:1.6

**At the time of preparing this report – Summer 2010 – the currency exchange rate was £1 = US$1.51 = Aus$1.73. A more appropriate technique for comparisons would use purchasing power parity statistics but even the crude comparison reveals that UK costs per test are less than those in the US or Australia*
SCOT = Scotland, JAP = Japan, USA = United States of America, AUS = Australia, UK = United Kingdom

If, for example, the estimated cost of I-CA was as estimated at Aberdeen Royal Infirmary[194] i.e. £320, then with the population CAD prevalence and MSCT-CA accuracy parameters defined in our study, the "MSCT-CA first" strategy would be at a net cost of £11,328 per 100 patients. Accurate determination of the cost of these investigations is extremely difficult and comparison of costs between different centres and countries even more so. For our study it was considered that the ISD Scotland National Tariff Project was

the most appropriate resource to estimate I-CA cost and as such, was used for our analysis.[195]

8.5.4 Implementation of MSCT-CA in health economic terms

A less conventional method of economic evaluation is a consideration of the "cost"-consequences of introduction of MSCT-CA into routine clinical practice. These "costs" are not exclusively monetary and may represent, in addition to financial burden, the effects on local and regional workload for cardiology and radiology services in terms of time, resources and capacity to attain government imposed waiting list targets.

When the present study was commenced in 2007 the national waiting list target was a maximum wait of eight weeks and it was correctly envisaged that by the time of completion of this study this would be reduced. Indeed the national target is now four weeks. It was considered that the introduction of MSCT-CA might have a significant role to play in terms of reducing waiting lists for I-CA particularly with the impending national primary percutaneous intervention for myocardial infarction service. However, without formally implementing MSCT-CA, these waiting list targets are already being met. In August 2009, the I-CA waiting time at the Golden Jubilee National Hospital in Glasgow was just one week for an elective I-CA and 24-48 hours for emergency cases. Statistics from other Scottish hospitals would suggest that the situation in Glasgow is not untypical (Table 8.3).

Table 8.3 Angiography waiting lists 31st March 2009

NHS Board of Treatment	Number on List	Over Local Target
NHSSCOTLAND	406	2
Golden Jubilee National Hospital	89	0
NHS Ayrshire & Arran	5	0
NHS Dumfries & Galloway	27	1
NHS Grampian	71	0
NHS Highland	19	0
NHS Lanarkshire	62	0
NHS Lothian	105	0
NHS Tayside	28	1

Whilst reducing the number of I-CAs performed may not be necessary in terms of waiting list targets for I-CA specifically, there would be benefits in terms of freeing up cardiac catheterisation laboratory time to permit waiting time targets for cardiac electrophysiology investigations and procedures in addition to studies and interventions for congenital heart disease such as insertion of percutaneous septal closure devices. Furthermore, it is anticipated that funding for trans-catheter aortic valve implantation may become available in Scotland and as such further catheterisation laboratory time would be required. Finally, increasing laboratory free time will also serve to improve training and education.

Data from the present study can be used to estimate the percentage of I-CAs across Scotland that could be avoided if MSCT-CA were to be introduced into routine clinical practice with its present accuracy parameters. In 2008, 17369 I-CAs were performed in Scotland, of which 10563 were elective. It is not clear what percentage of elective I-CAs were for investigation of suspected CAD as opposed to evaluation of known CAD but previous estimates from North Glasgow Minerva data have suggested that up to 60% of elective I-CAs are for suspected CAD. Extrapolating from our study, up to 60% of these patients (around 3800 patients annually) would have a low-intermediate pre-test probability of CAD and would be potential candidates for MSCT-CA. In fact, in our study, 86% of the low-intermediate pre-test probability group had no significant CAD on I-CA. However, with the accuracy parameters for MSCT-CA demonstrated in our study,

just under half the patients without significant CAD on I-CA were incorrectly defined by MSCT-CA as either "false positives" or "unevaluable" (effective false positives) and so would have gone on to have I-CA. If the number of unevaluable MSCT-CAs (effective false positives in a low prevalence population) could be reduced by better heart rate control, better reporter training and advancing scanner technology (as discussed in previous chapters) then a higher number of I-CA referrals could be avoided.

8.6 Conclusion

MSCT-CA is cost effective in the detection of significant CAD in a patient population with low-intermediate pre-test probability and hence fairly low prevalence of disease. Savings would be increased with improved MSCT-CA specificity. A strategy of screening patients being considered for I-CA on the basis of their risk level and referring 'low-intermediate risk' cases for MSCT-CA could affect up to 60% of patients and avoid I-CA in at least half of this 60%. The implications for I-CA waiting times are small because other policies have reduced these to a minimal level. There would, however, still be benefits for the system in terms of other waiting times for other catheterisation laboratory-based investigations and interventions and opportunities for training and education, although the latter are hard to quantify. If a regional or local MSCT-CA service is developed then future work should focus on ensuring appropriate training for those performing and reporting MSCT-CA and on the development of local guidelines dictating which patients would be suitable for MSCT-CA in preference to I-CA. Audit of MSCT-CA referrals could determine the extent of adherence to guidelines. Further research could be observational in nature with follow-up of patients who have MSCT-CA and are then referred for I-CA and also follow-up of those patients with "negative" MSCT-CA who do not have subsequent I-CA in terms of subsequent cardiac events or eventual I-CA.

CHAPTER 9

DISCUSSION AND CONCLUSION

Coronary artery disease is the leading cause of mortality in Scotland (population 5.2.million), accounting for 9000 deaths each year.[146] Accurate diagnosis of the presence and extent of CAD is essential to guide management. I-CA is the gold standard diagnostic investigation but is associated with a small risk of significant vascular complications.[6] The development of MSCT-CA as a non-invasive imaging modality capable of coronary artery visualisation has been met with much interest and enthusiasm and incremental advances in scanner technology and image reconstruction techniques have greatly improved the accuracy of MSCT-CA in comparison to I-CA.[90,91]

The introduction of MSCT-CA into routine clinical practice in Scotland is desirable in terms of patient safety and convenience. Furthermore, reducing the number of I-CAs performed would reduce pressure on cardiac catheterisation laboratory time. This is particularly attractive given the recent establishment of primary percutaneous intervention for myocardial infarction, the demands of waiting time guarantees and the potentially imminent introduction of trans-catheter aortic valve implantation. However, at the time of conducting this study the evidence for MSCT-CA accuracy was limited and only minimal guidance on appropriate use of MSCT-CA was available. Moreover, the majority of evidence was derived from specialist academic centres with substantial experience in the technique and the accuracy of MSCT-CA in smaller centres with variable expertise and a more heterogeneous population was unknown.

MSCT-CA for the evaluation of CAD has been, and continues to be, a rapidly expanding field and utilisation of this investigation is becoming widespread. However, limitations persist and correspondingly the ESC currently recommend MSCT-CA for assessment of symptomatic patients with an intermediate pre-test probability of CAD only if diagnostic image quality can be expected and the investigation can be expertly performed and reported.[103] Most recently, NICE recommended MSCT-CA in patients with a low

estimated likelihood of underlying CAD and some evidence of coronary artery calcification.[143] In view of these recent international and national recommendations consideration of our objective assessment of MSCT-CA accuracy in routine clinical practice in Scotland is vital.

Our work is the first UK study in a district hospital setting comparing 40-Slice MSCT-CA to I-CA for the detection of significant CAD. In the clinically relevant patient-based analysis sensitivity and NPV were high at 92% and 91% respectively and were comparable to previous tertiary centre studies.[90,91] However, specificity and PPV were poor at 48% and 52% respectively. This is in contrast to the corresponding accuracy parameters of 89% and 93% reported from experienced centres.[90,91] Only two previous studies (both Scandinavian) have reported 40-64-Slice MSCT-CA accuracy explicitly in a district hospital setting and, similarly to our study, specificity and PPV were reduced.[147,148]

One of the major issues with interpretation of MSCT-CA is that, for a variety of reasons, often not all coronary artery segments are evaluable. In this study one third of coronary artery segments identified on I-CA were deemed unevaluable by MSCT-CA. This is in contrast to previous studies where the number of unevaluable segments is typically less than 10%.[90,91] The effect of unevaluable segments on diagnostic accuracy undoubtedly depends on the strategy utilised for dealing with them and the prevalence of CAD in the population studied. In our study the high number of unevaluable segments adversely affected specificity and PPV. In the patient-based analysis all MSCT-CAs that were not fully evaluable were considered positive for significant CAD which, in the context of our intermediate patient prevalence of CAD, had the effect of increasing the number of false positive scans. We considered this strategy clinically appropriate, however, as in practice a patient with an unevaluable MSCT-CA would proceed to I-CA. This analytical approach

was not adopted by all authors of previous studies with many discounting unevaluable segments in the patient-based analysis.

Our study underscored the importance of optimising heart rate control during MSCT-CA. Inadequately controlled heart rates clearly influenced MSCT-CA image quality with significantly more unevaluable segments in the higher heart rate groups and a consequent deterioration in specificity and PPV. We utilised a multi-segment reconstruction algorithm at higher heart rates in an attempt to overcome motion artefact. While previous studies have demonstrated better image quality with this strategy,[17,19] others have indicated difficulties with the technique due to variations in coronary artery position with consecutive cardiac contractions.[21,176] Recent work has confirmed improved accuracy of MSCT-CA with lower heart rates achieved by intravenous beta blockade.[37] This may have improved accuracy in our study.

Our work also emphasized the necessity for careful patient selection prior to MSCT-CA particularly in terms of BMI and coronary arterial calcification. Increasing BMI correlates with increasing image noise[164] and has a significant and independent impact on image quality.[108] Arterial calcification degrades image quality due to partial volume effects and bloom artefacts.[37,45] Consequently, studies of MSCT-CA accuracy commonly exclude patients with high Agatston calcium scores.[57,99] In our study, the small noted reductions in the number of evaluable segments in the context of elevated BMI or arterial calcification were not statistically significant. However, incorrect reporting of "evaluable" segments due to artefact may have adversely influenced accuracy.

MSCT-CA accuracy evidently varies with CAD prevalence and as such determination of pre-test probability is prerequisite in consideration of which diagnostic test is most appropriate. The Duke Clinical Score appeared a reliable method for defining pre-test

probability groups in our population with only 10.5% of patients in the low pre-test probability group having significant CAD identified on I-CA in comparison to 73% in the high pre-test probability group.[88] Correspondingly, the NPV of MSCT-CA in the low-intermediate pre-test probability group was 93% in comparison to 75% in the high pre-test probability group. This is consistent with previous studies where CAD prevalence was high. In the multicentre study CorE-64 the prevalence of CAD was 56% and NPV in the patient-based analysis was 83%.[99] Similarly, a recent study of 40-Slice MSCT-CA where the prevalence of CAD was 77% reported NPV in the patient-based analysis to be 55%.[93] It is evident therefore that MSCT-CA is most appropriately utilised in assessment of patients with suspected CAD who are at low to intermediate risk as in these patients the high NPV may permit reliable exclusion of CAD.

A further key component in maximising the diagnostic accuracy of MSCT-CA is ensuring that those involved in performing and interpreting MSCT-CA have appropriate training and experience. The need for radiologists and cardiologists to undergo specific training and to achieve accreditation in MSCT-CA is recognised in international guidelines.[103,201] While the relative inexperience of our centre may have adversely affected diagnostic accuracy, two of our three reporters had achieved the requisite accreditation and we feel were representative of those likely to be performing and reporting MSCT-CA in district hospitals.

MSCT-CA is becoming increasingly accessible in both regional and district hospitals and appears attractive in comparison to I-CA as it permits a non-invasive evaluation of CAD. However, MSCT-CA and I-CA have a number of limitations in common. Both MSCT-CA and I-CA in isolation provide anatomical information rather than functional data and therefore do not permit assessment of myocardial perfusion or ischaemia. Furthermore, both techniques require the administration of iodinated contrast and a significant radiation

dose. MSCT-CA is further limited by its inferior temporal and spatial resolution and, as this study has demonstrated, image quality is adversely affected by common patient characteristics such as coronary artery calcification, elevated BMI and poorly controlled heart rates. Indeed, the potential requirement for intravenous beta blockade during MSCT-CA presents a further complication. One limitation of our study was the use of a 40-Slice MSCT scanner rather than the now widely distributed 64-Slice scanner. However, 40-Slice scanners are not considered significantly inferior to their 64-Slice counterparts with published accuracy parameters comparable to those from 64-Slice studies.[74,94,96] The development of the now commercially available dual source and 320-Slice scanners may overcome many of the technical difficulties of 40-64-Slice scanning and will certainly reduce the requisite radiation exposure.[106,125] However, until NHS funding is sufficient to install these scanners in multiple sites, there will be continued use of 40-64-Slice scanners and even 16-Slice scanners and so the findings of our study remain clinically relevant.

From a health economics perspective MSCT-CA is cost effective in the detection of significant CAD in a patient population with low-intermediate pre-test probability and hence fairly low prevalence of disease. Savings would be increased with improved MSCT-CA specificity. A strategy of screening patients being considered for I-CA on the basis of their risk level and referring 'low-intermediate risk' cases (defined using the Duke Clinical Score[88]) for MSCT-CA could affect up to 60% of patients. However, as described in chapter 6, this patient cohort may not all be suitable for MSCT-CA evaluation in terms of clinical characteristics. Specifically, obese patients and those with coronary artery calcifications are likely to have their scans deemed not fully evaluable and as such the strategy suggested above may avoid I-CA in only half of the 60% patients at low-intermediate risk.

The NICE guidelines published this year advocate the use of coronary artery calcium scoring in patients presenting with stable chest pain and a low estimated likelihood of underlying CAD of 10-29%. Thereafter, if the Agatston calcium score is greater than 0 but less than 400, 64-slice MSCT-CA is recommended for detection and evaluation of coronary artery disease. In the context of a calcium score of 0, consideration of other non-cardiac causes of chest pain is recommended while if the calcium score is greater than 400, I-CA rather than MSCT-CA is recommended.[143] If this guideline had been followed in our study then of the 100 patients referred for I-CA to determine the presence or absence of CAD, only seven patients would have qualified for assessment by MSCT-CA (low pre-test probability with some evidence of coronary artery calcification). In fact, ultimately, only two I-CAs would have been avoided in this group. NICE recommends that the intermediate pre-test probability group undergo non-invasive functional imaging and subsequent I-CA if testing is equivocal. There were 19 such patients in our study group and only one patient had significant CAD on I-CA. MSCT-CA in this group would have avoided almost two thirds of the I-CAs recommended by NICE by correctly identifying the absence of CAD. This would suggest that MSCT-CA may also be appropriate in patients with intermediate pre-test probability (as defined by the Duke Clinical Score) and equivocal stress testing and could avoid further unnecessary I-CAs.

If a regional or local MSCT-CA service is developed then future work should focus on ensuring appropriate training for those performing and reporting MSCT-CA and on the development of local guidelines dictating which patients would be suitable for MSCT-CA in preference to I-CA. Audit of MSCT-CA referrals could determine the extent of adherence to guidelines. Further research could be observational in nature with follow-up of patients who have MSCT-CA and are then referred for I-CA and also follow-up of those patients with "negative" MSCT-CA who do not have subsequent I-CA in terms of subsequent cardiac events.

CONCLUSION

This study demonstrated the high negative predictive value of 40-Slice MSCT-CA for ruling out significant CAD when performed in a district hospital setting in Scottish patients with a low-intermediate pre-test probability. The Duke Clinical Score appeared a reliable method for identifying these patients. Specificity and positive predictive value of MSCT-CA were compromised by a high number of unevaluable segments and by our strategy, albeit clinically appropriate, of regarding the MSCT-CAs affected as positive for significant CAD. Cost-effectiveness of MSCT-CA was demonstrated in patients at low-intermediate risk and future MSCT-CA in our population should be limited to this group in patients with minimal coronary arterial calcification. Effective heart rate control during MSCT-CA is essential. National guidelines should be utilised and local guidelines developed to govern patient selection and direct appropriate MSCT-CA reporter training and accreditation to ensure quality control.

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Appendix i

(Clinical Services Division)

DEPARTMENT OF CLINICAL PHYSICS AND BIO-ENGINEERING
Health Physics Service
West House (Ground Floor)
Gartnavel Royal Hospital
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memorandum

To: Dr Shona Jenkins
Cardiology Research Fellow
Stobhill Hospital
133 Balornock Rd
Glasgow
G12 9RZ

From: Mr A G Brennan

Date: 17 October 2006

Subject: **I-CA Vs MSCT-CA**
CSO reference No: CZG/2/266

1. Radiation Dose Assessment

Thank you for sending me the revised radiological protocol. A radiation dose assessment for the proposed examination protocol is tabulated below. My interpretation of the supplied data is that these patients would have a MSCT-CA at Stobhill & I-CA at GRI.

The dose constraint is 21.1 mSv, i.e. the maximum intended.

Radiological Protocol	Examinations	Total Effective Dose (mSv)	Additional Lifetime Fatal Cancer Risk	Risk
17/10/06 revised	MSCT-CA	12.7	1 in 1580	Moderate
Median	I-CA	4.7	1 in 4255	Intermediate
Maximum	I-CA	8.4	1 in 2380	Intermediate
Total Intended	MSCT-CA & I-CA	17.4	1 in 1150	Moderate

2. Risk Estimate

17.4 mSv effective dose is equivalent to 8 years background radiation and represents an additional risk of lifetime fatal cancer of 1 in 1150 (ICRP60, 1990). In terms of comparative lifetime risk of death, it is similar to the lifetime risk of a leisure cyclist dying from a road traffic accident (300 miles/annum), and is in the moderate risk category for bio-medical research (ICRP Publication 62, 1991).

This information should be included in the patient information sheet.

A G Brennan
Radiation Protection Adviser
& Consultant Medical Physicist

Appendix ii

Greater Glasgow Health Board
North Glasgow University Hospitals Division
Cardiac & Respiratory Division

Enquiries to Dr Shona Jenkins

Direct Telephone: 0141 201 3064

Cardiology Department
Stobhill Hospital
Balornock Road
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PATIENT INFORMATION SHEET

1a. Study Title.

Evaluation of the Potential Impact of Multi-Slice Computed Tomography (CT) Scanning on Waiting Lists for Invasive Coronary Angiography in the West of Scotland

A Study Comparing Two Different X-ray Tests for the Diagnosis of Heart Disease

2. Invitation to take part.

You are being invited to take part in a research study comparing two different X-ray tests for diagnosing heart disease. Before you decide it is important you understand why the research is being done and what it involves. Please read the following information carefully and discuss it with others if you wish. Ask us if anything is not clear or you would like more information. Take time to decide whether or not you wish to take part. If you decide to participate in the study you will be given a copy of this information sheet and a signed consent form to keep. Thank you for reading this.

3. What is the purpose of the study?

Coronary artery disease (CAD) is when the blood vessels supplying the heart, the coronary arteries, become narrowed. Risk factors for developing CAD are having high blood pressure or high cholesterol, being diabetic, smoking or having a family history of CAD. As the arteries become narrowed the flow of blood to the heart muscle becomes restricted. This can cause chest pain or shortness of breath during exercise as the heart muscle does not get enough blood supply.

The symptoms of chest pain and shortness of breath are not always the result of CAD and indeed may be due to problems with the lungs or the digestive tract. The best test we have to diagnose CAD is a coronary angiogram. The coronary angiogram test is the test that your doctor has already decided that you need and will have explained to you today. While it is a routine procedure it can be uncomfortable and there are a few risks involved. In particular, there is a small risk of having a heart attack or a stroke during the procedure.

A different way to assess narrowings in the coronary arteries is to carry out a CT scan of the heart. This is a new X-ray test that involves dye being injected into one of the veins in the back of the hand or in the arm and special x-ray pictures being taken with a CT scanner. This test is not uncomfortable, and there is no risk of having a heart attack or a stroke due to the procedure. Currently this test is not used routinely as further evidence of its accuracy in comparison to a regular coronary angiogram is required.

The purpose of this research study is to determine whether or not CT scanning of the heart is accurate enough to be used as an alternative to a coronary angiogram for some patients.

The study will involve around 200 patients, recruited over 18 months and each patient will undergo a CT scan of the heart prior to having their coronary angiogram.

4. Why have I been chosen?

You are being invited to consider participating in this study as you have symptoms suggestive of CAD and you are due to have an elective outpatient coronary angiogram to assess whether or not there are narrowings in your coronary arteries within the next 2 months.

5. Do I have to take part?

Taking part in this study is entirely voluntary and your decision. If you take part you will receive this information sheet to keep and be asked to sign a consent form. If you take part you are free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. If you choose not to take part you will simply have your outpatient coronary angiogram as planned without having the CT scan carried out first.

6. What will happen to me if I take part?

If you agree to take part you will be asked to attend the radiology department at Stobhill Hospital on an evening which will be 1 or 2 weeks prior to your outpatient coronary angiogram. Travelling expenses can be reimbursed. A venflon (small tube) will be inserted into one of the veins, either in the back of your hand or in your arm. You will then be asked to lie flat on a table and we will inject some contrast dye through the venflon into your venous system. A CT scan of your heart will then be carried out. The scan will only take about 12 seconds and during this time you will be asked to hold your breath. Following the scan the venflon will be removed and you can go home. You will have your outpatient coronary angiogram carried out 1 or 2 weeks thereafter at Glasgow Royal Infirmary.

7. What is the procedure being tested?

The procedure being tested is the CT-coronary angiogram. This is already a recognised method of visualising the coronary arteries and it is used routinely in the USA and in several countries in Europe. Experience of it in the UK, however, is very limited. This research study has been designed to determine whether or not the scan is accurate enough in Scotland's population to be used in patients with suspected CAD and in some cases to obviate the need for a coronary angiogram.

8. What are the possible disadvantages and risks of taking part?

Taking part in the study means that you will have a CT scan of your heart which you would not otherwise have had. This means that you will be receiving a dose of radiation that you would not otherwise have received. Radiation is used routinely in hospitals and is measured in mSv. A regular coronary angiogram gives a radiation dose of around 5mSv and the CT scan gives a radiation dose of 13mSv, giving a total dose of around 18mSv. This is similar to the dose from a CT scan of your chest and abdomen. It represents an additional possible lifetime risk of fatal cancer of 1 in 1580. In terms of comparative

lifetime risk of death, it is similar to the lifetime risk of a leisure cyclist dying in a road traffic accident.

There is a small risk that you might have an allergic reaction to the contrast dye. If this happens you may need some medication given through a drip.

There is a small risk that the contrast dye that is injected in both the CT scan and the coronary angiogram may upset your kidney function. If this happens then you may need some fluids given through a drip.

There is a small risk of bruising and a very small risk of developing an infection around the vein where the venflon is inserted.

It is possible that if the scan is carried out in a pregnant woman it will harm the unborn child. Pregnant women must not therefore take part in this study, neither should women who plan to become pregnant during the study. Women who are at risk of pregnancy may be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. Women who could become pregnant must use an effective contraceptive until the CT scan of the heart and the coronary angiogram have been carried out. Any woman who finds that she has become pregnant while taking part in the study should immediately tell her research doctor.

If you have private medical insurance you should check with them before agreeing to take part in the study to ensure that your participation will not affect your medical insurance.

If the research doctor discovers during the study that you have another medical condition of which you were previously unaware you will be referred to the appropriate doctor for treatment of this condition.

9. What are the possible benefits of taking part?

Taking part in the study won't necessarily be directly beneficial to you but if we can show that CT scanning of the heart is accurate in the diagnosis of CAD then some patients will not need to undergo regular coronary angiography which does carry with it the risk of having either a heart attack or stroke. This also means that for the patients in the future who really do need an angiogram the waiting list will be shorter.

10. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw the research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information the research doctor might withdraw you from the study in your best interests. He/she will explain the reasons and arrange for your care to continue**.**

11. What if something goes wrong?

There are no special compensation arrangements if you are harmed by taking part in this research project. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. The normal National Health Service complaints mechanisms are available if you wish to complain or have any concerns.

12. Will my taking part in this study be kept confidential?

If you consent to take part in the research your medical records may be inspected by the research doctor for purposes of analysing the results. Only government regulatory authorities and the research doctor will have access to your medical notes.

All information collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. Reports or publications resulting from the study will not contain any personal details. Your General Practitioner will be informed of your participation and clinical management.

13. What will happen to the results of the research study?

The results of the research study will be stored on a computer database and are likely to be published in cardiology journals. Reports or publications resulting from the study will not contain any personal details. The research doctor will provide a copy of the results on request.

14. Who is organising and funding the research?

Stobhill Hospital Cardiology Department is organising this research and it is being funded by the Chief Scientist Office.

15. Who has reviewed the study?

This study has been reviewed and approved by Glasgow Royal Infirmary Local Research Ethics
Committee which is an independent panel.

16. Contact for further information

If you have any concerns during the study please contact Dr Jenkins on 0141 201 3064. If Dr Jenkins is unavailable, contact your own general practitioner. Please advise Dr Jenkins if you are admitted to hospital or seen at a casualty department for any reason.

Thank you for considering taking part in this study

Appendix iii

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Evaluation of the Potential Impact of Multi-Slice Computed Tomography Scanning on Waiting Lists for Invasive Coronary Angiography in the West of Scotland

A Study Comparing Two Different X-Ray Tests for the Diagnosis of Heart Disease

Name of Researcher: Dr Shona Jenkins

1. I confirm that I have read and understand the information sheet dated 23/11/2006 for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by the research doctor or regulatory authorities. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study.

5, I agree to my GP being informed of my participation

Signature	**Name of Patient**	**Date**
Signature of person taking consent if different from researcher	**Name**	**Date**
Signature	**Researcher**	**Date**

Appendix iv

PATIENT IDENTIFICATION							
Patient Study No.							
Unit No.							
Consultant No.[1]		**Consultant Nos. - KJH - 1, NERG - 2, FGD - 3.**					
Clinic (FT or GC)							
Symptoms							
Chest Pain		Typical or Atypical?					
Dyspnoea							
Asymptomatic Ischaemia				Duration of Symptoms (months)			
Risk Factors							
Male (Yes/No)							
HTN (BP ≥ 140/85 or on antihypertensives)	BP						
Hypercholesterolaemia (Total Chol > 4)	Total Cholesterol						
DM	Type						
FHx (Male < 55, Female < 65)							
Smoker		Ex-Smoker		Pack Years			
CVD							
PVD							
Investigations							
ECG	Date	SR	Ischaemia		RBBB	LBBB	
ETT	Date	FBETT	MBETT	Max HR (y/n)	Time (min)	Clinically Positive	Electrically Positive
Nuclear Imaging	Date	Reversible Defect		Fixed Defect		LVEF	
ECHO	Date	WMA site	Mild LVSD	Mod LVSD		Severe LVSD	LVEF
Medication							

Medication	**Name**	**Total daily Dose**	**Medication**	**Name**	**Total Daily Dose**
Antiplatelet			K Sparing Diuretic		
Beta Blocker			ACE Inhibitor		
Rate-limiting CCB			ARB		
Other CCB			Sulphonylurea		
K + Agonist			Biguanide		
PO Nitrate			Insulin		
PRN Nitrate		N/A	Hypoglycaemic		
Diuretic			Statin		
Alpha Blocker			Ezetimibe		
Warfarin		N/A			

Appendix v

Duke Probability of having CHD using Clinical Variables This score is not applicable if patient is already known to have CHD		
AGE	Years	
SEX	Male	Female
Characteristics of presenting Chest Pain[166,202,203]	**YES**	**NO**
1 Precipitated by exercise / stress		
2 Brief duration (2-15min)		
3 Relieved promptly by rest / GTN		
4 Retrosternal		
5 Radiating to jaw, neck, left arm		
6 No other cause of chest pain		
Categorisation of Chest Pain	Non-anginal, Chest pain ? cause, Typical angina	
Clinical Risk Variables[88,168]	**YES**	**NO**
1 Current smoker		
2 Diabetes		
3 Previous MI		
4 Cholesterol > 6.5 mmol/l		
5 ECG: Q waves of old MI		
6 ECG: ST changes at rest		
Probability of Significant CAD[88]	%	
Risk	Low, Intermediate, High	

Appendix vi

PATIENT IDENTIFICATION		INVESTIGATOR IDENTIFICATION
Patient ID No.	**Unit No.**	**Investigator**
		Date of Report
Date of Investigation		**Time Taken to Report**
PATIENT DETAILS		
Height (m)		**Weight (Kg)**
Rate Limiter (Name)		**Total Daily Dose (mg)**
HR Pre MSCT-CA		**HR Post MSCT-CA**
Complications		**Radiation Dose (mSv)**

SEGMENT ANALYSIS			
Segment	**% Stenosis[1]**	**Image Quality (Good, Adequate or Non-Diagnostic)**	**Calcification (Heavy, Moderate or None)**
1. LM			
2. Proximal LAD			
3. Mid LAD			
4. Distal LAD			
5. D1			
6. D2			
7. Proximal Cx			
8. Distal Cx			
9. OM1			
10. OM2			
11. Proximal RCA			
12. Mid RCA			
13. Distal RCA			
14. PDA			
15. Posterolateral Artery (LV Branch)			

1. Stenoses should be recorded as 0, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 99%, 100% (occluded), Unevaluable or Artery Absent.

Appendix vii

PATIENT IDENTIFICATION		INVESTIGATOR IDENTIFICATION
Patient ID No.	**CHI No.**	**Investigator**
DOB	**Unit No.**	**Date of Report**
Date of Investigation		**Time Taken to Report**
SEGMENT		**% STENOSIS [1]**
1. LM		
2. Proximal LAD		
3. Mid LAD		
4. Distal LAD		
5. D1		
6. D2		
7. Proximal Cx		
8. Distal Cx		
9. OM1		
10. OM2		
11. Proximal RCA		
12. Mid RCA		
13. Distal RCA		
14. PDA		
15. Posterolateral Artery (LV Branch)		
Complications		
? Same Session PCI		

1. **Stenoses should be recorded as 0, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 99%, 100% (occluded) or Unevaluable.**

Appendix viii

The Importance of Patient Selection for Multislice Computed Tomography Coronary Angiography in the West of Scotland

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Scottish Cardiac Society Annual Meeting 2008

Background

Multislice computed tomography coronary angiography (MSCT-CA) permits non-invasive visualisation of the coronary arteries. Previous studies have demonstrated high sensitivities and negative predictive values for the detection of coronary stenoses ≥ 50%. The accuracy of MSCT-CA in patients with suspected coronary artery disease in the West of Scotland is unknown. This study aimed to assess this and to determine a role for MSCT-CA in this group of patients.

Method

Ninety consecutive patients (48 male, 42 female, mean age 57.6) referred for invasive coronary angiography (I-CA) with suspected coronary artery disease were recruited from 2 hospitals in Glasgow between January 2007 and May 2008. MSCT-CA was performed with 100mls of iodinated contrast using the Philips Brilliance CT scanner (40 x 0.625mm collimation, 0.4 second rotation, 120 kV) with ECG-gated tube current modulation. Images were reconstructed with retrospective ECG gating and were analysed by 2 independent blinded radiologists with discrepancies resolved by a cardiologist with training in MSCT-CA. I-CA was performed within 4 weeks of MSCT-CA and reported by 2 independent cardiologists with discrepancies resolved by consensus. The 15-segment coronary artery model of the American Heart Association was utilised to allow comparison. A stenosis of ≥ 50% was considered significant.

Results

MSCT-CA and I-CA were performed without complications in all 90 patients. Mean (SD) heart rate was 69.2 bpm (9.3). Prevalence of coronary artery disease defined as presence of stenosis ≥ 50% was 36.7%. Calcification of the coronary arteries was present on MSCT-CA in 56% of patients. Of 1305 coronary artery segments, 906 were evaluable by MSCT-CA. On a per-segment basis, sensitivity (Sn), specificity (Sp), and negative (NPV) and positive (PPV) predictive values were 37.9%, 94.8%, 94.8% and 37.9% respectively. On a per-artery basis, Sn, Sp, NPV and PPV were 74.6%, 73.4%, 92.7% and 39.1% respectively. In the per-patient analysis, segments assessed unevaluable by MSCT-CA were considered to represent significant stenoses. On a per-patient basis, Sn, Sp, NPV and PPV were 93.9%, 40.4%, 92.0% and 47.7% respectively. MSCT-CA Sp and PPV improved with lower patient heart rates (56.2% and 65.0% respectively). Subgroup analyses demonstrated that NPV was higher in patients with low pre-test probability, patients with a BMI less than 25kg/m^2, and patients with no coronary artery calcification (100%, 100% and 93.8% respectively), however the number of patients in each individual subgroup was small.

Conclusion

The high accuracy of MSCT-CA widely reported in the literature is not confirmed in this study. The major strength of MSCT-CA in patients with suspected coronary artery disease is its high NPV in patients with low pre-test probability, no coronary artery calcification and a normal BMI. Appropriate patient selection, therefore, is key in optimising the usefulness of this investigation.

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Appendix ix

Limited Clinical Utility of CT Coronary Angiography in a District Hospital Setting

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ABSTRACT

Background

Studies have demonstrated considerable accuracy of multi-slice CT coronary angiography (MSCT-CA) in comparison to invasive coronary angiography (I-CA) for evaluating coronary artery disease (CAD). The extent to which published MSCT-CA accuracy parameters are transferable to routine practice beyond high-volume tertiary centres is unknown.

Aim

To determine the accuracy of MSCT-CA for the detection of CAD in a Scottish district general hospital.

Design

Prospective study of diagnostic accuracy.

Method

One hundred patients with suspected CAD recruited from two Glasgow hospitals underwent both MSCT-CA (Philips Brilliance 40x0.625 collimation, 50-200ms temporal resolution) and I-CA. Studies were reported by independent, blinded radiologists and cardiologists and compared using the AHA 15-segment model.

Results

Of 100 patients (55 male, 45 female, mean(SD) age 58.0(10.7)years), 59% and 41% had low-intermediate and high pre-test probabilities of significant CAD respectively. Mean(SD) heart rate during MSCT-CA was 68.8(9.0)bpm. Fifty-seven per cent of patients had coronary artery calcification and 35% were obese. Patient prevalence of CAD was 38%. Per-patient sensitivity, specificity, positive and negative(NPV) predictive values for

MSCT-CA were 92.1%, 47.5%, 52.2% and 90.6% respectively. NPV was reduced to 75.0% in the high pre-test probability group. Specificity was compromised in patients with sub-optimally controlled heart rates, calcified arteries and elevated BMI.

Conclusion

40-Slice MSCT-CA has a high NPV for ruling out significant CAD when performed in a district hospital setting in patients with low-intermediate pre-test probability and minimal arterial calcification. Specificity is compromised by clinically appropriate strategies for dealing with unevaluable studies. Effective heart rate control during MSCT-CA is imperative. National guidelines should be utilised to govern patient selection and direct MSCT-CA reporter training to ensure quality control.

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of mortality in Scotland (population 5.2 million), accounting for around 9000 deaths each year.[1] Accurate diagnosis of the presence and extent of CAD is essential to guide management. Invasive coronary angiography (I-CA) is the gold standard diagnostic investigation but is associated with a small risk of significant vascular complications.[2] Over the last decade multi-slice computed tomography coronary angiography (MSCT-CA) has emerged as a non-invasive imaging modality capable of visualising the coronary arteries. Progressive advancements in scanner technology have greatly improved the accuracy of MSCT-CA in comparison to I-CA.[3,4]

The primary shortcoming of existing evidence is that it derives from specialist academic centres with substantial experience in MSCT-CA. The accuracy of MSCT-CA in smaller centres with variable expertise and a more heterogeneous population is unknown. Accordingly, the European Society of Cardiology advocate MSCT-CA for assessment of symptomatic patients with an intermediate pre-test probability of CAD only if diagnostic image quality can be expected and the investigation can be expertly performed and reported.[5]

Recently the National Institute for Health and Clinical Excellence (NICE) published UK guidelines for the investigation of patients with recent onset chest pain.[6] MSCT-CA was considered appropriate in patients with a low estimated likelihood of underlying CAD and some evidence of coronary artery calcification. In light of these recent national recommendations an objective assessment of MSCT-CA accuracy in routine clinical practice is vital.

We present a prospective, comparative study in a district general hospital in Scotland determining the accuracy of MSCT-CA in comparison to I-CA for the detection of significant CAD.

METHOD

Study population

Between January 2007 and May 2008, 100 patients from two Glasgow hospitals were recruited. Inclusion criteria were suspected cardiac ischaemia on the basis of symptoms and non-invasive stress testing with subsequent referral for elective I-CA to determine the presence or absence of CAD. Patients with previous myocardial infarction or previous CAD on I-CA were excluded. Patients with unstable symptoms, documented iodine contrast allergy, hyperthyroidism, significant renal dysfunction (defined as serum creatinine > 150μmol/l or > 120μmol/l in a diabetic patient) and possible pregnancy were excluded to minimise patient risk. Exclusion criteria based on anticipated technical difficulties with the MSCT-CA protocol were atrial fibrillation or frequent ectopic activity and inability to carry out a 12 second breath hold. The study protocol was approved by the North Glasgow Research Ethics Committee and all patients gave written informed consent.

Patient preparation

Symptoms, risk factors for CAD, medications, routine investigations and non-invasive stress test results were recorded. Treatment with oral beta-blockers or rate-limiting calcium channel blockers was commenced and titrated aiming for a resting heart rate < 65 beats per minute (bpm).[7] Pre-test probability was assessed using the Duke Clinical Score.[8] Patients were categorised in two groups: low-intermediate pre-test probability (Score 0-74%) and high pre-test probability (Score ≥ 75%).

MSCT-CA protocol

MSCT-CA was performed on the Philips Brilliance MSCT scanner with 40 simultaneous detector rows and 0.625mm collimation. Gantry rotation time was 400ms with a half-sector acquisition protocol and multi-sector reconstruction permitting an effective temporal resolution of between 50 and 200ms depending on patient heart rate. Tube voltage was 120kV or 140kV depending on patient weight and maximum effective tube current was 600 mA/slice. Prospective ECG-dependent tube current modulation was employed to minimise radiation exposure.

A single axial CT image defined the area to be scanned, from the bifurcation of the trachea to the diaphragm. A region of interest at the origin of the descending aorta was marked to permit subsequent use of automated contrast bolus tracking. Iodinated contrast media (Omnipaque 350 [Schering AG, Berlin, Germany] in patients 1-17 and Iomeron 400 [Bracco, Italy] thereafter) was injected via a wide bore cannula in a proximal peripheral vein. Contrast volume and rate of injection varied with patient weight from 90 to 120 ml and 5.3 to 6.9 ml/second respectively. The contrast injection was immediately followed by a 50 ml saline "chaser bolus" at a rate of 5 ml/second. Scanning was automatically triggered when contrast media in the pre-defined area of the descending aorta reached a density of 160 Hounsfield units. A single automated breath-hold command was given and helical scan acquisition commenced 3 seconds thereafter to minimise respiratory related fluctuation in heart rate. Overall scan time was between 10 and 15 seconds depending on cardiac size.

Image reconstruction

Data was reconstructed using either a mono- or multi-segmental algorithm depending on patient heart rate. A volume acquisition approach with a pitch of 0.2 was employed, reconstructing axial images with slice thickness of 0.9mm using a medium soft tissue reconstruction kernel. Retrospective ECG gating permitted reconstruction of images at

45%, 50%, 60%, 75% and 80% of the RR interval to allow evaluation of the coronary arteries at the cardiac phase with least vessel motion. Reconstructed data was transferred to a dedicated offline image analysis workstation (Philips Extended Brilliance Workspace).

MSCT-CA analysis

MSCT-CAs were reported according to the 15-segment model of the American Heart Association (AHA).[9] A segment with a luminal diameter reduction ≥ 50% was classified as a significant stenosis. MSCT-CAs were reported by 2 independent, experienced consultant radiologists and discrepancies involving stenoses considered by one radiologist, but not the other, to be ≥ 50% were resolved by an independent consultant cardiologist experienced in MSCT-CA. All reporters were blinded to each other's MSCT-CA reports and to the I-CA reports.

For each vessel the optimal RR interval percentage reconstruction was identified. Stenoses identified in at least 2 independent orthogonal planes had their percentage of luminal reduction assessed on a semi-quantitative basis (from 0 to 100% in 10% increments or "unevaluable"). The percentage of stenosis was ascertained by use of planimetry on an axis perpendicular to the course of the segment. Visualisation techniques varied between segments and included straight and curved multi-planar reformations, maximum intensity projections and volume rendering. The degree of calcification of each segment's vessel wall was assessed subjectively as heavy (indicating high density lesions extending longitudinally along the vessel wall, resulting in beam hardening and partial volume artefact), moderate (indicating small, isolated eccentric high density lesions in the vessel wall), or none.[10]

I-CA protocol

I-CAs were carried out a minimum of 6 days after MSCT-CA to limit the risk of a further contrast load and a maximum of 4 weeks following MSCT-CA. I-CA was performed

applying the Judkins approach via the trans-radial or trans-femoral route and acquiring standard projections.

I-CA analysis

I-CAs were reported according to the 15-segment model of the AHA[9] with luminal diameter reductions ≥ 50% considered significant. Each ICA was reported by 2 of 4 independent consultant cardiologists experienced in performing and reporting I-CA. All reporters were blinded to each other's I-CA reports and to the MSCT-CA reports. The degree of stenosis in each diseased coronary artery segment was assessed semi-quantitatively in 2 orthogonal planes. Discrepancies concerning stenoses considered by one consultant, but not the other, to be ≥ 50% were resolved by consensus. This method was considered to best represent current clinical practice.

Statistical analysis

Statistical analysis was performed using R version 2.9.1. Standard descriptive statistics were used. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were calculated for MSCT-CA in comparison to I-CA for the detection of stenosis ≥ 50% on a per-patient, per-artery and per-segment basis with 95% confidence intervals (CI) calculated from binomial expression. Categorical variables were compared between groups using exact Fisher tests and continuous variables were compared between groups using t-tests or Wilcoxon tests as appropriate. Inter-observer agreement data were expressed as Cohen's kappa statistics (κ) with bootstrap confidence intervals (1000 replicates).

RESULTS

Patient characteristics

Over 17 months a total of 100 patients (55 male, 45 female, mean (SD) age 58.0 (10.7) years) underwent both MSCT-CA and I-CA without complication and all were included in analysis. Patient characteristics are summarised in Table 1.

Table 1

Baseline Patient Characteristics (n=100)

	Mean (SD) or %
Patient Characteristics	
Male	55%
Mean Age - years	58.0 (10.7)
Hypertension*	54%
Hypercholesterolaemia*	87%
Smoker (current or previous)	57%
Family History CAD*	40%
Diabetes Mellitus	11%
Mean BMI kg/m^2	28.6 (5.2)
BMI ≥ 30 kg/m^2	35%
BMI < 30 kg/m^2	65%
Beta-Blocker	66%
Rate-Limiting Calcium Channel Blocker	24%
Presentation and Investigations	
Chest Pain	94%
Typical Angina	56%
Median Symptom Duration - months (IQR)	5.0 (2.0-13.0)
Low Pre-Test Probability†	19%
Intermediate Pre-Test Probability†	40%
High Pre-Test Probability†	41%
Previous Exercise Tolerance Test	92%
Previous Myocardial Perfusion Imaging	29%
MSCT-CA Characteristics	
Mean Heart Rate during MSCT-CA - bpm	68.8 (9.0)
Mean Radiation Dose - mSv	15.6 (3.0)
Moderate Coronary Calcification on MSCT-CA	22%
Heavy Coronary Calcification on MSCT-CA	35%
I-CA Characteristics	
No Significant Coronary Artery Disease (No stenosis $\geq 50\%$)‡	62.9%
Single Vessel Disease (1 vessel with stenosis $\geq 50\%$)‡	11.3%
Two Vessel Disease (2 vessels with stenoses $\geq 50\%$)‡	11.3%
Triple Vessel Disease (3 vessels with stenoses $\geq 50\%$)‡	14.4%

** Hypertension, hypercholesterolaemia and family history of CAD were defined respectively by the Joint British Societies' Guidelines 2005[11] as BP ≥ 140/90 (or current antihypertensive therapy), cholesterol > 5mmol/l (or current statin therapy) and angina or myocardial infarction in a male relative age < 55 years or a female relative age < 65 years*

† Pre-test Probability determined by the Duke Clinical Score[8]

‡Based on I-CA of 97 patients as in each of 3 patients 1 vessel was considered unevaluable on I-CA

Accuracy of MSCT-CA

Of 100 patients, 99 were included in a per-patient analysis. One patient was excluded as their I-CA was not fully evaluable. The MSCT-CAs of 32 patients were considered not fully evaluable due to there being at least one unevaluable segment of a major artery. To permit a clinically relevant per-patient analysis these patients were all considered to have significant CAD, subsequently generating 8 true positives and 24 false positives. Of 38 patients identified on I-CA as having at least 1 stenosis ≥ 50%, MSCT-CA correctly identified 35 patients (92%). In the 3 patients where MSCT-CA failed to detect CAD diagnosed on I-CA, a 70% distal circumflex lesion, an 80% left ventricular branch lesion, a 70% obtuse marginal vessel lesion and a 60% proximal right coronary artery lesion in the presence of moderate arterial calcification were missed. Of 61 patients with no significant CAD on I-CA, 29 were correctly identified by MSCT-CA, 8 were incorrectly considered to have a stenosis ≥ 50% and in 24 patients the MSCT-CA was not fully evaluable. Table 2 demonstrates the accuracy parameters and 95% CIs for MSCT-CA for the detection of significant CAD in comparison to I-CA in per-patient, per-artery and per-segment analyses.

Table 2

Accuracy of MSCT-CA compared to I-CA for the detection of CAD ≥ 50%

Analysis	Number (Excluded)	ICA Stenosis ≥ 50%	MSCT Stenosis ≥ 50%			Sensitivity [95% CI]	Specificity [95% CI]	NPV [95% CI]	PPV [95% CI]
			No	Yes	UE				
Per-Patient *	99 (1)	No	29	8	24	92.1 [79.2, 97.3]	47.5 [35.5, 59.8]	90.6 [75.8, 96.8]	52.2 [40.5, 63.7]
		Yes	3	27	8				
		UE	1	0	0				
Per-Artery *	397 (3)	No	239	17	56	71.8 [61.4, 80.2]	76.6 [71.6, 81.0]	90.9 [86.8, 93.8]	45.5 [37.3, 54.0]
		Yes	24	36	25				
		UE	2	0	1				
Per-Segment†	953 (490)	No	833	29	440	36.3 [27.1, 46.5]	96.6 [95.2, 97.6]	93.5 [91.7, 94.9]	53.2 [41.0, 65.1]
		Yes	58	33	50				
		UE	8	2	47				

** In the per-patient and per-artery analyses, unevaluable segments of major arterial branches were considered to have stenoses ≥ 50% in order to ensure clinical relevance of the analyses. The excluded patient and the 3 excluded arteries were those considered not fully evaluable by I-CA*
† In the per-segment analysis segments unevaluable by MSCT-CA were excluded
UE - unevaluable, CI - confidence interval

Effect of heart rate, arterial calcification and body mass index on MSCT-CA accuracy

Rate-limiting medication was prescribed to 90% of patients (66% beta-blockers, 24% calcium channel blockers). Mean heart rate during MSCT-CA was 68.8 (9.0) bpm. Average heart rate during MSCT-CA was < 70 bpm in 54 patients and ≥ 70 bpm in 46 patients. The mean number of MSCT-CA evaluable segments per patient was 10.3 (3.1) in the < 70 bpm group and 8.8 (3.6) in the ≥ 70 bpm group ($p = 0.019$). Correspondingly the percentage of MSCT-CAs deemed overall not fully evaluable was 28.3% and 37.0% in the < 70 bpm and ≥ 70 bpm groups respectively. The accuracy parameters of MSCT-CA in the different heart rate groups demonstrated similar sensitivity and NPV but specificity and PPV were higher in patients with lower heart rates (Table 3).

Of 100 patients, 22 patients had moderate calcification and 35 patients had heavy calcification on MSCT-CA. Calcification was significantly more common in males than females (74.5% versus 35.6%, $p < 0.001$), and with increasing age ($p < 0.001$). The mean number of MSCT-CA evaluable segments per patient with no or only moderate arterial calcification was 10.0 (3.1) while the mean number of evaluable segments in the presence of heavy calcification was 8.9 (3.9). This difference was not statistically significant. However, arterial calcification lowered NPV from 100.0% to 75.0% and increased PPV from 4.5% to 75.6% (Table 3).

Mean body mass index (BMI) was 28.6 (5.2) kg/m^2 with no significant difference between males and females. Seventy-five per cent of patients had a BMI ≥ 25 kg/m^2 and 35% had a BMI ≥ 30 kg/m^2. The percentage of unevaluable segments in the 4 BMI groups, < 25 kg/m^2, ≥ 25 kg/m^2, < 30 kg/m^2 and ≥ 30 kg/m^2 was 30%, 32%, 35% and 37% respectively. This perceived difference was not, however, statistically significant and did not significantly affect accuracy parameters across the groups. There was no significant

difference in presence or absence of arterial calcification or in mean heart rate during MSCT-CA between the BMI groups.

Effect of pre-test probability on MSCT-CA

Fifty-nine per cent of patients had a low-intermediate pre-test probability and 41% a high pre-test probability of CAD. Significantly more males than females had a high pre-test probability (39 and 2 respectively, $p < 0.001$). There were no significant differences in BMI or mean heart rate between the pre-test probability groups but arterial calcification was present more frequently in the high pre-test probability group (87.8% vs 35.6%, $p < 0.001$). The prevalence of significant CAD in the high pre-test probability group and the low-intermediate pre-test probability group was 73.2% and 13.8% respectively. Correspondingly, the sensitivity and PPV of MSCT-CA were higher in the high pre-test probability group while specificity and NPV were lower (Table 3).

Interobserver Agreement

Interobserver agreement κ between I-CA reporters and MSCT-CA reporters in the detection of significant CAD was 0.74 [95% CI 0.58-0.87] and 0.61 [0.38-0.85] respectively for stenoses $\geq$ 50% and 0.84 [0.60-0.89] and 0.83 [0.45 - 1.00] respectively for stenoses $\geq$ 70%. For this analysis of agreement unevaluable segments were excluded.

Table 3

Accuracy of MSCT-CA in Comparison to I-CA for the Detection of CAD ≥ 50% - Subgroup Analyses

Sub-Group	Sn % [95% CI]	Sp% [95% CI]	NPV% [95% CI]	PPV% [95% CI]
Males	93.5 [79.3, 98.2]	50.0 [31.4, 68.6]	85.7 [60.1, 96.0]	70.7 [55.5, 82.4]
Females	85.7 [48.7, 99.3]	45.9 [31.0, 61.6]	94.4 [74.2, 99.7]	23.1 [11.0, 42.1]
Heart Rate ≥ 70 bpm	92.3 [66.7, 99.6]	39.4 [24.7, 56.3]	92.9 [68.5, 99.6]	37.5 [22.9, 54.7]
Heart Rate < 70 bpm	92.0 [75.0, 97.8]	57.1 [39.1, 73.5]	88.9 [67.2, 96.9]	65.7 [49.2, 79.2]
No Calcification	100.0 [5.1, 100.0]	48.8 [34.3, 63.5]	100.0 [83.9, 100.0]	4.5 [0.2, 21.8]
Moderate/Heavy Calcification	91.9 [78.7, 97.2]	45.0 [25.8, 65.8]	75.0 [46.8, 91.1]	75.6 [61.3, 85.8]
BMI ≥ 25 kg/m^2	92.3 [75.9, 97.9]	45.8 [32.6, 59.7]	91.7 [74.2, 97.7]	48.0 [34.8, 61.5]
BMI < 25 kg/m^2	91.7 [64.6, 99.6]	53.8 [29.1, 76.8]	87.5 [52.9, 99.4]	64.7 [41.3, 82.7]
Low/Intermediate PTP*	75.0 [40.9, 92.9]	52.0 [38.5, 65.2]	92.9 [77.4, 98.0]	20.0 [9.5, 37.3]
High PTP*	96.7 [83.3, 99.8]	27.3 [9.7, 56.6]	75.0 [30.1, 98.7]	78.4 [62.8, 88.6]

**PTP - Pre-Test Probability by Duke Clinical Score[8]*
Sn - Sensitivity, Sp - Specificity

DISCUSSION

This is the first UK study comparing MSCT-CA to I-CA in a district general hospital. Only 2 previous studies (both Scandinavian) have reported 40-64-Slice MSCT-CA accuracy explicitly in a district hospital setting.[12,13] In the per-patient analysis, sensitivity, specificity, PPV and NPV for 40-Slice MSCT-CA were 92%, 48%, 52% and 91% respectively. Whilst our results are at variance with a recently published meta-analysis of 64-Slice MSCT-CA accuracy where sensitivity, specificity, PPV and NPV were 99%, 89%, 93% and 100% respectively,[4] they are comparable to those of CATSCAN, the first multi-centre study of MSCT-CA accuracy,[14] and to a previous Norwegian study

of 16-Slice MSCT-CA in a community hospital setting[15] where specificity and PPV were also low (respectively 54% and 50%; and 29% and 57%).

MSCT-CA accuracy in this district general hospital study was compromised by a high number of unevaluable segments. Based on the AHA 15-segment model, 34% of all coronary artery segments were deemed unevaluable by MSCT-CA. This is in contrast to previous studies where the number of unevaluable segments is typically less than 10%.[3,4] Specificity and PPV in this study were lowered by our strategy for dealing with those unevaluable segments. In the per-patient analysis all MSCT-CAs that were not fully evaluable were considered positive for significant CAD which in effect increased the number of false positive scans. We consider this strategy clinically relevant, however, as in practice a patient with an unevaluable MSCT-CA would proceed to I-CA. This analytical approach was not adopted by all authors of previous studies with many discounting unevaluable segments in the per-patient analysis.

Sub-optimal heart rate control during MSCT-CA undoubtedly contributed to the high percentage of unevaluable segments in this study. Despite 90% of patients in our study taking rate controlling medication, just over half had heart rates < 70 bpm and only a third had heart rates < 65 bpm. This clearly influenced MSCT-CA image quality with significantly more unevaluable segments in the higher heart rate group and a noticeable deterioration in specificity and PPV. We utilised a multi-segment reconstruction algorithm at higher heart rates in an attempt to overcome motion artefact. While previous studies have demonstrated better image quality with this strategy,[16,17] others have indicated difficulties with the technique due to variations in coronary artery position with consecutive cardiac contractions.[18,19] Recent work has confirmed improved accuracy of MSCT-CA with lower heart rates achieved by intravenous beta blockade.[20] This may have improved accuracy in our study.

Segment evaluability may also have been adversely affected by characteristics of the patient population studied. More than one third of patients were obese with BMI ≥ 30 kg/m^2 while over half had arterial calcification on MSCT-CA. Increasing BMI correlates with increasing image noise[21] and has a significant and independent impact on image quality.[22] Arterial calcification degrades image quality due to partial volume effects and bloom artefacts[20,23] (Figure 1). Consequently, studies of MSCT-CA accuracy commonly exclude patients with high Agatston calcium scores.[14,24] In our study, the small noted reductions in the number of evaluable segments in the context of elevated BMI or arterial calcification were not statistically significant. However, incorrect reporting of "evaluable" segments due to artefact may have adversely influenced accuracy.

MSCT-CA accuracy evidently varies with CAD prevalence. The NPV of MSCT-CA for ruling out significant CAD on a per-patient basis in our study was 91%. As expected, the NPV was higher (93%) in the low-intermediate pre-test probability group where the prevalence of CAD was lower. Conversely, NPV in the high pre-test probability group was 75%. This is consistent with previous studies where CAD prevalence was high. In the multicentre study CorE-64 the prevalence of CAD was 56% and NPV in the per-patient analysis was 83%.[24] Similarly, a recent study of 40-Slice MSCT-CA where the prevalence of CAD was 77% reported NPV in the per-patient analysis to be 55%.[25]

Appropriate patient selection is imperative in order to emulate the high accuracy of MSCT-CA demonstrated in studies from large, academic centres in routine practice. The training and experience of those involved in performing and reporting the scans is equally important. The need for radiologists and cardiologists to undergo appropriate training and to achieve accreditation in MSCT-CA is recognised in international guidelines.[5,26] Level 2 competence is defined as the minimum experience required for independent performing and interpretation of MSCT-CA. In our study one of the radiologists had

achieved level 2 competence prior to commencing the study and the other completed this during the study. The cardiologist involved in resolving discrepancies between the 2 radiologists' reports was level 2 competent and the most experienced of the 3 reporters. Notably the less experienced radiologist's reported MSCT-CA accuracy was equivalent to the level 2 competent radiologist's accuracy when results were separated out per reporter. While the relative inexperience of our centre may have adversely affected diagnostic accuracy we feel our reporters were representative of those likely to be performing and reporting MSCT-CA in district hospitals. Our findings are consistent with the multi-centre studies of MSCT-CA where accuracy was reduced even despite reporting being standardized in core laboratories.[14,24,27]

MSCT-CA is becoming increasingly accessible in both regional and district hospitals and appears attractive in comparison to I-CA as it permits a non-invasive evaluation of CAD. However, MSCT-CA and I-CA have a number of common limitations. Both MSCT-CA and I-CA in isolation provide anatomical information rather than functional data and therefore do not permit assessment of myocardial perfusion or ischaemia. Furthermore, both techniques require the administration of iodinated contrast and a significant radiation dose. MSCT-CA is further limited by its inferior temporal and spatial resolution and, as this study has demonstrated, image quality is adversely affected by common patient characteristics such as coronary artery calcification, elevated BMI and poorly controlled heart rates. Indeed, the potential requirement for intravenous beta blockade during MSCT-CA presents a further complication. One limitation of our study was the use of a 40-Slice MSCT scanner rather than the now widely distributed 64-Slice scanner. However, 40-Slice scanners are not considered significantly inferior to their 64-Slice counterparts with published accuracy parameters comparable to those from 64-Slice studies.[28-30] The development of the now commercially available dual source and 320-Slice scanners may overcome many of the technical difficulties of 40-64-Slice scanning and will certainly

reduce the requisite radiation exposure.[31,32] However, until NHS funding is sufficient to install these scanners in multiple sites, there will be continued use of 40-64-Slice scanners and even 16-Slice scanners and so the findings of our study retain clinical relevance.

CONCLUSION

This study demonstrates the high negative predictive value of 40-Slice MSCT-CA for ruling out significant CAD when performed in a district hospital setting in Scottish patients with a low-intermediate pre-test probability. The Duke Clinical Score appeared a reliable method for identifying those patients. Specificity and positive predictive value of MSCT-CA are compromised by clinically appropriate strategies for dealing with unevaluable studies. Future MSCT-CA in our population should be limited to patients at low-intermediate risk with minimal arterial calcification. Effective heart rate control during MSCT-CA is imperative. National guidelines should be utilised to govern patient selection and direct appropriate MSCT-CA reporter training and accreditation to ensure quality control.

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Figure 1

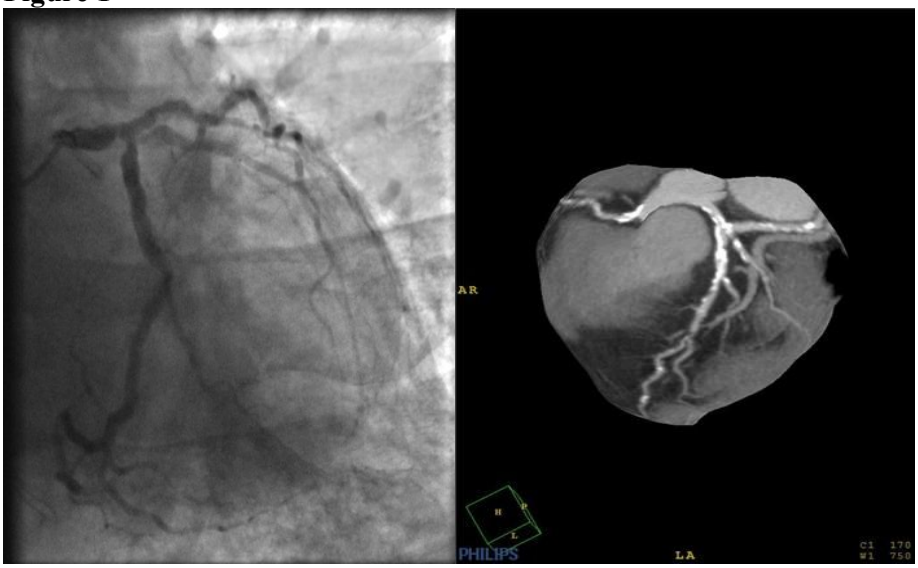

Figure 1 (a) Figure 1 (b)

Figure 1(a) I-CA LAO Caudal view demonstrating significant left main stem, circumflex and left anterior descending artery stenoses in an elderly gentleman. Figure 1(b) MSCT-CA volume rendered image of the elderly gentleman in 1(a) demonstrating heavily calcified arteries which compromised evaluation of luminal stenoses.

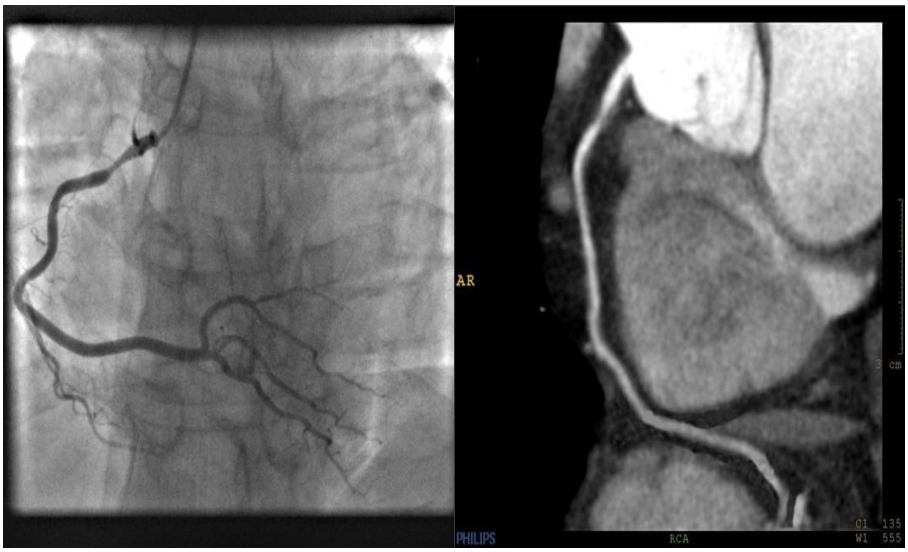

Figure 1 (c) Figure 1 (d)

Figure 1(c) I-CA of RCA in LAO 30^0 demonstrating a significant proximal RCA stenosis > 50%. Figure 1(d) MSCT-CA curved multi-planar reconstruction demonstrating the same proximal RCA stenosis as 1(c) with severity of stenosis easily assessed due to the presence of soft rather than calcified plaque.